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Toxic Enactments: Materializing Estrogen and Regulation Under Canada's Food and Drugs Act, 1939-1953

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TOXIC ENACTMENTS: MATERIALIZING ESTROGEN AND REGULATION UNDER CANADA'S *FOOD AND DRUGS ACT*, 1939-1953

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ABSTRACT

The study describes how estrogen was standardized in Canada, in the 1940s and early 1950s, under the *Food and Drugs Act*. Contributing to interdisciplinary conversations, it provides an empirical case of how regulatory practices enact material realities. Using archival material, the study describes how estrogen was achieved, in part, through heterogeneous practices of the Canadian Committee on Pharmacopoeial Standards, National Health, and government solicitors. These regulators disagreed on whether, how, and by whom estrogens should be standardized. Rather than resolve these disagreements, Canada enacted multiple regulations purporting to standardize estrogen, and government solicitors practiced “techniques of validating” to render the regulations as lawful. I argue that these regulatory enactments materialized estrogen as a potent, unpredictable, and multiple object. Further, I show how estrogen spawned novel regulatory techniques in Canada, particularly the use of consumer product labels. In this way, estrogen catalyzed an early example of risk regulation in Canada.

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An introduction

All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy. – adage credited to Paracelsus (1493-1541)

Take a moment to consider the temporalities of toxicity; or less rhetorically, and better refining the realities being put into relation, to consider the historicity of hormone disruption. How has hormone disruption been materialized in the past? When have estrogenic chemicals, drugs and cosmetics been potent in bodies? When has the dose made the poison?

Today, in Canada, hormone (or endocrine) disruption is a well-established phenomenon.[1] That synthetic industrial chemicals could disrupt the endocrine systems of humans and wildlife alike burst into popular consciousness in the mid-1990s, with the publication of *Our Stolen Future*.[2] In translating the emerging science to policy makers and publics, researchers and activists have often leveraged the fact that endocrine disrupting chemicals can mimic estrogen in bodies.[3] Some have drawn connections between these chemicals and the synthetic estrogen DES,[4] or troubled distinctions between so-called "natural" hormones and "synthetic" chemicals.[5] Some have perpetuated repronormative, heterosexist, transphobic, or ableist discourses that reinforce sex panics about endocrine disruption of normative bodies;[6] others in queer and trans studies, and critical animal studies, have explored the chemical (and multispecies) productions

[1] See e.g. House of Commons, *Healthy Environment, Healthy Canadians, Healthy Economy: Strengthening the Canadian Environmental Protection Act – Report of the Standing Committee on Environment and Sustainable Development* (June 2017) (Chair: Deborah Schulte), online: <https://www.ourcommons.ca/DocumentViewer/en/42-1/ENVI/report-8>.

[2] Theo Colborn, Dianne Dumanoski & John Peterson Myers, *Our Stolen Future: Are We Threatening Our Fertility, Intelligence and Survival? – A Scientific Detective Story* (London: Little, Brown and Company, 1996).

[3] Such that these chemicals were called "environmental estrogens" in the 1980s. That term has fallen out of use as scientists have come to understand that endocrine disrupting chemicals have many different and complex modes of action. In addition to estrogenic activity, EDCs can have androgenic or anti-androgenic effects. Further, they do not only mimic hormones in bodies by attaching to hormone receptors, but can block hormone receptors, among myriad other participations and interferences. For one scientist's account summarizing the field since the DES crisis in the early 1970s, see JA McLaclan, "Environmental signaling: from environmental estrogens to endocrine-disrupting chemicals and beyond" (2016) 4 *Andrology* 684.

[4] See e.g. Nancy Langston, *Toxic Bodies: Endocrine Disrupters and the Lessons of History* (New Haven: Yale University Press, 2010) ["Langston 2010"].

[5] See e.g. Celia Roberts, *Messengers of Sex: Hormones, Biomedicine and Feminism* (New York: Cambridge University Press, 2007) ["Roberts 2007"].

[6] For critique of these moves, see e.g. Giovanna Di Chiro, "Polluted politics? Confronting Toxic Discourse, Sex Panic and Econormativity" in Catriona Mortimer-Sandilands and Bruce Erickson, eds, *Queer Ecologies, Sex, Nature, Politics, Desire* (Bloomington: Indiana University Press, 2010); Dayna Nadine Scott, "Gender-benders": Sex and Law in the Constitution of Polluted Bodies" (2009) 17 *Fem Leg Stud* 241; and Malin Ah-King & Eva Hayward, "Toxic Sexes: Perverting Pollution and Queering Hormone Disruption" (2014) 1 *O-Zone: A Journal of Object-Oriented Studies* 1.

of sex,[7] and celebrated the queer intimacies and pleasures of endocrine disruption.[8] Without mongering these fears or indulging these pleasures, it can be said that endocrine disrupting chemicals can change birth weights and fetal reproductive and neurological development; can impact fertility, metabolism, and behaviour; and can cause cancer, among multitudinous other effects and affects.

Endocrine disrupting chemicals have upset the toxicological truism that the "dose makes the poison". Conventionally, the greater the amount of a substance administered to an organism, the greater the physiological response – a relationship that, in pharmacology, is referred to as *potency*. In recent years, however, novel facts have crystallized. Not only do some endocrine disrupting chemicals cause adverse effects at low doses, but they can have relatively *greater* toxicity at lower doses, and little or no effects at high doses.[9] This non-conventional dose-response relationship has major implications for risk assessment and for public policy, as it suggests that there is no safe threshold for exposure to these chemicals.[10]

Nonetheless, truisms about dose remain embedded in regulatory habits. As one discrete (if not isolated) example, in 2011, when environmental and health organizations asked Health Canada to explain why it was not applying an existing legal prohibition against the sale of cosmetic products containing an "estrogenic substance" to endocrine disrupting chemicals such as phthalates and parabens, the Minister's response emphasized that "in their present practices of use", these ingredients were "less potent than the natural estrogens in the body".[11] That prohibition, created at the peak of concern about estrogenic drugs in the 1970s, brings to mind further examples. By the beginning of that decade, the contraceptive pill had been tied to a

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[7] See e.g. Anne Fausto-Sterling, *Sexing the Body: Gender Politics and the Construction of Sexuality* (New York: Basic Books, 2000) [Fausto-Sterling 2000]; Anne Pollock, "Queering Endocrine Disruption" in Katherine Behar, ed, *Object-Oriented Feminism* (Minneapolis: University of Minnesota Press, 2016); Donna Haraway, "Awash in Urine: DES and Premarin® in Multispecies Response-Ability" (2012) 40:1-2 *WSQ* 301 ["Haraway 2012"]; and Eva Hayward, "Transxenoestrogenesis" (2014) 1:1-2 *TSQ* 255.

[8] See e.g. Paul B Preciado, *Testo Junkie: Sex, Drugs, and Biopolitics in the Pharmacopornographic Era* (New York: The Feminist Press, 2013) ["Preciado 2013"]; and Mel Y Chen, *Animacies: Biopolitics, Racial Mattering, and Queer Affect* (Durham, NC: Duke University Press, 2012).

[9] See e.g. Laura Vandenberg et al, "Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses" (2012) 33:3 *Endocr Rev* 378; and World Health Organization, "State of the science of endocrine disrupting chemicals", in *An assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme and WHO* (Geneva: WHO Press, 2013).

[10] See e.g. Dayna Nadine Scott, "Conclusion: Thinking about Thresholds, Literal and Figurative" in Dayna N Scott, ed, *Our Chemical Selves: Gender, Toxics, and Environmental Health* (Vancouver: UBC Press, 2015) ["Scott 2015"]; and Sheldon Krimsky, "Low-Dose Toxicology: Narratives from the Science-Transcience Interface", in Soraya Boudia & Nathalie Jas, eds, *Powerless Science? Science and Politics in a Toxic World* (New York, NY: Berghahn, 2014).

[11] Health Canada, "Health and environmental impact of endocrine disrupting chemicals used in cosmetics", Response to Petition No. 310 to the Commissioner on Environment and Sustainable Development (June 2011, Canada), online: <http://www.oag-bvg.gc.ca/internet/English/pet_310_e_35780.html>.

range of adverse health effects;[12] soon thereafter, its association with ovarian cancer saw the original pill removed from markets, replaced with a pill just one-tenth the dose.[13] In 1971, the synthetic estrogenic chemical DES – three times more potent than estradiol – was found to cause a rare vaginal cancer in the daughters of women who had been given the drug while pregnant.[14] In the second half of the 1970s, high-profile studies found that women taking hormone replacement therapy ("HRT") were four to 14 times more likely to develop endometrial cancer. Cancer was more likely the higher the dose of drug that the women had taken, and the longer they had taken it.[15] At some times, in some bodies, dose clearly mattered.

If (different) doses make the poison, what is to be done? Who – or what – shall be delegated to do it? Thinking with these examples hints at a pattern, different though its repetitions may be. During the 1970s, DES was banned for use in pregnancy, though its lack of therapeutic efficacy was arguably as weighty a factor as its toxicity. For more efficacious estrogens, however, another regulatory technique emerged. By the late 1970s, North American regulators required packages for both oral contraceptives and HRT to include patient package inserts ("PPIs"), with detailed information about the health risks of these prescription drugs that patients could read for themselves.[16] In shifting power from physicians to their patients, PPIs also delegated responsibility; patients considering birth control or HRT must now exercise (a more informed) choice about whether to assume the risks. Moving from feminist health activism of the 1970s to the neoliberal market-based advocacy of the present, and from drugs to cosmetics, the strategy now favoured by North American regulators to mitigate risk of cosmetics is to require ingredient

[12] Including blood clots, heart attack, stroke, depression, weight gain, and loss of libido; see e.g. Barbara Seaman, *The Doctor's Case Against the Pill* (New York: P.H. Widen, Inc., 1969).

[13] Barbara Seaman, *The Greatest Experiment Ever Performed on Women: Exploding the Estrogen Myth* (New York: Hyperion, 2003) ["Seaman 2003"] at 30.

[14] Arthur L Herbst, Howard Ulfelder & David C Poskanzer, "Adenocarcinoma of the Vagina: Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women" (1971) 284:15 *N Engl J Med* 878.

[15] Harry K Ziel & William D Finkle, "Increased Risk of Endometrial Carcinoma among Users of Conjugated Estrogens" (1975) 293:23 *N Engl J Med* 1167; and Donald C Smith et al., "Association of Exogenous Estrogen and Endometrial Carcinoma" (1975) 293:23 *N Engl J Med* 1164. These December 1975 findings were corroborated by two studies in the June 1976 issue of the *New England Journal of Medicine.* By the decade's end, US researchers were unanimous that HRT substantially increases the risk of endometrial cancer, with nine more studies showing that women using HRT were four to 20 times more likely to develop it; see Frances McCrea, "The politics of menopause: the discovery of a deficiency disease" (1983) 31 *Social Problems* 111 ["McCrea 1983"] at 115. British researchers, however, were less convinced; see Frances B McCrea & Gerald E Markle, "The Estrogen Replacement Controversy in the USA and UK: Different Answers to the Same Question?" (1984) 14:1 *Soc Stud Sci* 1. See also Elizabeth Watkins, *The Estrogen Elixir: A History of Hormone Replacement Therapy in America* (Baltimore: Johns Hopkins University Press, 2007) ["Watkins 2007"] at 92-98; she also notes that two 1976 studies considered effects on all estrogen users, regardless of whether they had uteruses or ovaries, finding a very slight correlation with increased risk of breast cancer.

[16] In the late 1970s, the US Food and Drug Administration required PPIs for four types of prescription drugs, all of which were hormonal drugs for women: oral contraceptives, DES as a postcoital contraceptive, other estrogenic products (i.e. HRT), and progestational products. See Marsha Wertzberger Gardner, "Increasing Patient Awareness in Drug Therapy: Ramifications of a Patient Package Insert Requirement" (1978) 66 *Geo LJ* 837 at 839-841.

labels on product packaging.[17] As a technique of responsibilization and governance of the self,[18] ingredient labels delegate to women, as consumers, responsibility for ensuring safety from toxics by virtue of "precautionary consumption".[19] While it can be tempting to represent product packaging as apolitical – consumer advocates might ask who suffers from having the "right to know" – the adoption of labelling for potent substances, marketed to women, has a political and regulatory history. How did the labelling of estrogenic drugs and cosmetics come to be required by law in Canada, and with what distributive consequences?

Now take all these questions and elements, and stir them into one concentrated concoction, by asking: if the dose made the poison, then what made the dose?

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While it is now scientifically accepted that endocrine disrupting compounds can have greater effects at lower doses, in the field of pharmacology in the 1940s, the conventional paradigm ruled supreme. It structured determinations of whether a substance was safe for therapeutic use, as pharmacologists evaluated what precise amounts and strengths a substance should be, in pharmaceutical form, to induce physiological effects and to avoid toxicity. Such investigations of potency were especially important for drugs made from biological substances, which had to be standardized. And perhaps no substances were so resolutely characterized as potent, in the 1940s, as were sex hormones.[20] So-called "natural" estrogens like estrone and estradiol, and "synthetic" estrogens like DES, had been crystalized or synthesized in researchers' labs in the late 1920s and throughout the 1930s, and pharmaceutical firms were eager to capitalize.

How exactly, though, did these potent molecules get transformed into therapeutic drugs? As of 1939, menopause had only just begun to be constructed as a disorder;[21] estrogens could

[17] Mandatory ingredient labelling for cosmetic products was introduced in the United States in 1977, and in Canada in 2004. However, as shown in Chapters 5 and 6, in Canada the first uses of ingredient labels to regulate potent substances, in lieu of regulatory standards, were for estrogenic drugs in 1944 and estrogenic cosmetics in 1949.

[18] For a summary of the huge body of Foucauldian scholarship on governmentality, aimed at socio-legal scholars, see Nicholas Rose, Pat O'Malley & Marianna Valverde, "Governmentality" (2006) 2:1 *Annu Rev Law Soc Sci* 83.

[19] Norah MacKendrick, "Media Framing of Body Burdens: Precautionary Consumption and the Individualization of Risk" (2010) 80:1 *Sociol Inq* 126; Norah MacKendrick, "More work for mother: chemical body burdens as a maternal responsibility" (2014) 28:5 *Gend Soc* 705; and Norah MacKendrick & Lindsay Stevens, "'Taking Back a Little Bit of Control': managing the contaminated body through consumption" (2016) 31:2 *Sociol Forum* 310.

[20] The expression "sex hormones" is fraught with difficulty and has been problematized in Nelly Oudshoorn 1994, Anne Fausto-Sterling 2000 and Celia Roberts 2007. Like them, I continue to use the term in its historical context. Scientists and bureaucrats on the Canadian Committee on Pharmacopoeial Standards did not always use this expression. At risk of overgeneralizing here, members tended to speak of "sex hormones" when contemplating end-use drug products (and relatedly, in the context of the Sex Hormone Regulations), and in other contexts spoke of estrone, estradiol, stilboestrol, or collectively the "oestrogens".

[21] Susan E Bell, "Changing ideas: The medicalization of menopause" (1987) 24:6 *Soc Sci Med* 535 ["Bell 1987"]; McCrea 1983.

"best be described as drugs looking for diseases".[22] Moreover, evidence from lab studies in the 1930s demonstrated that estrogens were carcinogenic in animals.[23] How then did sex hormones begin their explosive transformation into drugs and cosmetics that, in the second half of the century, would be used by millions of women?[24]

Feminist scholarship in the history of science, sociology, and science and technology studies (STS) has given rich insight into this question.[25] Perhaps most foundational is Nelly Oudshoorn's study showing how hormonal drugs emerged in "the triangle of the laboratory, the pharmaceutical industry and the clinic".[26] However, my research suggests that the better geometric metaphor is a square – as regulators were critical actors. In Canada in the 1940s, regulators laboured to enumerate, standardize, and control estrogens, facilitating the circulation of certain materialized forms of drugs and cosmetics in products, markets, and bodies.

Contributing to interdisciplinary conversations in socio-legal studies, legal history, STS, and pharmaceutical history by providing an empirical case of how regulatory practices enact material realities, this study composes a series of toxic enactments. Using archival material not previously written about by historians, the study describes how the enactment of estrogen in Canada was achieved, in part, through heterogeneous practices of regulators brought together in 1942 through the Canadian Committee on Pharmacopoeial Standards ("the Committee"). Comprised of physicians, pharmacists, pharmaceutical researchers, and federal bureaucrats,

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[22] Nelly Oudshoorn, *Beyond the Natural Body: An Archeology of Sex Hormones* (London: Routledge, 1994) ["Oudshoorn 1994"] at 108.

[23] See Chapter 1, section 1.i.

[24] There appears to be no research into how many millions of Canadian women used estrogenic drugs (or cosmetics) in the twentieth century; however, "millions" is a very safe estimate when extrapolating from American research. As growth hormones, estrogens were also transformed into growth promoters for livestock, administered through feed or implants; see Langston 2010 and Jean-Paul Gaudillière, "DES, Cancer, and Endocrine Disruptors: Ways of Regulating, Chemical Risks, and Public Expertise in the United States" in Soraya Boudia & Nathalie Jas, eds, *Powerless Science? Science and Politics in a Toxic World* (New York, NY: Berghahn, 2014) ["Gaudillière 2014"]. However, those technologies are beyond the scope of this thesis.

[25] Susan E Bell, "Gendered Medical Science: Producing a Drug For Women" (1995) 21:3 *Fem Stud* 469 ["Bell 1995"]; Fausto-Sterling 2000; Jean-Paul Gaudillière, "Better prepared than synthesized: Adolf Butenandt, Schering Ag and the transformation of sex steroids into drugs (1930–1946)" (2005) 36 *Stud Hist Phil Biol & Biomed Sci* 612 [Gaudillière 2005a"]; Jean-Paul Gaudillière,"The Visible Industrialist: Standards and the Manufacture of Sex Hormones", in Christoph Gradmann & Johnathan Simon, eds, *Evaluating and Standardizing Therapeutic Agents, 1890-1950* (New York: Palgrave Macmillan, 2010) ["Gaudillière 2010"]; Gaudillière 2014; Haraway 2012; Nancy Krieger *et al*, "Hormone replacement therapy: cancer, controversies, and women's health: historical, epidemiological, biological, clinical, and advocacy perspectives" (2005) 59:9 *J Epidemiol Community Health* 740 ["Krieger *et al* 2005"]; Langston 2010; Allison Li, "Marketing Menopause: Science and the Public Relations of Premarin" in Georgina Feldberg et al, eds, *Women, Health and Nation: Canada and the United States since 1945* (Montreal and Kingston: McGill-Queen's University Press, 2003) ["Li 2003a"]; Bob Ostertag, *Sex Science Self: A Social History of Estrogen, Testosterone, and Identity* (Amherst and Boston, MA: University of Massachusetts Press, 2016) ["Ostertag 2016"]; Oudshoorn 1994; Sheila M Rothman & David Rothman, *The Pursuit of Perfection: The Promise and Perils of Medical Enhancement* (New York: Vintage Books, 2003) ["Rothman & Rothman 2003"]; Roberts 2007; Seaman 2003; Chandak Sengoopta, *The Most Secret Quintessence of Life: Sex, Glands, and Hormones, 1980-1950* (Chicago: University of Chicago Press, 2006) ["Sengoopta 2006"]; and Watkins 2007. This list excludes historiography on the contraceptive pill.

[26] Oudshoorn 1994, at 82.

with its proposed regulations reviewed by federal solicitors, the Committee was coordinated by the Department of Pensions and National Health ("the Department" or "National Health").[27] When it came to standardizing estrogen(s) and their potency, these actors practiced numerous, divergent scientific and statutory techniques for enumerating substances, prescribing test methods, and mandating labelling. Analytically, my study shows how these practices often "hinged" on practices of delegation, used both in a doctrinal administrative law sense and with a more Latourian valence, in which desired behaviours are inscribed into technology.[28] In brief, responsibility for ensuring safety was repeatedly directed away from the Department. Following Annemarie Mol's praxiological reformulation of actor-network theory,[29] I argue that these varied regulatory practices materialized estrogen as a potent and multiple object. Further, drawing on notions of co-production, I show how estrogen spawned novel regulatory techniques in Canada. Toxic enactments potentiated legal substances, and substantiated potent laws.[30]

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Part I sets the historical, conceptual and methodological stage. Chapter 1 relates numerous families of history and theory. It begins by recalling mid-twentieth century histories on the emergence of sex hormones and on the standardization of biological drugs. Swerving from history to theory, the chapter turns to review the more theoretical literature that grounds this story. Distilled here to one word, the key concept is *enactment*. Rather than a grand explanatory theory of historical events, enactment describes how realities are done in practice. In this, I draw heavily on the ontological and praxiological concepts of Annemarie Mol, an STS scholar and philosopher of medicine. The rest of the chapter canvases literature by some of Mol's scholarly relatives: first, Larry Busch's political sociology of standards; and second, intersections between

[27] I refer to "the Department" or "National Health" to capture the department's various names during 1939-1951. In October 1944, a reorganization divided what had been the Department of Pensions and National Health into the new Department of Veterans Affairs and new Department of National Health and Welfare, the latter of which continued to house the Food and Drugs Division. See *An Act to establish a Department of National Health and Welfare,* SC 1944-1945, c 22. See also AL Davidson, *The genesis and growth of food and drug administration in Canada.* (Ottawa: Ministry of National Health and Welfare, 1949) ["Davidson 1949a"] at 88; and AL Davidson, *Canada Pioneers in Food and Drug Control: The Story of the Food and Drug Directorate* (Canada: Department of National Health and Welfare, Information Services Division, 1949) ["Davidson 1949b"].

[28] Bruno Latour, *Pandora's Hope* (Cambridge, Mass: Harvard University Press, 1999) [Latour 1999a] at 185; and Bruno Latour, "Where Are the Missing Masses? The Sociology of a Few Mundane Artifacts" in Wiebe W Bijker & John Law, eds, *Shaping Technology/Building Society: Studies in Sociotechnical Change* (Cambridge, Mass: MIT Press, 1992) [Latour 1992] at 226-236.

[29] Annemarie Mol, *The Body Multiple: Ontology in Medical Practice* (Durham, NC: Duke University Press, 2002) ["Mol 2002"].

[30] "Legal substances" comes from Javier Lezaun, "The Pragmatic Sanction of Materials: Notes for an Ethnography of Legal Substances" (2012) 39:1 *J Law & Soc* 20 ["Lezaun 2012"].

socio-legal studies and STS,[31] including not only Sheila Jasanoff's concept of co-production, but newer work by Javier Lezaun, Emily Grabham, and Emilie Cloatre that takes a material turn.

Chapter 2 details the research methods practiced in this study. To the extent that studies of enactment-in-practices are fundamentally empirical,[32] the first chapter already addresses methodology. Yet it says nothing of the disciplinary kin to which this thesis – arguably – most closely relates, namely legal history.[33] Thus, the second chapter ponders relations of (legal) history-in-theory and theory-in-(legal)-history. Recalling concern with the familiar method that centers law as nucleus and everything else merely as extended family (or "context"), the second chapter identifies recent engagements of legal history with materiality that allow (legal) historians to compose a different object, one in which law and matter are imbricated.

Part II provides my account of how estrogen co-emerged with regulatory techniques in Canada, between 1939 and 1953. Necessarily arbitrary, these dates bracket a time of explosive growth in the variety of sex hormone products available;[34] DES arrived on the market in Canada in 1939, Premarin in 1941.[35] Moreover, the 1940s belonged to an era in pharmaceutical history often referred to as the "therapeutic revolution", in which drug development, and the economic and political power of the drug industry, grew immensely.[36] The 1940s also witnessed a major expansion of National Health's aims and ambitions; in the wake of the Treaty of Westminster, senior officials seized the opportunities, including those presented by WWII, to unleash a suite of food and drug regulations and to build the Department's bureaucratic machinery. During this decade, the *Food and Drugs Act* aimed to protect public health through a scheme heavily premised upon delegation. Notably, while the *Act* did not at the time require pre-market approval for new drugs (unlike in the US), drug *standards* could still be imposed by delegated legislation.

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[31] To contest and collapse the distinctions between "law", "society" and "science" inherent to this formula, Cloatre and Pickersgill propose instead the "social studies of law"; see their introduction to Emilie Cloatre & Martyn Pickersgill, eds, *Knowledge, Technology and Law* (London: Routledge, 2015) ["Cloatre & Pickersgill 2015"] at 8-9.

[32] Mol follows Latour and others in querying whether ANT can properly be characterized as a "theory". Annemarie Mol, "Actor-Network Theory: sensitive terms and enduring tensions" (2010) 50:1 *Kölner Zeitschrift für Soziologie und Sozialpsychologie* (Sonderheft) 253 ["Mol 2010"] at 253-254, 261-262.

[33] Some historiography canvassed here, such as environmental history by Nancy Langston and pharmaceutical history by Jean-Paul Gaudillière, examines patterns in regulatory decision-making, providing close readings of judicial decisions and exploring transformations in regulatory logics regarding sex hormones. But these scholars do not situate their work as legal history *per se.*

[34] Note that this is not the same as claiming there was explosive growth in the *use* of estrogenic drugs in the 1940s.

[35] Both DES and Premarin were already on the Canadian market before they were approved for sale in the U.S.

[36] Vivianne Quirke, "From alkaloids to gene therapy: a brief history of drug discovery in the 20th century", in Stuart Anderson, ed, *Making Medicines: A brief history of pharmacy and pharmaceuticals* (London: Pharmaceutical Press, 2005) ["Quirke 2005"] at 177.

Alongside these legal, political, and economic dynamics, the human and nonhuman actors in this story are also introduced in Chapter 3. There is no analytic magic to the word actor;[37] one could also use actants,[38] agents,[39] participants,[40] or actives (with its pharmacological invocation of active ingredients). Nor does it reflect a puritanical commitment to an imagined actor network theory ("ANT").[41] There is, however, much more deliberation behind *estrogen,* the term chosen for the leading actor. Readers may protest that this term is ahistorical or unscientific, carries too much gendered or heteronormative baggage,[42] or, if they are especially perceptive, that the term is a self-serving attempt to render semantically singular what is a group of substances, in order to better dramatize the argument that estrogen is multiple. After all, estrogen carries no single specific meaning for biochemists, endocrinologists, physicians, or pharmacists, nor did it in the 1940s. Thinking of steroidal estrogens, the molecules produced endogenously in human bodies, this umbrella term colloquially refers to what biochemists have known, since the 1930s, was a class of hormones – the three main such estrogens being *estradiol, estrone* and *estriol*.[43] Other "natural" estrogens also used in pharmaceuticals are endogenous not to human but to equine bodies, like equilin and equilenin, extracted from pregnant mares' urine and conjugated into the hormone replacement therapy branded so memorably as *Premarin*.[44] The best known "synthetic" estrogen, referred to here as *DES*,[45] was synthesized in 1939 as an inexpensive

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[37] Mol 2010, at 255: "It is easy, everyone knows what an actor is – an actor does things – it, he, she acts. But no, of course it is not easy, because in different theoretical repertoires an 'actor' is made to be different things. Look at these sentences. First, they state that an actor acts and then that an 'actor' is made to be. From one sentence to the next there is a shift from a real life actor who acts to the term actor which is made to be and, at the same time, a shift from the active to the passive. Making such shifts and playing with them to see what happens, is one of the pleasures of engaging in 'actor-network theory'."

[38] Adopted originally from semiotics, "actant" has been used in material-semiotic traditions such as ANT; see e.g. Bruno Latour, "On Recalling ANT" (1999) 47:1 *Sociol Rev* 15 ["Latour 1999b"] at 19-20.

[39] In *Messengers of Sex,* Celia Roberts conceives of hormones as "active agents in bio-social networks that constitute material-semiotic entities such as 'sex'"; Roberts 2007 at 22.

[40] In the specific context of endocrine disrupting chemicals, see Dayna Nadine Scott, Jennie Haw & Robyn Lee, "'Wannabe Toxic-Free?' From precautionary consumption to corporeal citizenship" (2017) 26:2 *Environ Politics* 322 at 332; and Max Liboiron "Redefining pollution and action: The matter of plastics" (2016) 21:1 *J Material Cult* 87 ["Liboiron 2016"] at 97.

[41] Latour has often disclaimed the terms actor, network and theory (and the dash); see e.g. Latour 1999b.

[42] While estrogen and androgen hormones are produced in bodies of all sexes and serve many physiological functions, culturally these steroid hormones continue to be positioned as female and male (Fausto-Sterling 2000; Roberts 2007). The names historically assigned to them are examined in detail by Anne Fausto-Sterling; see Fausto-Sterling 2000, at 170–194. Unlike androgen, which means to produce a man, estrogen means to produce estrus. In her analysis, not only does this entrench a hormonal model of sex, but it reduces "woman" to reproductive fecundity; at 188. Continued use of the word estrogen to refer to these hormones arguably continues to produce reproductive femininity and cis-heterosexuality as biologically natural.

[43] These are the three principle forms of estrogen in human bodies, although there are others. Estradiol is the most potent and abundant in women's bodies before menopause; estrone forms from estradiol and predominates after menopause; estriol is abundant during pregnancy. Progesterone and testosterone, other steroid hormones, also play roles in menopause. By 1939, biochemists "had crystalized at least seven estrogenic molecules", including equilin and equilenin; Fausto-Stirling 2000 at 189.

[44] It is thought that Premarin was so named for pre(gnant) mar(e) (ur)in(e).

[45] From its origin, DES was assigned different proper names in different countries' pharmacopoeia and regulations. In the US, it was diethylstilbestrol, while in Britain, it was stilboestrol. In Canada, after some debate, the 1944 Sex Hormone Regulations

alternative to estradiol preparations, and other synthetic estrogens followed.[46] While the phrase "*estrogenic substance*" gets closer to my intended meaning, it is encumbered as a term of art in the Sex Hormone Regulations,[47] and it may run a risk of re-enacting the nature-culture divide, implying a substance with fixed, natural, essential attributes that active cultural actors may then manipulate. Crafting terminology adequate to a performative approach to socio-materiality has been vexing; the closest concept might be "estrogenizer". Assigning effects to substances is also vexing, as it requires measurement practices. Yet, as will be seen, when presented with legal opportunities to standardize measurements for defining sex hormones and their activities, Canadian regulators demurred. Trying to hold together undefined estrogenic effects and their many materialized forms, I have settled on the term estrogen.

What of the argument that it is self-serving to lump a class of substances under a singular noun? In arguing that estrogen was multiple, I am striving to capture something beyond simply its many material compositions (as oestrone, oestradiol, estriol, DES, estrogenic substances, conjugated equine estrogens, the drug and cosmetic products containing them, etc.). Estrogen is capacious enough also to encompass these entities' many onto-epistemological modes, in which different human practices of knowing are implicated in the active becoming of matter,[48] whether as chemical structures, biological sources, physiological functions, pharmacological effects, forms of administration, or industrial intentions. Put at its simplest here, estrogen was multiple because it was *done* multiply. And not just by humans. Nonhuman supporting actors in this estrogenic cast will also be credited – mice and rats, vaginas and ovaries, bioassays and monographs, delegation and validity, telephones and stenographers, reference materials and labels, hot flashes and skin wrinkles, injections and inunctions, inscriptions and prescriptions.

The human actors introduced in Chapter 3 suffer from fewer nomenclatural difficulties, although identifying professors as regulators may seem, to some, to extend that word too far.

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assigned it the proper name "stilboestrol", while the Canadian Supplement to the British Pharmacopoeia, and Part V of Schedule B to the *Food and Drugs Act*, used the term "stilboestol" (with "diethylstilbestrol" indicated as a synonym in the Canadian Supplement) and the term "stilboestrol diproprionate" (a derivative ester). This study uses "DES" to refer both to the substance and its esters, unless otherwise noted.

[46]Another well-known synthetic estrogen is ethinyl estradiol. Derived from estradiol, and patented by German scientists in 1938, it is seventeen times more potent than estradiol. It was approved by the FDA for use in humans in 1949 and has been used in most oral contraceptives since the 1960s. See Seaman 2003, at 31, 34.

[47] The 1944 Sex Hormone Regulations, at s C.02.006(b)(i), assigned "estrogenic substances" as the proper name of the category of "mixed or impure" estrogenic sex hormone products. By contrast, the other category of sex hormone products was that of "pure synthetic or natural crystalline products", which included oestrone, oestradiol, oestriol, and stilboestrol. Also, as of 1977, cosmetic products containing an "estrogenic substance" – which, consistent with the Sex Hormone Regulations, meant a mixed or impure sex hormone product – were banned from import or sale in Canada; see *Cosmetic Regulations*, CRC, c 869, s 15(b).

[48] Karen Barad, "Posthumanist Performativity: Toward an Understanding of How Matter Comes to Matter" (2003) 28:3 *Signs* 801 ("Barad 2003"). At 829, she describes onto-epistem-ology as "the study of practices of knowing in being".

Yet even without drawing on the enormous literature "decentering" the concept of regulation,[49] it should be sufficient to recall that the Committee was empowered by an order-in-council and its members appointed by the Minister to advise on new drug standards and regulations.

Chapter 4 examines the events, decisions, and practices that first materialized estrogen under the *Food and Drugs Act,* homing in on a series of technical and legal controversies. At the Committee members' first meeting in Ottawa in January 1943, and in the next two years of their deliberations and deferrals, no substances were as contentious and complicated as estrogens. Their nature was contested – were they biological substances, chemicals, or pre-made products? What were the best methods for measuring their potency? Who should decide on the methods? Disagreement bedeviled discussion of whether, how, when, and by whom estrogen should be standardized or regulated. When solicitors were consulted, matter(s) became further destabilized. The chapter shows how resolution officially arrived through legally debated and experimental techniques – including delegating to industry the power to standardize sex hormones' potency, through regulating *via* labels rather than by standards. In the fall of 1944, Committee members came to the realization that these heterogenous and incommensurable practices for standardizing drugs had, ironically, led to multiple versions of single substances.

In the second half of the decade, estrogen increasingly shaped regulations under the *Food and Drugs Act*. Chapter 5 describes estrogen's legal trajectories in the late 1940s and early 1950s. Regulatory tinkering aimed to close controversies and gather estrogen together as a singular, stable, and safe object. However, concurrent with new statutory powers, other amendments extended regulatory coverage to estrogenic cosmetics while sustaining National Health's retreat from setting standards for products sold to women. Not only did new regulations and their implementation (re)enact estrogen as indeterminate and unpredictable, they were an early foundation for conceptualizing risk in Canadian law. Absorbed into new domains, estrogen spawned novel techniques of delegating to consumers, through labelling, the responsibility for ensuring a product's safety. In these ways, the regulation of estrogen was coterminous with its materialization as a potent substance – law and toxicity were being co-produced.[50]

Part III offers some brief concluding reflections – on potency, on power, and on possibility.

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[49] This literature is far too large to adequately capture here. For a leading intervention, see Julia Black, "Decentring Regulation: Understanding the role of regulation and self-regulation in a 'post-regulatory' world" (2001) 54:1 *Current legal problems* 103.

[50] On the co-production of knowledge and order, see Jasanoff's essays "The Idiom of Co-production" and "Ordering Knowledge, Ordering Society", in Sheila Jasanoff, ed, *States of Knowledge: The co-production of science and social order* (London and New York: Routledge, 2004) [together, "Jasanoff 2004"]. For scholarship addressing the co-production of toxicity and regulation, see e.g. Soraya Boudia & Nathalie Jas, "Introduction: The Greatness and Misery of Science in a Toxic World"", Soraya Boudia & Nathalie Jas, eds *Powerless Science? Science and Politics in a Toxic World* (New York: Berghahn, 2014) ["Boudia & Jas 2014"].

Chapter One

History and theory: toxic enactments

> ...hormones message across this mobile boundary, between social and biological, disrupting any attempts at delineating what belongs in each category, or indeed where the outline of the categories might lie. – Celia Roberts (2007)
>
> By what strange alchemy is a legal obligation transformed into a material constraint? – Javier Lezaun (2012)

My story of the enactment of estrogen and legal techniques in Canada in the 1940s is animated by many strands of history and theory. This chapter weaves those literatures together.

1. Sex hormones and drug standardization in the 1930s-1940s

This chapter summarizes two related mid-twentieth historiographies, which recount the emergence of sex hormones and the standardization of biological drugs.

1.i. Sex hormones on the edge of transformation

Over the last 80 years, estrogen has become among "the most widely used drugs in the history of medicine."[1] Beginning in the 1950s, estrogen became an ever-present "elixir", used for combatting aging, promoting beauty, and, later that decade, for practicing birth control.[2] However, in Canada in the late 1930s and early 1940s, sex hormones were still marginal drugs. What changed, and how did regulatory practices contribute to this transformation?

This thesis appears to be the first study of the standardization of estrogen in Canada. With the exception of Allison Li's research on Premarin, there are no Canadian histories of sex hormones.[3] Nor, more generally, have historians attended to the Canadian Committee on Pharmacopoeial Standards or its role in standardizing and regulating drugs, or to the *Food and Drugs Act* and its implementation in the 1940s.[4] Beyond Canada, a rich body of research exists

[1] Oudshoorn 1994 at 9. However, note that Oudshoorn makes this claim as of 1994.

[2] Watkins 2007. The US FDA approved Enovid for menstrual irregularities in 1957 and for birth control in 1959.

[3] Li 2003a. Although see Haraway 2012, which weaves Canadian strands into a tale of Premarin's many entanglements.

[4] Two exceptions addressing this period, with a range of methodologies, are Joel Lexchin, *Private profits versus public policy: the pharmaceutical industry and the Canadian state* (Toronto: University of Toronto Press, 2016) ["Lexchin 2016"]; and Matthew Herder, "Denaturalizing transparency in drug regulation" (2015) 8:2 *McGill JL & Health* S57 ["Herder 2015"] at S101-S115.

on sex hormones in this period, arising from sociology, history of science and medicine, and science and technology studies (STS).[5] Hormones are "interesting precisely because they sit at the boundary between 'sex' and 'gender'";[6] thus, not surprisingly, much of this scholarship examines how hormonal knowledges have produced or problematized sex and gender.

Of this work, perhaps most foundational and influential is Nelly Oudshoorn's study, *Beyond the Natural Body*.[7] Oudshoorn provides an account of the development of endocrinology in the 1920s and 1930s, a period in which scientists rushed to identify, isolate, and purify hormones in an endocrinological "gold rush",[8] and "established the basic concepts and techniques that have served as cornerstones in structuring our knowledge of hormones to this day."[9] Drawing on Foucauldian concepts regarding the materiality of discourse-building, she investigates not only how these scientists used "cultural notions as resources in their research practice", but also, and indeed primarily, the "complex instruments, research materials, careful preparatory procedures and testing practices" that were the material conditions of endocrinal knowledge.[10] With special attention to the Dutch context, Oudshoorn painstakingly sets out the scientific alliances and material practices through which scientific claims about sex hormones were naturalized into universalized facts and stabilized as technological artefacts in the form of drugs.

Focused on steroidal hormones, she describes how, in the 1920s and early 1930s, biochemists like Adolf Butenandt and Edward Doisy created techniques to extract "female" and "male" sex hormones from glands, isolate them from urine, and purify them as crystalline preparations.[11] In the process, they established new facts about sex hormones – which, by the late 1930s, they apprehended as the molecules estrone, estriol, and estradiol – that profoundly challenged a binary model of sex centered on reproductive organs: estrogens were in all male bodies and androgens in all female bodies, ovaries secreted not only estrogen but also testosterone, and these hormones were not made only in gonads but in adrenal glands. Rather than anatomical, sex increasingly appeared to be chemical.[12] Oudshoorn argues that this new

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[5] See Introduction at note 25. As noted, that list excludes historiographies of the contraceptive pill.

[6] Emilia Sanabria, *Plastic Bodies: Sex Hormones and Menstrual Suppression in Brazil* (Durham, NC: University Press, 2016) ["Sanabria 2016"] at 105; see also 5, 149.

[7] Oudshoorn 1994.

[8] On the "gold rush" or "golden age" in endocrinology, see Li 2003a at 103, and Fausto-Stirling 2000 at 170. The metaphor appears to have originated with leading reproductive endocrinologist Alan S Parkes; see e.g. Alan S Parkes, "The rise of reproductive endocrinology, 1926-1940" (1966) 34:3 *J Endocrinol* 20.

[9] Oudshoorn 1994 at 9.

[10] *Ibid* at 10-11 and 12-13; see also 148-150 and fn 17 at 154-155.

[11] *Ibid* including at 46-48, 71-79.

[12] *Ibid* at 24-34, 145.

endocrinological knowledge radically transformed views of sex and the body. Nonetheless, most scientists continued to produce the same dualistic model of sexual difference.[13]

In one chapter of her book, Oudshoorn describes the bioassay methods and standardization techniques developed by laboratory scientists, and, critically, how these testing tools contributed to transform sex hormones into material realities.[14] In subsequent chapters, she examines two other means by which sex hormones materialized. Research materials – gonads and urine – were required by laboratories and served to connect laboratory scientists' practices to clinics and pharmaceutical firms. The ability of industrial and clinical actors to supply materials, and pre-existing gynecological (and not andrological) clinical practices, led to a concentration of research activity on "female" sex hormones.[15] While these practices ultimately materialized sex hormones as chemical products, they were further shaped into estrogenic drugs through the socially networked practices of clinical trials and industrial marketing. In short, before companies could create markets, they needed to work with clinicians to help them identify diseases for their drugs. Oudshoorn's history illustrates how the properties of estrogenic drugs were not fixed before being marketed. Rather, marketing practices, themselves deeply shaped by gendered cultural norms, materialized sex hormones as drugs for menstruation and female menopause (and not for contraception or male menopause).[16] As Li notes, this challenges "the traditional linear model of drug development in which it is assumed that a new drug is tested and its purpose defined before it is taken to the marketplace."[17] In examining these structural relationships and material practices, Oudshoorn concludes that estrogenic drugs emerged in the interactions within "the triangle of the laboratory, the pharmaceutical industry and the clinic".[18]

Oudshoorn's historical findings have been built upon and distinguished by scholars in many disciplines.[19] Often this scholarship aims to trouble hormonally deterministic constructions of sex and gender, demonstrating how feminists can engage with the materiality of bodies without simply rejecting biological knowledge as a social construction. In *Sexing the Body,* biologist and

[13] *Ibid* at 144-148. See also Fausto-Stirling 2000 at 182-191.

[14] I leave more detailed engagement with this chapter of Oudshoorn's book, on measuring sex hormones, to my discussion of the historiography on standardization of biologicals (including estrogen); see Chapter 1, section 1.ii, below.

[15] *Ibid* at 65-81.

[16] *Ibid* at 82-111, and 140-141.

[17] Li 2003a at 102; see also Oudshoorn 1994 at 3.

[18] Oudshoorn 1994 at 83.

[19] In this paragraph I discuss the work of scholars who, while not disciplinarily situated in history *per se,* have partly framed their inquiries historically. I exclude from this discussion scholarship on sex hormones that is purely ethnographic, regardless that it explores similar questions about pharmaceutical ontology, such as Sanabria 2016.

gender theorist Anne Fausto-Sterling also considers endocrinology during the interwar period.[20] Agreeing that scientists created chemical sex through practices used to isolate and purify, measure and standardize, and define and name the "sex hormones", she also describes their work as deeply informed both by prevailing gender norms and by social struggles against them. Scientists intersected with other social worlds – "feminists, advocates of homosexual rights, eugenicists, birth control advocates, psychologists, and charitable foundations" – which empowered and shaped hormone research, not least through philanthropic and political support.[21] Further, while emphasizing how "scientists are a diverse lot" and indeed how some scientists of the time resisted efforts to fit new, unexpected test results into existing gender constructs, Fausto-Stirling examines closely the ways that many scientists embraced and incorporated pre-existing cultural assumptions in developing new endocrinological facts.[22]

Feminist theorist Celia Roberts further augments this body of work in *Messengers of Sex*.[23] While lauding Oudshoorn's account of how sex hormones "were not 'discovered' in nature, but rather were produced through scientific interaction and work",[24] she takes pains to distinguish her approach from what she paints as Oudshoorn's use of social network analysis.[25] She argues that, in studying how hormones were produced in interactions of human actors, Oudshoorn circumscribes networks of practice in a way that "tends to leave important questions open".[26] The critique typifies frustrations that normatively-oriented scholars, including feminist scholars, can have with network or assemblage analyses that describe *how* but do not explain *why* realities materialize. Unsatisfied by Oudshoorn's description, for example, of how existing gynecological practices facilitated translation of hormones into drugs, Roberts asks "why were clinics set up around women's bodies and not around men's? Which 'practices of masculine supremacy, or … other systems of structural inequality' were built into this practice fact?"[27] To approach such questions, Roberts attempts to avoid separating culture from science, or to deploy it as an ahistorical explanation for science. Developing STS network approaches,[28]

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[20] Fausto-Sterling 2000.

[21] *Ibid* at 148; see generally 170-177.

[22] *Ibid* at 190; see generally 147-148 and 177-194.

[23] Roberts 2007.

[24] *Ibid* at 44.

[25] *Ibid* at 36; see generally 37-45. See also Oudshoorn 1994 at 153-154 (at fn 13), addressing her use of social network theory rather than ANT.

[26] *Ibid* at 44; see also generally 36-46.

[27] *Ibid.* At 38-39, Roberts also asks why new endocrinological facts of the 1920-30s did not mean "the end of the two-sex model", a question that was likewise investigated in Fausto-Stirling 2000.

[28] *Ibid* at 41. In this respect, Roberts considers Bruno Latour's ANT approach alongside Donna Haraway's reservations that ANT can over-emphasize technical aspects of science and under-emphasize power.

including by adopting Serres' notion of crumpled or folded time to explain the persistence of notions of sexual difference in the history of hormones,[29] she expands her analytical focus beyond technoscientific practices to include non-human actors – most particularly, by foregrounding "the activities of sex hormones themselves." She theorizes hormones not merely as biological substances, but as *bio-social actors* that "actively participate in the enactment of particular versions of the biological (or nature) and the social (or culture) and of sex".[30] In the form of HRT technologies, hormones have social and biological effects that are produced through networks of representation and that cannot be parsed. Nor can these effects be isolated from the culturally and historically situated and already sexed/gendered bodies in which they are circulated and with which they interact.[31] As messengers, hormones create a relationality reflected by the hyphen in bio-social, "which represents a constituting, active relation between two entities (the biological and the social) that do not pre-exist on their own but are constituted through their connection with each other."[32] These methodological and conceptual differences signal a modified answer to the question of how estrogen became a drug for menopausal women. In Roberts' view, pre-existing cultural conceptions of racial and sexual difference were folded into the new science of endocrinology in the 1920s and 1930s, and were carried through into the estrogenic technologies that developed during the twentieth century. Embedded in HRT, specifically, were discourses in which femininity was inextricably linked to reproductivity and in which menopause was unnatural.[33]

None of these scientific and cultural histories consider how regulators' activities may have contributed to transforming sex hormones into drugs. Other historical subdisciplines, however, have since brought regulators into the picture. In *Toxic Bodies,* environmental historian Nancy Langston gives a detailed account of the regulatory history of DES.[34] In 1938, the biochemist Edward Dodds invented DES as a coal-tar based synthetic substitute for steroidal estrogens. While dissimilar in chemical structure to the steroids, it was a potent analog of estrogens.[35] DES "could cornify the lining of mouse vaginas far more potently than anything produced by living

[29] *Ibid* at 46-50.

[30] Ibid at 47. Notably Roberts describes these enactments as historically contingent: "such enactments are historically specific materializations (to use Judith Butler's term) or articulations (to use Donna Haraway's term)".

[31] *Ibid* at 155-158.

[32] *Ibid* at 181.

[33] *Ibid* at 114-34.

[34] Langston 2010. For other work that integrates political, legal and/or regulatory history into scientific and social histories of DES and steroid hormones, see Gaudillière 2014; Gaudillière 2005a; and Gaudillière 2010.

[35] Langston 2010 at 32; and Gaudillière 2014 at 78.

bodies", making it "more estrogenic than estrogens".[36] Langston unearths the record of the US FDA's deliberations, in 1939 to 1941, on whether to approve DES as a drug for menopause (and of later US regulatory decisions, in 1947, to approve DES for use by pregnant women and for poultry).[37] She does not, however, query whether the US FDA played a role in materializing DES. This is perhaps unsurprising, as the statutory setting of her DES story in the US tends to obscure such questions. As of 1939, the US *Food, Drugs and Cosmetics Act* required all new drugs to obtain pre-market approval; in that context, it is more difficult to perceive how a drug can be approved if it does not yet exist. In Canada, by contrast, where drugs did not require approval and yet were increasingly shaped by regulatory standards, I argue that regulators' activities were more constitutive, and that, in their practices of enumerating and standardizing estrogen, regulators were not simply sanctioning pre-existing substances but enacting them.

Beyond DES, many other new estrogenic products were marketed in the 1930s, despite little evidence of therapeutic efficacy. Proof of efficacy was not a legal precondition for the US FDA's approval of DES, nor a precondition for its clinical use.[38] For steroid estrogens, in the late 1920s and 1930s, drug companies promoted a plethora of indications, "starting from a restricted group of menstrual disorders and extending, by the late 1920s, to include the treatment of menopause, infertility, problems of the genitals, psychiatric conditions such as schizophrenia and depression, dermatological diseases such as eczema, and even diseases of the joints".[39] Estrogen even instigated the proliferation of new disease categories, largely related to menstruation and sterility.[40] Despite this, estrogen therapies were not popular in the 1930s.[41] In expanding Oudshoorn's research into clinical domains, Chandak Sengoopta shows that physicians were not convinced that estrogen was an effective remedy for anything. He asks "[w]hat exactly happened in the clinic once the sex hormones were available as potent, standardized and reliable therapeutic preparations? Did they bring about the therapeutic revolution prophesied by

[36] Ostertag 2016 at 63-64.

[37] Langston 2010 at 32-47. In his work on DES, contrary to (and without citing) Langston, Jean-Paul Gaudillière asserts that DES was never approved by the US FDA for use by pregnant women but was prescribed off-label; Gaudillière 2014 at 68, 78-79.

[38] Oudshoorn 1994 at 89; Gaudillière 2014 at 78-79; Rothman & Rothman 2003 at 70; and Watkins 2007 at 28-29.

[39] Li 2003a at 104; see also Oudshoorn 1994 at 97-98; Gaudillière 2014 at 78-79; and Watkins 2007 at 21-22.

[40] Rothman & Rothman 2003 at 72: "…the traditional category of amenorrhea was divided and then subdivided into infantilism (underdevelopment of sexual organs), Fröhlich's syndrome (infantilism due to a pituitary dysfunction), primary amenorrhea (delayed or imperfect development of secondary sex characteristics), secondary amenorrhea (premature menopause), polymenorrhea (short menstrual cycle), hypomenorrhea (too little menstrual flow), oligomenorrhea (delayed menstruation due to pituitary dysfunction), and endocrinopathic amenorrhea and sterility…".

[41] Fausto-Stirling 2000 at 184, 341 (at fn 68); Rothman & Rothman 2003 at 74-75; Langston 2010 at 30; Krieger *et al* 2005 at 741; and Watkins 2007 at 22-23.

so many in the 1920s?" For menstrual disorders, by the late 1930s, most gynecologists had answered this question in the negative – clinical results were "notoriously unsatisfactory".[42] That being said, gynecologists also believed that the therapeutic efficacy of estrogens was closely connected to the dosage level.[43] Despite this centrality of dose to medical discourses, radical variability continued to characterize the dosages of therapeutic estrogen preparations, the bioassays used to measure their potency, and the units used to express potency.[44]

The change, if you will, began in the early 1940s. Some firms, like the Dutch firm Organon, had sought as soon as the early 1930s to position sex hormones as a remedy for menopause.[45] Yet throughout that decade many women, and many gynecologists, did not see menopause as a disease.[46] Physicians tended to view it as a stage of life that, for a minority of women, involved unpleasant symptoms for a short period. However, the very possibility of relieving these women's discomfort with dependable estrogenic drugs, even in the short-term, "resulted in the reconceptualization of menopause as a deficiency disease".[47] Put differently, "before Ayerst could sell the drug, it had to sell the disease".[48] The rush to sell estrogen – and with it, menopause – took off after the US FDA approved DES in September 1941. Before DES was available, most preparations on the North American market were estradiol or estrone products, but in comparison, DES was much cheaper to produce, and as it was unpatented, many firms promptly began manufacturing DES products.[49] Less than a year later, conjugated estrogen, branded as Premarin, received US FDA approval as a new menopause therapy.[50] By some measures, Premarin was nearly as potent as DES, but without the notoriously noxious side effects. As a tablet, it was easier to administer than DES or oestradiol preparations, typically given by intramuscular injection. Further, by aggressively marketing it as a "natural" product,

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[42] Sengoopta 2006 at 71, citing Novak, "The Therapeutic Use of Estrogenic Substances" (1935) 104:20 *JAMA* 1815 ["Novak 1935'"] at 1817.

[43] Sengoopta 2006 at 159-163; and Krieger *et al* 2005 at 741.

[44] *Ibid* at 162, citing Novak 1935 at 1817. For further discussion of the role of standardized bioassays in materializing and measuring the potency of estrogenic drugs, see Chapter 1, Section 1.ii, below.

[45] Oudshoorn 1994 at 97-98.

[46] Bell 1987; McCrea 1983; Sengoopta 167-168; Langston 2010 at 31; and Watkins 2007 at 22-24. Even those gynecologists who, in the 1930s, promoted estrogen for relief from menopause saw it as only appropriate for a small number of severe cases; see e.g. Novak 1935 at 1819. Some historians have found that, while gynecologists in the 1930s "perceived their use to control the symptoms of menopause as something suspicious...many women backed the use of these drugs"; see Gaudillière 2005a at 608.

[47] Li 2003a at 104, drawing on Margaret Lock, *Encounters with Aging:* Mythologies of Menopause in Japan and North America (Berkeley, CA: University of California Press, 1994) at 342-344.

[48] Ostertag 2016 at 66.

[49] Langston 2010 at 30-32; Seaman 2003 at 13, 43; Ostertag 2016 at 64; Watkins 2007 at 29; and Gaudillière 2014 at 78.

[50] Li 2003a at 103; and Watkins 2007 at 29. In Canada, Premarin was introduced to the market in 1941; see Watkins 2007 at 23.

Ayerst quickly established Premarin as the main competitor to DES.[51] Together these "two products became the treatment of choice" for menopause,[52] though as Premarin grew in popularity over the decade, drug companies began promoting DES for other purposes (notably, to reduce miscarriage and promote healthy pregnancies).[53] This proliferation of potent products, and the consolidation of menopause as a disorder, caused skeptical physicians to reconsider their views in the years after WWII, when there was an explosion of "menopausal disorders" and drugs to treat them.[54]

The number of commercial preparations grew in the 1930s not only despite tenuous evidence of efficacy, but in the face of carcinogenic hazards. Historians generally concur that, while data published in major American journals was not conclusive, the "possibility that estrogen use caused cancer" was "well appreciated in the late 1930s and early 1940s".[55] With respect to DES, within mere months after it was synthesized and then continuing throughout the 1940s, researchers were linking it with cancer, and with genital and reproductive abnormalities.[56] By 1939, "nearly all researchers agreed that natural estrogens had the potential to be carcinogenic in laboratory animals, and that DES was at least as carcinogenic, if not more so, than natural estrogens because it was more potent", though researchers and physicians were often dismissive of the significance of these animal studies to human health.[57] Throughout the 1930s, steroidal estrogens had also been found carcinogenic in laboratory experiments by biochemists and endocrinologists, though "for clinicians, these studies translated to debates about the correct dose to be given".[58] Furthermore, studies were published showing that "high doses of estrone over prolonged periods could produce malignant breast tumours in hitherto healthy mice";[59] whether sex hormones were carcinogenic or not – and debates raged in major journals

[51] Li 2003a at 102; and Watkins 2007 at 25-26.

[52] Rothman & Rothman 2003 at 70-71. *Cf* Ostertag 2016 at 65 (claiming that Premarin "immediately displaced" DES as the drug of choice for menopause).

[53] Langston 2010 at 48-60; see also Ostertag 2016 at 69; and Gaudillière 2014 at 68.

[54] Rothman & Rothamn 2003 at 71; Sangoopta 2006 at 168-170; Bell 1987; McCrea 1983; and Watkins 2007 at 30-31. See also e.g. Emil Novak, *Gynecology and Female Endocrinology* (Boston: Little, Brown, 1941) at 447.

[55] Rothman & Rothman 2003 at 79, and 80-81; see also Krieger *et al* 2005 at 741-742, 743-744, and 746-747 (fns 25-43, 68-70).

[56] Langston 2010 at 10-11, 31-33; Seaman 2003 at 14, 38; Rothman & Rothman 2003 at 80-81; Gaudillière 2014 at 78-79. As just one example, see e.g. CL Buxton & Earl Engle, "Effects of the Therapeutic Use of Diethylstilbestrol" (1939) 113:26 *JAMA* 2320.

[57] Langston 2010 at 33; see also 34-39. However, as Langston shows, specifically with respect to DES, some research had also shown, as early as 1939, that toxicity did not relate to the amount of dose, and that "low doses of DES could be more toxic than high doses"; at 38. "As early as the 1930s, however, researchers knew that estrogens do not act in linear or predictable ways"; at 38. Some physicians at the time also recognized "the same harm may be obtained through the use of small doses of estrogen if they are maintained over a long period"; see "Contraindications to Estrogen Therapy", editorial, (1940) 114:16 *JAMA* 1560**.**

[58] Krieger *et al* 2005 at 741; see also Watkins 2007 at 34-35 and 43.

[59] Sengoopta 2006 at 195.

– there was also little doubt that they stimulated existing breast malignancies in humans.[60] Sengoopta argues that while some practitioners in the 1930s "strongly suspected a link between the sex glands and certain kinds of cancer", it was not widely accepted that hormones may cause breast, uterus and prostate tumours until the 1940s.[61] Yet other scholars date this acceptance to the late 1930s.[62] As early as 1933, even those gynecologists enthusiastically promoting estrogen acknowledged that "estrogenic substances administered in large doses and for prolonged periods in certain experimental animals, have been shown to produce cancer".[63] Thus, regardless of when precisely the hazard of cancer hardened into a fact, throughout the 1930s and 1940s, the question of estrogen's safety was widely conceived as a matter of dose.

1.ii. Standardization of biological drugs in the mid-twentieth century

In order to contextualize the activities of the Committee and National Health officials, and their approaches to enumerating, standardizing and regulating estrogen in the 1940s, I summarize the relevant pharmaceutical historiography.[64] Until the 1990s, pharmaceutical history tended towards disciplinary stratification; in particular, historians of pharmacy adopted methodological approaches that limited their inquiries to the techniques of pharmacists, or to the changing professional boundaries between pharmacy and medicine in various times and places.[65] More recently, some social historians have tried to reunite history of pharmacy and pharmaceutical history, so as to encompass "the entire history of medicines and those who make them".[66] Yet, even that approach was inadequately interdisciplinary, as understanding

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[60] Sengoopta 2006 at 195-196.

[61] *Ibid*; see also e.g. EC Dodds, "Hormones in Cancer" (1944) 2 *Vitam Horm* 353.

[62] Oudshoorn 1994 at 107; Langston 2010 at 31-33; and Rothman & Rothman 2003 at 79-81.

[63] Rothman & Rothman 2003 at 80, citing Novak 1935.

[64] There is little historiography on drug standardization in Canada in the 1920s-40s, other than for insulin; see e.g. Christianne Sinding, "Making the unit of insulin: Standards, clinical work and industry, 1920-1925" (2002) 76:2 *Bull Hist Med* 213. Generally on the Canadian history of pharmacy, see Canadian Academy of the History of Pharmacy, *One Hundred Years of Pharmacy in Canada, 1867–1967: Centennial Symposium* (Toronto: Canadian Academy of the History of Pharmacy, 1969); Arnold Raison, *A Brief History of Pharmacy in Canada* (Toronto: Canadian Pharmaceutical Association, 1969) ["Raison 1969"]; JW Preston, *The Canadian Pharmaceutical Association, 1907-1957: a review* (Toronto: Canadian Pharmaceutical Association, 1957); and Claire Gillis & Melanie Rantucci, *Canadian Pharmacists Association, 1907-2007: 100 years of leadership in pharmacy* (Ottawa: Canadian Pharmacists Association, 2007).

[65] In the 1960s, the major historiography included Leslie G Matthews, *History of Pharmacy in Britain* (London: Livingstone, 1962); George Trease, *Pharmacy in History* (London: Bailliere, Tindall and Cox, 1964); FNL Poynter, *Evolution of Pharmacy in Britain* (London: Pitman Medical Publishing Co, 1965); and Glenn Sonnedecker, *Kremers and Urdang's History of Pharmacy,* 4th ed (Madison, WI: American Institute for the History of Pharmacy, 1976).

[66] See e.g. Stuart Anderson, ed. *Making Medicines: A brief history of pharmacy and pharmaceuticals* (London: Pharmaceutical Press, 2005) ["Anderson 2005"]. Other work giving greater emphasis to social or political history included Sydney Holloway, *Royal Pharmaceutical Society of Great Britain 1841 to 1991: A Political and Social History* (London: Pharmaceutical Press, 1991);

pharmaceuticals requires following the interactions of medicine, science, technology, industry, and law. Fortunately, within the last fifteen years, a more sociologically-inflected, disciplinarily-integrated historiography of pharmaceuticals has emerged.[67] Enriching our understanding of drugs as enacted by historically and locally specific medical, laboratory, technological, and legal practices, these studies place drugs "at the centre of complex networks that bind together the various professionals involved in their invention, the companies responsible for their production, the doctors who prescribe them, and the pharmacists who sell them, as well as the patients and consumers who take them."[68] They take, as entry points to more integrated histories of scientific, technological and medical practices, topics previously disregarded in the history of medicine – including *biological drugs* (or *biologics*), and *drug standardization*.[69] The efforts of the Committee and National Health, including negotiations between physicians, pharmacologists, pharmacists, manufacturers, bureaucrats, and lawyers, are properly placed within this pharmaceutical history. After all, the Committee was not a sex hormone committee, but a committee on pharmacopoeial standards. By thus situating my story, I aim to more fully historicize the Canadian debates on standardization of estrogen, the decision to define drugs in the Canadian Supplement by chemical and biological methods, and the ways in which Canada regulated sex hormones differently than other (biological) drugs in the 1940s.

Narratives about pharmaceuticals in the twentieth century have often been chemical. Gaudillière summarizes this historiography as typified by an emphasis on drugs' molecular structure and on the industrialization of synthetic drug manufacturing (and relatedly, the marginalization of pharmacists),[70] and by a diminishment of the role of physicians in shaping drugs and their uses.[71] Whatever its merits, this chemical narrative is troubled by the biological

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Dennis Worthen, *Pharmacy in World War II* (London: Haworth Press, 2004) ["Worthen 2004"]; and David Cohen & William Helfand, *Pharmacy: An Illustrated History* (New York: Harry N Abrams, 1990).

[67] See e.g. John Pickstone "Ways of Knowing: Towards a Historical Sociology of Science, Technology and Medicine" (1993) 26:4 *Br J Hist Sci* 433; Jean-Paul Gaudillière, "Introduction: drug trajectories" (2005) 36 *Stud Hist Phil Biol & Biomed Sci* 603 ["Gaudillière 2005b"]; Christoph Gradmann & Johnathan Simon, eds, *Evaluating and Standardizing Therapeutic Agents, 1890-1950* (New York: Palgrave Macmillan, 2010); Alexander Von Schwerin, Heiko Stoff & Bettina Wahrig, eds, *Biologics, A History of Agents Made from Living Organisms in the Twentieth Century* (London: Picking & Chatto, 2013); and Jean-Paul Gaudillière & Volker Hess, eds, *Ways of Regulating Drugs in the 19th and 20th Centuries* (New York: Palgrave Macmillan, 2013).

[68] Gaudillière 2005b at 603. Nelly Oudshoorn's work, discussed above, is a relatively early example of this approach.

[69] Gaudillière 2005b at 610; Gaudillière 2010 at 175; Alexander Von Schwerin, Heiko Stoff & Bettina Wahrig, "Biologics: An Introduction" in Alexander Von Schwerin, Heiko Stoff & Bettina Wahrig, eds, *Biologics, A History of Agents Made from Living Organisms in the Twentieth Century* (London: Picking & Chatto, 2013) ["Von Schwerin, Stoff & Wahrig 2013"]; and Christoph Gradmann & Johnathan Simon, "Introduction," in Christoph Gradmann & Johnathan Simon, eds, *Evaluating and Standardizing Therapeutic Agents, 1890-1950* (New York: Palgrave Macmillan, 2010) ["Gradmann & Simon 2010"] at 3-4.

[70] Gaudillière 2005b at 604-605; and Gaudillière 2005a at 613.

[71] Gaudillière 2005b at 604-605. In Gaudillière's view, this diminishment of physicians' role is achieved through narratives in which drugs are invented to respond to existing diseases or demand (suggesting a unidirectional relationship from manufacturers to clinicians), and which position physicians as wary of growing industrialization.

drugs that "dominated the world of pharmacy until the Second World War" – both by the plant extracts long described in pharmacopoeias and, in the interwar years, by the drugs derived from biologically active substances in living organisms like vaccines, antibiotics, sera, vitamins, and hormones.[72] As historians are quick to note, biologics were not understood in strict opposition to chemicals. In some cases, biological extracts were converted easily into artificially synthesized chemical compounds; further, some substances could simultaneously "in one setting be viewed (and handled) as a biological while in another context as a chemical".[73] The ongoing efforts, in this period, to chemically synthesize biological substances arguably "dissolved the boundaries between natural and artificial substances".[74] Still, despite this lack of essential difference, "[b]iologicals were often more complex, more difficult to handle, and less standardized than the chemical drugs".[75] Many biological substances were highly potent and unstable, with multiple physiological effects that "oscillate between desirable and harmful".[76] Rather than see these as side effects, Alexander Von Schwerin, Heiko Stoff and Bettina Wahrig argue that biologics were ontologically precarious. This precariousness arose precisely from their "historical construction as both natural and artificial objects", as the "naturalness" of biologics made them culturally desirable and pharmaceutically promising, and yet difficult for humans to produce and control.[77]

The task of stabilizing these "natural" substances, and converting them into drugs, fell to standardization. At a technical level, drug standardization referred to "a formal agreement to use the same instrument, the same substance or the same procedure in order to enforce the comparability and the replication of measures and – more generally – of technical operations."[78] Replicability had multiple goals: industrially, to produce identical high-quality goods; clinically, to ensure safe use; and scientifically, to measure properties and effects.[79]

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[72] Gaudillière 2010 at 176.

[73] Gaudillière 2005b at 606.

[74] Von Schwerin, Stoff & Wahrig 2013 at 29.

[75] Gaudillière 2005b at 606.

[76] Von Schwerin, Stoff & Wahrig 2013 at 28.

[77] Von Schwerin, Stoff & Wahrig 2013b at 29, see also 26-30. Gaudillière has also theorized biologics as not just made from biological substances, but as sociotechnical objects whose naturalness was socially and industrially produced; Jean-Paul Gaudillière, "Biologics in the Colonies: Emile Perrot, Kola Nuts and the Industrial Reordering of Pharmacy", in Alexander Von Schwerin, Heiko Stoff & Bettina Wahrig eds, *Biologics, A History of Agents Made from Living Organisms in the Twentieth Century* (London: Picking & Chatto, 2013) ["Gaudillière 2013"] at 48, 62-63.

[78] Gaudillière 2010 at 175. Pharmaceutical historians also theorize drug standards as moral and social devices, entangled with economic interests; further, they describe the different goals and logics of laboratory, industrial, and regulatory standards. Standardization should be analyzed as "political discourses and practices that connect molecules in a historically specific regime of knowledge and power"; Von Schwerin, Stoff & Wahrig 2013 at 25-26. I leave more general discussion of types, functions, and effects of standards, beyond the drug context, to Chapter 1, section 2.ii. below.

[79] Gaudillière 2005b at 606-607.

Importantly, although this is much oversimplified, whether a drug substance was taken as chemical or biological changed the approach to its standardization. Chemical approaches involved purifying a chemical substance, measuring its weight, and determining the amount to be included in a drug product based on a (linear) dose-response curve. A pure chemical was a more compliant ingredient, making it easier to guarantee product identity and uniformity; further, chemicals attracted greater patent protection. By contrast, biological substances, in their natural variability, required more complexly constructed dose-response curves based on repeated physiological tests using different species and evaluating different physiological effects.[80] Bioassays aimed to "know – or to fix – a product's activity by performing animal experiments".[81] They were necessary to measure potency, ideally by making it quantifiable in potency units. By translating anticipated physiological effects into the *activity* of a biological substance, expressed and measured in units, the therapeutic efficacy of the substance could be fixed numerically. Such tests were then the basis for determining dosage, and as such were critical to patients and physicians.[82] Mobilizing this technical distinction more ontologically, I broadly contemplate that chemical standardization apprehends what a drug *is* – its properties, essence, composition – while biological standardization apprehends what a drug *does* – its activity, capacity, potency.

Historians have shown how these elements all crystallized in estrogen. Oudshoorn examines how test methods in the 1920s and 1930s contributed to transforming sex hormones into material realities.[83] With a comparable methodology, Jean-Paul Gaudillière has examined bioassay techniques in sex hormone networks, but with a different emphasis; while Oudshoorn focused primarily on laboratory research, Gaudillière zeroed in on industrial testing.[84] Their histories explore how bioassays were "magic tools" for standardizing estrogen and determining its potency, and a necessary means for scientific evaluation of physiological effects, industrial control of drug manufacturing, and pharmacological decisions about dosage.[85]

In describing and analyzing work by laboratory scientists in the 1920s and 30s to biologically standardize sex hormones, Oudshoorn begins with their efforts to define which substances would be defined as "male" or "female".[86] For the "female" substance, they agreed that the

[80] See e.g. Gradmann & Simon 2010; Gaudillière 2005b; Gaudillière 2010. It should be noted, however, that even where bioassay methods were used to standardize hormones, the characterization of these substances still involved chemical assays; see e.g. Gaudillière 2010 at 197.

[81] Gradmann & Simon 2010 at 3.

[82] Gaudillière 2010 at 175-176; Gradmann & Simon 2010 at 1, 5-6.

[83] For the other means by which sex hormones materialized, as analyzed by Oudshoorn, see Chapter 1, section 1.i.

[84] Gaudillière 2005a at 615, stating how he similarly aims at a unified history of biology, medicine and technology.

[85] Gaudillière 2005a at 617.

[86] Oudshoorn 1994 at 43-54.

standard should be a physiological function that changed in an organism after ovariectomy.[87] While they also agreed that ovarian extracts should be used to test for the "female principle", when it came to methods for testing these extracts, gynecologists and laboratory scientists diverged. The former tested the weight of the uterus, often in ovariectomized rabbits. The latter tested a wide variety of physiological changes – on "the feathers of domestic fowl; the growth of mammary rudiments in male mice; the growth of the vulva and the mammary glands in infantile female rat; and muscular activity basal metabolism, and the levels of calcium and sugar in blood, both in mice and women" – such that, by the late 1920s, there was a "bewildering variety" of test methods.[88] During the 1920s, use of the vaginal smear test, created by American physiologist Edgar Allan and biochemist Edward Doisy, gained momentum. The Allen-Doisy test involved injecting an ovariectomized female rodent – a mouse or a rat – with an ovarian preparation and, three days later, examining a vaginal smear under a microscope for any changes in epithelial cells considered characteristic of estrus. These tests effectively defined a female sex hormone as "any extract, purified product or any synthetic compounds bearing some resemblance to the natural preparation inducing a 'female' reaction in such a standardized test."[89] As summarized by Fausto-Stirling, while these tests "distanced animal masculinity from reproduction, linked animal femininity directly to the cycle of generation, and made less visible the effects of these hormones on nonreproductive organs in both males and females", the particular tests that scientists chose to use were not somehow required by "nature".[90] Further, using biological standards allowed substances other than steroid hormones to make the estrogenic grade; DES could be perceived "as a potent estrogen rather than as an aromatic compound with an ethylene side chain".[91] With these tests, estrogen – and sex – materialized.

Moreover, these bioassays also measured the potency of the estrogen that they materialized, through numerical units that could be used to quantify the potency of any estrogenic substance. To continue with our example, the Allen-Doisy test defined one mouse-unit (or sometimes, one rat-unit) as the minimum dose of substance potent enough to induce changes in vaginal epithelial cells characteristic of estrus in the spayed female rodent.[92] Here, too, methods proliferated. Specifically, estrogenic activity (potency) was expressed using a variety of different

[87] *Ibid* at 43-45.

[88] *Ibid* at 44, 46. See also Fausto-Stirling 2000 at 183-184.

[89] Gaudillière 2005a at 617; see also Oudshoorn 1994 at 46.

[90] Fausto-Stirling 2000 at 186-187.

[91] Gaudillière 2014 at 78-79.

[92] Oudshoorn 1994 at 47; Gaudillière 2005a at 617; and Gaudillière 2010 at 183.

units connected to different bioassay tests – rat units, mouse units, rabbit units, and eventually international units. Some scientists were vexed by the existence of many units to express the potency of the same substance, and British scientists with the National Institute for Medical Research (NIMR), led by Henry Dale, spearheaded efforts for greater standardization.[93] In 1932, at an international conference on the standardization of sex hormones, organized through the League of Nations, a group of elite physiologists and biochemists adopted the Allen–Doisy vaginal smear test for producing estrus as the international standard (or definition) for "female sex hormone". Ironically, they adopted *two* standard units – either mouse units or rat units, which reflected European versus American lab practices respectively – as the 'international unit' of female sex hormone.[94] After 1935, related in part to new abilities to isolate estrogen from urine, a shift to a more chemical paradigm of standardization and testing emerged, although chemical testing did not completely supplant bioassays.[95] The conferences also spurred creation of an official reference material to be kept by NIMR – a pure substance prepared from the urine of pregnant mares – against which estrogenic hormones could be compared. As a result, "the unit of estrogen would no longer be an animal unit, but a weight unit, even if the relationship between weight and potency remained based on biological assays."[96]

This push by laboratory researchers for molecular standardization of estrogen was not, however, widely reflected in clinical use or industrial practices in the mid or late 1930s. Instead, these practices were marked by national and corporate variation. As Gaudillière has shown, different firms' laboratories used different species, strains, and numbers of animals (which reacted in different ways); they used different modes of administration (i.e. single versus fractionated inoculations, and subcutaneous versus intravenous injections); and even different timing changed results (for example, "mice did not react well in dry, cold weather"). Units used by manufacturers were wildly variant, as the Allen-Doisy rat unit was still common in the US, and "[t]here were other 'rat units' too – not to mention 'mouse units' – and many manufacturers were slow to standardize their products in the new 'international units'." For example, the

[93] Noting that standardization was a central agenda of sex hormone experts in the 1930s, Fausto-Stirling notes that "[t]raditionally, scientists address such crises, which often plague new and rapidly expanding fields, by agreeing to standardize. If only everyone used the same method of measurement, if only everyone quantified their products in the same manner, and if only all could agree on what to call these proliferating substances that had somehow escaped the boundaries of the bodies to which they were supposed to belong—then finally, scientists hoped, they could straighten out what had become a messy situation"; see Fausto-Sterling 2000 at 182.

[94] Oudshoorn 1994 at 46-48; and Fausto-Stirling 2000 at 184-185. The name of female sex hormone was modified at a second international conference in 1935, after the discovery of progesterone forced abandonment of a single "female sex hormone"; see Oudshoorn 1994 at 47-48, and fn24 at 158; and Fausto-Stirling 2000 at 189.

[95] *Ibid* at 48.

[96] Gaudillière 2010 at 196-197; Fausto-Stirling 2000 at fn71 at 341; and Von Schwerin, Stoff & Wahrig 2013 at 25.

German firm Schering made its products using a rat unit equivalent to almost five international units, while the US firm Parke Davis employed a rat unit equivalent to 3.3 international units.[97]

With rigorous attention to different institutional and commercial research and production sites such as Schering, IG Farben, Bayer, and Butenandt's research institute (and the intricate collaborations among them), Gaudillière details the heterogeneity of sex hormone bioassays and potency units in Germany and France in the interwar years and during WWII.[98] While this diversity did not necessarily diminish quality control within each firm, for estrogenic products, "comparability and robustness remained local achievements".[99] Scientists and engineers in German firms adapted existing bioassays, and generated new techniques to test commercial preparations.[100] Some laboratory scientists viewed this multiplicity as a "source of discrepancies and chaos that one could only overcome with stronger standardization that could cut across laboratories, firms and national lines". However, as Gaudillière points out, this heterogeneity had important benefits. Using a variety of bioassays for estrogen allowed for a greater number of physiological effects to be identified – which also multiplied a drug's indications, and its marketable forms.[101] Bioassays thus always had a "double meaning", serving many masters – as "the boundaries between research and control were often blurred … this porosity could become an industrial asset".[102] The role of industry in standardizing estrogenic drugs meant that bioassays were also entangled with medical practices and normalization, most directly through relationships to dosage, mode of administration, and indications, as mediated by clinical testing.[103] Notably, in this time, the German state did not seek to impose standards on firms, nor, unlike in the US, did this demand arise from "elite physicians in teaching hospitals".[104]

In concluding this brief review of pharmaceutical history, I also highlight Jean-Paul Gaudillière and Volker Hess's theoretical framework on "ways of regulating drugs".[105] While they stress that ways of regulating are "sociohistorical products" which have been "utterly variable" in their

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[97] Gaudillière 2010 at 183.

[98] Gaudillière 2005a; Gaudillière 2010; and Jean-Paul Gaudillière, "Genesis and development of a biomedical object: styles of thought, styles of work and the history of the sex steroids" (2004) 35 *Stud Hist Phil Biol & Biomed Sci* 525 ["Gaudillière 2004"].

[99] Gaudillière 2010 at 196.

[100] Gaudillière 2004 at 537; Gaudillière 2010 at 181.

[101] *Ibid.*

[102] Gaudillière 2010 at 197.

[103] Gaudillière 2010 at 193-198; see also Gaudillière 2004.

[104] Gaudillière 2010 at 196.

[105] Jean-Paul Gaudillière & Volker Hess, "Introduction", in Jean-Paul Gaudillière & Volker Hess, eds, "*Ways of Regulating Drugs in the 19th and 20th Centuries* (New York: Palgrave Macmillan, 2013) ["Gaudillière & Hess 2013"]. See also the volume's essays, including Gaudillière 2013, which applies this framework to compare industrial and professional ways of regulating herbalists, in the context of industrialization in mid-century Germany and France.

historical articulations, as a basic framing heuristic, the framework "seeks to bring to light the internal logic of specific combinations of practices and procedures, describing the various rationalities underpinning the management of therapeutic agents".[106] Pharmaceutical historiography has largely conceived of regulation as legal control by state actors of drug-making and marketing activities (despite that obviously many actors, and not just firms, are involved in making markets). Yet the diversity of sociohistorical practices involved in shaping drugs – including a range of standardization practices both between and within laboratories, factories, and clinics – suggests that drug regulation should be defined more broadly.[107] More specifically, based on the distinct social actors, and their aims and values, forms of evidence and expertise, and intervention tools, Gaudillière and Hess propose five ways of regulating drugs: professional, industrial, administrative, public, and juridical.[108] Of these, the first three are relevant to this thesis. The professional way of regulating drugs has involved state delegation to physicians (with grants of autonomy) and pharmacists (with grants of monopoly). Professional regulation has often relied on "pharmacology, animal models, dosage, indications" as key forms of evidence, and employed "pharmacopoeia, prescription, guidelines" as key regulatory tools.[109] In many states, with the emergence of mass-produced and widely-marketed pharmaceuticals, a transition from professional to industrial ways of regulating drugs marked the interwar years and WWII, even if one mode did not automatically replace the other but rather they often operated in parallel.[110] Industrial regulation by firms, aided by representative associations, has aimed not only at profit but at product quality. It has used tools of intellectual property rights, quality control, and scientific publicity; it has engaged scientific evidence and cost-benefit analyses.[111] While administrative ways of regulating have attracted relatively greater attention, this scholarship often focuses on the postwar period, when most industrialized states first adopted

[106] Gaudillière & Hess 2013 at 7.

[107] *Ibid* at 5-7; see also Gaudillière 2013 at 67. Other social studies of medicine likewise urge a broader definition of regulation, especially in relation to standardization; see Alberto Cambrosio, "Standardization Before Biomedicine: On Early Forms of Regulatory Objectivity" in Christoph Gradmann & Johnathan Simon, eds, *Evaluating and Standardizing Therapeutic Agents, 1890-1950* (New York: Palgrave Macmillan, 2010) ["Cambrosio 2010"]. At 259-260, Cambrosio writes: "the analysis of the different forms of regulation should not be separated from the analysis of the constitution of the entities, processes and activities that are the subject of regulation. But if this is so, then the challenge for historians is to find a way of producing historical narratives that, far from relying on a common sense understanding of a small set of "usual suspects", each cleanly assigned to a pre-established, watertight domain (state, industry, science), and of the categories (political, economic, cultural, technical) within which their activities allegedly fall, will instead focus on the shifting composition and modalities of actions of the collective".

[108] Gaudillière & Hess 2013 at 7-8.

[109] *Ibid* at 8-9.

[110] Gaudillière 2013 at 67-68.

[111] Gaudillière & Hess 2013 at 8-9.

and implemented legislation that required pre-market approval supported by evidence from clinical trials.[112] Administrative actors include not only state agencies but also governmental committees; their regulatory tools include not just approvals or enforcement but also labelling.[113]

Understanding pharmaceuticals, then, involves tracing interactions between ways of regulating that were often multiple, overlapping, and dynamic.[114] The authors propose that historians ask "[w]hich values guide the regulation process? Which problems or adverse practices are targeted? Who are the most important actors? What are the forms of evidence accepted in decision making? Which regulatory tools are mobilized to oversee and control the fate of drugs?"[115] By asking such questions, which drive not only at "who benefits" but "through what regulatory practices", historians can take their studies of pharmaceuticals beyond historical contingency and draw out the unequal power gradients at the "very core of drug regulation".[116]

2. Theoretical literatures on enactment

Moving from historiography and towards a framework for theorizing law in-and-of estrogen, the remainder of this chapter contemplates enactment. First, it summarizes Annemarie Mol's contributions to theorizing how realities are enacted in practices, and places her work both in relation to actor-network theory (ANT) and the material turn more broadly. It next considers Lawrence Busch's typologies of standards, which draw on Mol's performative approach, and the new embrace by socio-legal studies of Mol and other STS scholars' approaches to materiality.

2.i. Annemarie Mol and the enactment of multiple ontologies

The theorist that most empowers the history of estrogen told here is Annemarie Mol. Her now canonical study, *The Body Multiple*, has been hugely influential in STS and social studies of medicine.[117] Empirically, it is an ethnography of atherosclerosis practices in a Dutch hospital. Methodologically, she argues that studies of science, technology, and medicine should abandon

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[112] Few European countries required pre-marketing approval or other controls on drugs before the mid-1960s; John Abraham & Graham Lewis, *Regulating Medicines in Europe: Competition, expertise and public health* (New York: Routledge, 2000).

[113] Gaudillière & Hess 2013 at 8-9.

[114] Gaudillière 2013 at 93.

[115] Gaudillière & Hess 2010 at 8.

[116] *Ibid* at 12. They remind us, here, that "[d]efining power relations as only financial would…be a caricature". For a leading study of the history of the US FDA's regulatory power, see Daniel Carpenter, *Reputation and Power: Organizational image and pharmaceutical regulation at the FDA* (Princeton: Princeton University Press, 2010) ["Carpenter 2010"].

[117] Mol 2002.

an epistemological focus on their objects of analysis, and take a praxiological approach.[118] That is, rather than approaching objects as being one fixed reality represented or known by multiple perspectives, Mol argues that reality is enacted in practice – reality is performed, achieved, done.[119] As practices in medicine are not singular and coherent, but are often incommensurable or contradictory in the various techniques, tests, materials, and actors that are involved, the diseases enacted in these practices are also multiple. From the leg pain felt by patients, to tissue studied on microscope slides, to arterial surgeries, atherosclerosis is *multiple*. The realities of diseases and bodies are enacted multiply in diverse socio-material practices.[120]

This begs the question of how this multiplicity manages to "hang together".[121] Mol shows how it is that "the singularity of objects, so often presupposed, turns out to be an accomplishment".[122] This achievement is the work of various forms of *coordination*,[123] which include simply adding diverse testing practices together without concern for their cohesion, hierarchizing diverse measurement techniques if one must be prioritized, ignoring and bracketing discrepancies, and, as described in ANT studies, translation of tests and outcomes to make them comparable.[124] Sometimes, incoherent practices cannot be smoothed away; here, rather than resort to the STS metaphor of "closure" where differences are "settled" and matter stabilized, Mol looks at how in practice differences are diffused and distributed, controversies dissolved rather than solved.[125]

In labelling her approach "empirical philosophy", Mol re-emphasizes the need for questions about ontologies – how objects and orders come to be and do – are best approached through detailed evidence of the provisional, relational practices that perform them. [126] This also raises the question of where to begin – who or what enacts, who or what is enacted. The term enactment intentionally leaves open who or what the actor is, and who or what is acted upon.[127]

Enactment is, of course, also a legal term. Loosely speaking, enactment refers both to the making of a piece of legislation – an act – and to the law that is the outcome of that process. More technically, at least with respect to federal law in Canada, an enactment means "an Act or regulation or any portion of an Act or regulation". Further, "to enact" includes "to issue, make or

[118] *Ibid* at 31.

[119] *Ibid* at 31-33.

[120] *Ibid* at 70-72.

[121] *Ibid* at 49.

[122] *Ibid* at 119.

[123] *Ibid* at 119, 55.

[124] *Ibid* at 63-78, 84.

[125] *Ibid* at 87-88, 117.

[126] *Ibid* at 1, 4-7.

[127] *Ibid* at 20-26, 143.

establish".[128] In the theoretical tenor suggested in this thesis, toxic enactment simultaneously captures how regulatory practices perform toxicity and how toxicity shapes and infuses laws.[129] Toxic enactment does not reflect any pretensions of a new theoretical development. Rather, I am trying to experiment, if rather unfaithfully, with Mol's approach, by expanding and extending enactment to regulatory practices. This thesis tests whether enactment is as generative a concept for studying regulatory practices, as performances that shape the material world, as it has been for investigating other techniques, scientific, medical, or technological, for doing realities. It also aims to contribute to discussions on the nature of toxicity, by apprehending a potent and changeable substance as the effect of multiple regulatory practices. While using a concept developed within social studies of medicine in a legal history context may seem like a stretch, as this thesis examines drug standardization and the activities of scientist-regulators, I suggest this is a natural extension.

It should be noted that enactment, as does ANT, comes largely out of ethnomethodological and ethnographical traditions. That ethnographers would embrace a praxiological approach to studying ontological questions makes sense, as ethnography provides immediate access to what (living) people say and do. Admittedly, historians may be limited to primarily documentary records to find evidence about (often dead) people's practices; they lack direct access to physical performances of humans or nonhumans in past times. There is no reason in theory though that historical methods cannot provide access, if more mediated, to past practices, and efforts to do so have offered historians of medicine a productive way to keep material practices in sight.[130]

Similarly, environmental historians have taken, if in modified theoretical vocabularies, praxiological approaches to studying how toxicity is materialized within human and nonhuman assemblages. In her wide-ranging study into the ontologies of low-dose chemical exposure, historian Michelle Murphy argues that "exposures were brought into existence in multiple, often conflicting circumstances – the result of not just specific environments but new arrangements of

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[128] *Interpretation Act*, RSC 1985, c I-21, s 2(1). In some other jurisdictions in Canada, such as Ontario, technically only the legislature "enacts" laws and only Acts of the legislature are "enactments", while regulations are by contrast "made"; see *Legislation Act, 2006,* SO 2006, c 21, Sched F, ss 5-6 and 17-18.

[129] The word "toxic" is not deployed metaphorically in this thesis, as, for example, "bad" or "harmful". While that metaphor may resonate for some readers, by "toxic enactments", I do not intend to convey either "bad laws" or "bad performances".

[130] Latour's study of bacteriology in France was, of course, partly a historical account; see Bruno Latour, *The Pasteurization of France* (Cambridge, MA: Harvard University Press, 1993) ["Latour 1993"]. For more recent praxiological histories of medicine, see e.g. Alberto Cambrosio & Peter Keating, *Cancer on Trial: Oncology as a new style of practice* (Chicago: University of Chicago Press, 2011), and Geertje Mak, *Doubting sex: Inscriptions, bodies and selves in nineteenth-century hermaphrodite case histories* (Oxford: Oxford University Press, 2012). For further discussion of praxiological approaches to law and materiality in the specific context of legal history, see Chapter 2.

technologies and practices through which laypeople, scientists, and corporate experts *apprehended* the health effects of buildings on bodies,"[131] using the term "apprehended" to grasp both the epistemic and physical capture of phenomena. Weaving together numerous histories, from the organizing activities of women office workers embracing epidemiology to the toxicological dose-response curves originating from industrial hygiene, she argues that sick building syndrome formed as a phenomenon in the encounters between these multiple practices and knowledges.[132] As with estrogen, materialized in diverse historical practices of laboratory science, clinical medicine, and pharmaceutical developments, and in Canada through particular arrangements – in other idioms, networks, assemblages, entanglements – of heterogenous regulatory practices, sick buildings also came into existence "with divergent and even contradictory qualities",[133] and their "very existence contained uncertainty, multiplicity, and nonspecificity".[134] In short, multiple historical practices lead to a multiple object: "[m]ultiplicity was itself one of the ways that historical actors brought sick buildings into being. That is, multiplicity was a quality with which objects, like buildings, could be imbued".[135]

Focusing on the "contested ontological politics" that materialized indoor chemical exposure, Murphy shows that while these multiple histories helped to mobilize some people into action, they also precluded certain causal narratives about low-dose exposures.[136] This produces what she calls regimes of imperceptibility.[137] As toxicological instruments and methods "required toxic exposures to be both regular and specific", this in turn served to render "ubiquitous and low-level exposures unprovable and imperceptible."[138] Considering, then, the ways in which experts deploy toxicological technologies – whether in laboratories or in regulations – can render perceptible the historicity of toxicity and of hormone disruption. Sliding back from history to ethnography, anthropologists are now elaborating on Murphy's concepts, aiming to move beyond documenting the existence and dominance of historical regimes of imperceptibility and

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[131] Michelle Murphy, *Sick Building Syndrome and the Problem of Uncertainty* (Durham, NC: Duke University Press, 2006) ["Murphy 2006"] at 8. Murphy does not expressly relate her theoretically-grounded history to Mol's anthropologically-based theorizing, though she cites Mol's writings as an example of works that "*emphasize the multiplicity of objects and ontologies*"; see 182 (fn 7). Moreover, Murphy's work historicizing low-dose toxicity as a material effect of expertise and power is indebted intellectually to concepts developed by Michel Foucault and Judith Butler, which also heavily influenced Mol's theoretical approach in *The Body Multiple.* However, the concept of multiplicity that Murphy uses is not Mol's but reflects that provided by Gilles Deleuze and Félix Guattari, incorporated into otherwise her "largely Foucauldian analytic toolbox"; at 183 (fn 14).

[132] *Ibid* at 107-110.

[133] *Ibid* at 149.

[134] *Ibid* at 108.

[135] *Ibid* at 150.

[136] *Ibid* at 149-150. Murphy here deploys, albeit without attribution, Mol's well-known concept of "ontological politics".

[137] *Ibid* at 91-92.

[138] *Ibid* at 108.

towards theorizing the techniques by which such regimes are accomplished and constituted. Nicholas Shapiro has documented how divergent scientific and legal practices, in US federal regulatory agencies and in court proceedings, have strategically shaped the "unknowing" of formaldehyde exposures in FEMA-issued trailers following Hurricane Katrina.[139] Drawing on participant observation in a law firm, expert evidence, and internal FEMA emails, he analyzes multiple "techniques of un-knowing" that actively functioned to induce ignorance of and disavow adverse health effects,[140] including "secrecy, assessment postponement, scientific disqualification/knowledge subjugation, knowledge avoidance, and the ontological obfuscation of environmental triggers".[141] By extending analyses of the enactment of chemical exposure, moving beyond technoscientific practices to encompass regulatory and legal practices, the processes by which toxic harms are concealed and ignored – whether intentional, willfully ignorant, or through "unpremeditated discursive blinders" – can be better apprehended.[142] These historicizations and theorizations of toxic techniques afford a rich conceptual language to articulate how estrogenic potency was achieved in Canada. As will be seen, despite the dominance of dose-response discourses in pharmacology in the 1940s, specific dose-response relationships for estrogenic drugs were rendered imperceptible and unknowable in the 1944 Sex Hormone Regulations. Dose-response logics did not disappear in estrogen regulation, however; in 1950, National Health resurrected them for estrogenic cosmetics, materializing dose through novel labelling techniques, and mobilizing response from consumers rather than manufacturers.

It should also be noted that, while Mol does not expressly situate her study on atherosclerosis in ANT,[143] her work on enactment is an extension – perhaps better, a transmutation – of that material-semiotic tradition.[144] Where ANT scholars inquired into (social) construction of reality through networks, Mol considers the (multiple) enactments of realities through practices.[145] The metaphor of enactment is more contingent, situational, precarious, fluid, and arguably more

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[139] Nicholas Shapiro, "Un-knowing exposure: Toxic emergency housing, strategic inconclusivity and governance in the US Gulf South" in Emilie Cloatre & Martyn Pickersgill, eds, *Knowledge, Technology and Law* (London: Routledge, 2015) at 190-191.

[140] *Ibid* at 191-193.

[141] *Ibid* at 203.

[142] *Ibid*.

[143] Rather, the strongest apparent influences on Mol's concept of enactment, and how she theorizes relationships between knowledge and materiality, are Michel Foucault and Judith Butler.

[144] ANT has been a fluid and changing project. It is often discussed in the past tense (post-ANT, after-ANT), and some ANT originators have abandoned "ANT" for relational materialism or material-semiotics; see John Law, "Actor-network theory and material semiotics" in Bryan S Turner, ed, *The New Blackwell Companion to Social Theory,* 3rd ed (Oxford: Blackwell, 2008).

[145] For a reply to a series of articles critiquing "the ontological turn" in STS, that thoughtfully considers the nature and degree of distinction between enactment and construction, see Steve Woolgar & Javiar Lezaun "Missing the (Question) Mark? What *is* a turn to ontology?" (2015) 45:3 *Soc Stud Sci* 462 [Woolgar & Lezaun 2015"].

feminist. As practices change, so do realities – the material world becomes less fixed. Enactment moves us away from ANT's masterful, masculinist, Machiavellian mobilizer and maker of reality, with his efforts to translate facts and actors into ever-further domains, to stabilize interactions within a constructed network, to enroll others to play supporting roles, to inscribe materials with scripts that ensure control from a distance.[146] Further, the temporality of enactment differs from construction, which suggests a hard dividing line before and after reality is built. Social construction tends to describe "social processes that result in durable realities", while performance describes practices "that produce ephemeral effects – effects essentially coextensive with the practices that create them".[147] Yet there are also many similarities and overlaps. Both approaches claim to be more methodological and empirical, mapping relations in action, than they are theoretical.[148] Both attempt to describe and, importantly, to expand the repertoire of actions – translation, stabilization, delegation, in the case of early ANT, or coordination, distribution, inclusion, in the case of Mol's enactment – that bring about worlds.

Drugs and their diseases have been a favoured focus of ANT-inspired or material-semiotic analyses.[149] In ANT, pharmaceutical substances do not have inherent, stable properties that are interpreted varyingly; rather, their properties are "the outcome of multiple events and scripts that they embed and carry".[150] Andrew Barry gives an especially rich theorization of chemical ontology.[151] Building on Stengers and Bensaude-Vencent's notion of *informed materials* – a concept conveying that chemistry is not the discovery of "bare molecules" but rather involves invention – Barry posits that, even before bodies consume them, pharmaceutical chemicals are "constituted in their relations to informational and material environments".[152] Informational

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[146] See early feminist critiques of ANT by e.g. Susan Leigh Star and Donna Haraway, *infra* note 165.

[147] Woolgar & Lezaun 2015 at 463. See also Annemarie Mol, "A reader's guide to the "ontological turn" – Part 4" (2014), online: <http://somatosphere.net/2014/03/a-readers-guide-to-the-ontological-turn-part-4.html> ["Mol 2014"].

[148] This claim is also made in socio-legal studies, where ANT is routinely described as a methodology; see e.g. Ron Levi & Mariana Valverde, "Studying Law by Association: Bruno Latour Goes to the Conseil d'État" (2008) 33:3 *Law & Soc Inq* 805 ["Levi & Valverde 2008"]; and Simon A Cole & Alyse Bertenthal, "Science, Technology, Society, and Law" (2017) 13 *Annu Rev Law Soc Sci* 351 ["Cole & Bertenthal 2017"].

[149] Emilie Cloatre, *Pills for the Poorest: An Exploration of TRIPS and Access to Medication in Sub-Saharan Africa,* (London UK: Palgrave MacMillan, 2013) ["Cloatre 2013"] at 19-20. Some canonical examples include e.g. Latour 1993, and Steven Epstein, *Impure Science: AIDS, Activism, and the Politics of Knowledge* (Berkeley and Los Angeles, CA: University of California Press, 1998). In socio-legal studies, ANT has been used by Cloatre to research practices of patent protection for drugs in two African countries, and Emily Grabham to study HIV-AIDS treatment and advocacy; see Chapter 1, section 2iii., below.

[150] Cloatre 2013 at 20, citing Barry 2005 *infra* note 151. For a foundational ANT essay on the inscription of technological objects, see Madeleine Akrich, "The De-Scription of Technical Objects" in Wiebe Bijker & John Law, eds, *Shaping Technology/Building Society: Studies in Sociotechnical Change* (Cambridge, Mass: MIT Press, 1992) ["Akrich 1992"].

[151] Andrew Barry, "Pharmaceutical Matters: The Invention of Informed Materials" (2005) 22:1 *Theory, Culture and Society* 51 ("Barry 2005"). For another very rich material-semiotic account of a therapeutic substance, see Emilie Gomart, "Methadone: Six Effects in Search of a Substance" (2002) 32:1 *Soc Stud Sci* 93.

[152] Barry 2005 at 52, 53, 59. Barry also draws on the ideas of philosopher A.N. Whitehead and of sociologist Gabriel Tarde.

enrichment of these molecules happens in laboratory practices, as well as through legal and economic relations, for example those mediated by intellectual property law.[153]

Rather than discovery narratives, then, close study of institutional, epistemic, and regulatory practices will disclose how chemicals and drugs are enacted. In this vein, Mol has criticized calls for a "turn to ontology" by the "so-called 'new materialists'", whom she views as essentializing matter and dichotomizing materiality and discursivity, discarding hard-earned STS lessons and "naively echoing natural science textbooks and journal articles".[154] In contrast, as she argues that objects are not essentially stable or singular but afforded their essences only in relational interactions (or intra-actions), Mol positions her own work as *relational materialism*.[155] Nonetheless, Mol's materialism is reasonably situated within an ascendant trend in the humanities and social sciences, over the last 15 years,[156] that centers the interaction of matter and meaning. This material turn has found tremendously diverse expression.[157] Without minimizing the important differences in these literatures, for the limited purpose of considering practices that enact law and materiality,[158] some high-level commonalities can be identified. First, the trend reacts to a perceived over-emphasis on discursivity in postmodern scholarship, which underplays materiality.[159] Further, these literatures often reject rigid analytic dichotomies between "subject (human, social, representational) and object (thing, material, real)".[160] Rather than inert substance awaiting cultural interpretation, nonhuman matter is active or agential; as Barad puts it, matter kicks back.[161] These theoretical commitments all challenge nature-culture

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[153] *Ibid* at 55-59, 64.

[154] Mol points to Coole & Frost 2010, *infra* note 159*,* as exemplary of the new materialism that she critiques, and in contrast, she endorses Barad's intra-active relational approach (also often labelled new materialism); see Annemarie Mol, "Mind your plate! The ontonorms of Dutch dieting" (2012) 43:3 *Soc Stud Sci* 379 ("Mol 2012") at 380-81.

[155] *Ibid.*

[156] In choosing this periodization, I am clearly at risk of erasing (eco)feminist contributions. Feminist theory turned earlier than other fields to embrace materiality, including theorizing linkages between gender and nature, investigating sexist and racist histories of science, and deconstructing nature-culture binaries, well before "new materialism" or "posthumanism" were christened. Whether ecofeminism, (Donna Haraway, Val Plumwood, Susan Bordo), queer ecofeminism (Greta Gaard, Cate Sandilands), corporeal feminism (Elizabeth Grosz, Rosi Braidotti), or the "new" material feminisms (Stacy Alaimo and Susan Hekman), much of this work interrogated binaries between male and female, human and nonhumans, culture and nature, representation and reality. For a critique of "new" materialism's erasures, see Catriona Sandilands, "Feminism and biopolitics: a cyborg account" in Sherilyn MacGregor, ed, *Routledge Handbook of Gender and Environment* (New York: Routledge, 2017).

[157] Including e.g. ANT, object-oriented ontology, thing theory, agential realism, posthumanism, speculative realism, non-representational theories, material feminisms. Many of these approaches have quite different disciplinary origins.

[158] Margaret Davies, *Law Unlimited: Materialism, Pluralism and Legal Theory* (New York: Routledge, 2017) at 32-37.

[159] See e.g. Barad 2003; and Diana Coole & Samantha Frost, eds, *New Materialisms: Ontology, Agency, and Politics* (Durham, NC: Duke University Press, 2010) ["Coole & Frost 2010"].

[160] Tom Johnson, "Medieval Law and Materiality: Shipwrecks, Finders, and Property on the Suffolk Coast, ca. 1380–1410" (2015) 120:2 *Am Histl Rev* 407 ["Johnson, 2015"] at 408.

[161] Barad 2003.

divides – regardless of whether conceptual labour is supplied by feminist material-semiotics,[162] Haraway's natureculture,[163] Barad's onto-epistemology,[164] or Mol's relational materialism.

These versions of (new, relational and/or feminist) materialisms all wrestle, moreover, with the political implications of their ontologies, particularly in the wake of critiques of ANT. In viewing power largely as an effect of the relational associations or networks being investigated, rather than as a ready cause or explanation of events, ANT's originators have long been criticized by feminist scholars as reproducing narratives of the powerful and masterful, and as sidestepping any meaningful analysis of power (or of patriarchy, racism, capitalism, or colonialism).[165] Put differently, while material-semiotic approaches can map very effectively the relational webs that enact, maintain, transform, or dissolve material realities, they may do "little to navigate one through the theoretical thickets of legitimacy, obeisance, and power that are the 'standard fare of sociolegal research'".[166] Unlike some theorists building on ANT traditions, Mol has tried to directly confront *ontological politics*. Mol first articulated this term two decades ago,[167] and STS scholars continue to leverage the concept.[168] Opening up consideration of how the "real is implicated in the political and *vice versa"*,[169] at its simplest, ontological politics recognizes that, once one accepts that multiple versions of realities are enacted in different practices and relations, then one should next ask "[w]hich version might be better to live with? Which worse? How, and for whom?"[170] Mol rejects that this is simply a matter of "choice", recalling how the scientific and medical practices that perform realities differently rarely emerge

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[162] Donna Haraway, *Simians, Cyborgs and Women: The Reinvention of Nature* (New York: Routledge, 1991) ["Haraway 1991"].

[163] Donna Haraway, *The Companion Species Manifesto: Dogs, People, and Significant Otherness* (Chicago: Prickly Paradigm Press, 2003) ["Haraway 2003"].

[164] While coming from a different philosophical tradition, and despite her alignment with new materialism which Mol disavows, Barad's theory has much in common with Mol. Without doing justice to her conceptual innovations, in brief, Barad develops a performative account of how reality is enacted, which posits that ontological realities, and the epistemological practices and apparatuses through which they are known, are entangled and co-constitutive. Rather than "interaction", which connotes individual entities relating, she employs the term "intra-action" to recognize the co-constitution of measured and measuring entities. As Mol seeks to escape what she calls perspectivalism, Barad aims to escape representationalism. Both address, if tentatively, the ethical commitments that accompany their onto-epistemologies / relational ontologies. See Barad 2003.

[165] See e.g. Susan Leigh Star, "Power, technologies and the phenomenology of conventions: on being allergic to onions" in John Law, ed, *A sociology of monsters: Essays on power, technology and domination* (London: Routledge, 1991) ["Star 1991"]; and Donna Haraway, "The promise of monsters: A Regenerative Politics for Inappropriate/d Others" in Lawrence Grossberg, Cary Nelson, Paula A Treichler, eds, *Cultural Studies* (New York: Routledge, 1992) ["Haraway 1992"].

[166] Cole & Bertenthal 2017 at 361, citing Levi & Valverde 2008 at 822.

[167] Annemarie Mol, "Ontological Politics: A word and some questions" (1999) 47:1 (supp) *Sociol Rev* 74. In this article, Mol credits John Law with inventing this term and for allowing her to develop it; see fn 1 at 87.

[168] Michelle Murphy, "Studying Unformed Objects: Deviation", July 15, 2013, *Cultural Anthropology* website, https://culanth.org/fieldsights/364-studying-unformed-objects-deviation ["Murphy 2013"].

[169] Mol 1999 at 74.

[170] Mol 2012 at 381.

explicitly in any decisive moment or definitive place,[171] how the political implications of each of these realities are themselves extensive and complex,[172] and how "choice" wrongly implies that multiple realities do not co-exist or depend on one other.[173] Tentatively, Mol begins to grapple with the ontological politics of clinical versus surgical ways of enacting atherosclerosis;[174] the same questions are possible for regulatory ways of enacting estrogen. Additionally, ontological politics is one further reminder to be self-reflexive and accountable in approaching the objects that we study – recalling that our own scholarship performatively participates in their invention and, as Murphy cautions those swept up in an ongoing always becoming, scholarly "exuberance for unformed objects" is not necessarily "a critical or politically-charged commitment".[175]

2.ii Enactment and the sociology of standards

Informed in part by these performative approaches, a growing sociological literature seeks to theorize standards and standardization. To understand Canadian drug standards in the 1940s, I draw on Lawrence Busch's work on standards, especially his readily applicable typologies.[176]

Busch describes how, given their ubiquity, standards are rarely noticed until they break down. Both material and ideational, "standards are where language and world meet; better still, the widespread use of standards and their virtual inescapability illustrates the interpenetration of language and world".[177] Standards "always incorporate a metaphor or simile, either implicitly or explicitly"; indeed, they make metaphors real. Maybe the most tangible example of this is reference materials, prepared by state agencies, against which substances can be calibrated.[178] In short, standards are "means by which we perform the world" and "recipes for reality, or perhaps for realities".[179] Busch takes inspiration from Mol's ontological theory, in which our

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[171] Mol 2002 at 79-80.

[172] *Ibid* at 81-83.

[173] *Ibid* at 83-85.

[174] *Ibid* at 172-184.

[175] Murphy 2013: see also Mol 2002 at 153.

[176] Lawrence Busch, *Standards: Recipes for Reality* (Cambridge, Mass: MIT Press, 2013) ["Busch 2013"]. Busch's work builds on the classic STS text: Geoffrey C Bowker & Susan Leigh Star, *Sorting Things Out: Classification and its Consequences* (Cambridge, Mass: MIT Press, 1999) ["Bowker & Star 1999}. See also Martha Lampland & Susan Leigh Star, eds, *Standards and Their Stories: How Quantifying, Classifying, and Formalizing Practices Shape Everyday Life* (Ithaca, NY: Cornell Univ. Press, 2009), Stefan Timmermans & Steven Epstein, "A World of Standards but not a Standard World: Toward a Sociology of Standards and Standardization" (2010) 36:1 *Ann Rev of Sociol* 69 ["Timmermans & Epstein 2010"); Alison Marie Loconto & David Demortain, "Standardization as Spaces of Diversity" (2017) 3 *Engaging Science, Technology, and Society* 382 ["Loconto & Demortain 2017"].

[177] Busch 2013 at 2-3; see also 24.

[178] *Ibid* at 10-12. On reference materials, see also Lezaun 2012.

[179] *Ibid* at 13, 73-74. Other scholars echo this view, noting it is a "generic finding" that "a world in which standards proliferate is not necessarily more homogenous and standardized world. Standardization processes produce homogeneity, but also new

techniques do not just allow us to know the world, but to enact it multiply. Standards *accomplish* realities, providing "the scripts, the playbooks, the librettos, the recipes that guide practice".[180]

Busch's typologies of standards help to clarify estrogen regulation in Canada in the 1940s. He posits that all standards fall into one of four types which he calls Olympics, filters, ranks, and divisions.[181] Relevant to this thesis are *filters* and *divisions.* Filters are designed to "eliminate the unacceptable" by requiring things to "pass through the filter"'. Foods that pass through a food safety standard, for example, can then be considered safe. Divisions are unranked categories, often aimed at product differentiation; for example, apples are divided into categories like McIntosh and Granny Smith. Such divisions allow "different" products to be sold without price competition, and the constructed differences can then be "linked to an implied or demonstrably superior quality".[182] Relatedly Busch outlines different purposes or logics of standardization, distinguishing between *industrial* and *merchant standards* (among others). Commonly acting as filters, industrial standards aim to ensure things are all "the same" and "make the grade". Often numerically premised, industrial standards promote precision and accuracy, fundamentally aiming at replicability. Reference materials are an obvious example. In contrast, drawing on work by sociologist and STS scholar Michel Callon, Busch describes merchant standards as intended "to qualify things to enter the marketplace", by letting otherwise incommensurable things be made comparable. Targeted at product identity, such standards are often indicated by labels designed to facilitate market transactions.[183] While drug standards have been naturalized as proxies for quality, safety, and replicability, and thus understood as industrial standards and filters, efforts to standardize estrogen in Canada also involved market standards and divisions.

Also very useful is Busch's distinction between *standards, tests*, and *indicators,* interrelated concepts that can easily be conflated. He gives the simple example of citizenship: the standards for citizenship would be set out in legislation, the test to meet this standard usually "requires

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diversities;" Loconto & Demortain 2017 at 383. Loconto and Demortain further point to the diversities that arise when approaching standardization from different sites, including "standards in the making" and "standards in action". Standards in the making is "where standards-making bodies, experts and other interested stakeholders assemble to construct standards as outcomes of negotiations and strategic action amongst these various actors … This is the classically studied process of standardization as a site in which the negotiation around key values, qualities, knowledge, and semantics take place. Here, the process of creating a standard is the closing down of possible contestations in order to create a static, codified object – a standard." For standards in action, "despite the immutability of the standard, politics also thrive in this space as both the values and the actors co-evolve to fit each other"; Loconto & Demortain at 385. See also Timmerman & Epstein 2010.

[180] *Ibid* at 74-5. Without elaboration, Busch also claims, at page 27, that the dominant approach taken in his book is a "phenomenological approach". Though some similarities exist between ANT and phenomenology. I would not characterize Mol's work as phenomenological, particularly given Mol's efforts to escape representationalism.

[181] Busch 2013 at 13, 42. He acknowledges, at 42, that these four types can blend into each other at their margins.

[182] *Ibid* at 43-44 and 46-47.

[183] *Ibid* at 252-255.

being born in or swearing allegiance to a given nation", and an indicator that this test has been met is a passport.[184] Notably, standards cannot be implemented unless tests exist for measuring compliance with them. However, constructing tests or measurements for standards is often complicated and iterative. To prevent a disconnect between a standard and its test, Busch argues that tests must robustly measure the key dimensions of concern in the standard, be rigorous enough to "prevent exaggerated claims or even outright fraud", and involve neither too much nor too little "precision and accuracy for the purposes at hand".[185] This distinction between standards, tests, and indicators, and the role of tests in the performance of standards, allows for better apprehension of the Sex Hormone Regulations and of the estrogen they enacted, as explored in Chapter 4.[186]

Finally, readers are also reminded of the ethical and political implications of standards. Not only can standards create path dependence and thus burden future generations, they have distributive consequences, as their benefits and costs are differentially allocated.[187] In the context of estrogen, dose and potency standards not only have health implications, they distribute risk and power differentially to women, physicians, manufacturers, and state actors; less obviously, tests used to identify estrogen arguably produce sex and gender differently. In considering how estrogen standards, tests, and indicators were "constructed, contested, modified, enforced and abandoned" in regulatory practices, this thesis therefore opens up political questions.[188]

2.iii Enactment in interdisciplinary legal studies

While ostensibly a work of legal history,[189] this thesis has as its main theoretical guide a philosopher and anthropologist of medicine who works in STS and ANT-inflected veins. How have legal studies incorporated STS insights? Have STS approaches to materiality, and particularly Mol's theory of enactment, been taken up in socio-legal studies? If so, how?

In recent years, socio-legal scholars have begun to embrace STS approaches to materiality. Working within ANT, Emilie Cloatre has researched local practices and socio-legal assemblages

[184] *Ibid* at 13, 52.

[185] *Ibid* at 53, 304.

[186] The four sections comprising the Sex Hormone Regulations nominally address standard (ss. 1-2, under headings "Definition" and "Standards"), test (s. 3 under the heading "Potency"), and indicator (s.4 under the heading "Labelling"). As will be seen in Chapter 4, section 3, the relations between standard, test and label were essentially inverted in the Sex Hormone Regulations.

[187] *Ibid* at 246, 303-304.

[188] *Ibid* at 13.

[189] For how *legal history* has interacted with approaches within STS to materiality or ontology, see Chapter 2, section 1.

related to the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which inscribe pharmaceuticals with multiple scripts. Weaving together an ANT-inspired methodology with other philosophical and methodological traditions, Emily Grabham has written about law, materiality, and the enactment of time. Before relating to their work, I summarize more generally certain types of interaction – or imbrication – between legal studies and STS. Legal scholars deploy STS in different ways. While legal scholars are notoriously late to every party – as Simon Cole and Alysa Berthenthal note, "STS found law before law found STS" – the contention regarding when, exactly, law "found" STS reflects the diverse ways in which legal studies engage STS.[190]

Perhaps the most dominant framework used is *coproduction.* Popularized in a 2004 volume edited by Sheila Jasanoff that gathered together a wide variety of literatures,[191] coproduction is:

> "…shorthand for the proposition that the ways in which we know and represent the world (both nature and society) are inseparable from the ways in which we choose to live in it. Knowledge and its material embodiments are at once products of social work and constitutive of forms of social life".[192]

Jasanoff's basic argument is that scientific knowledges and social orders, whether historically or presently, are properly understood only if conceived as being produced together. Studying how knowledge-making practices are integrated within state-making practices or other forms of governance, and conversely how governance practices shape knowledge, provides greater explanatory power of complex sociotechnical worlds. While often focusing on expertise and epistemic authority, coproduction studies can have an ontological focus, in viewing knowledge as "crystallizing in certain ontological states – organizational, material, embodied".[193] Jasanoff characterizes coproduction not as a theory but as a framework, and speaks of research in a co-production idiom.[194] Nonetheless, beyond the rich description that results from considering

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[190] Cole & Bertenthal 2017 at 354. These authors date synergies between socio-legal and STS scholarship to 1994. However, as they note, Valverde dates the convergence to 2003; see Mariana Valverde "Authorizing the production of urban moral order: appellate courts and their knowledge games" (2005) 39:2 *Law & Soc Rev* 419 ["Valverde 2005"] at 420. Others point to the late 2000s as when "SLS and STS scholars and texts … started to intermingle more widely"; Alex Faulkner, Bettina Lange & Christopher Lawless, "Material Worlds: Intersections of Law, Science, Technology, and Society" (2012) 39:1 *J Law & Soc* 1 ["Faulkner, Lange & Lawless 2012"] at 12.

[191] Notably, in neither of her own two chapters, in Jasanoff 2004, does Jasanoff cite to any socio-legal scholarship. This supports Valverde's view that socio-legal scholars were not engaging STS prior to 2004; see Valverde 2005.

[192] Jasanoff 2004 at 2.

[193] *Ibid* at 3. However, not all scholarship employing Jasanoff's coproduction framework neatly aligns with either an epistemological or ontological mode of analysis. For example, a think piece on chemical regulation by Elizabeth Fisher largely asks an epistemic question of how chemical regulation "understands" or "conceives" of the chemicals being regulated, it occasionally slides toward a more ontological and more constitutive question of how chemicals assume different identities in different regulatory regimes. See Elizabeth Fisher, "Chemicals as Regulatory Objects" (2014) 23:3 *RECIEL* 163 ["Fisher 2014"].

[194] *Ibid* at 3-6.

connections between knowledge and power, it is claimed that coproduction carries explanatory and normative force – in its abilities to analyze the formation of new sociotechnical objects, and to find power in non-traditional places – and indeed even holds predictive power, insofar as it allows us to better perceive contingent patterns in sociotechnical networks.[195] While the latter claim seems overblown and unnecessarily scientistic, coproduction has no doubt helped to further dismantle instrumental notions of law as purely a "tool" that is epistemically and normatively distinct from, and that simply reacts and responds to, the separate domain of science and technology. Instead, it brings a less linear and more entangled relationship into view, in which legal processes have constitutive power in stabilizing facts and shaping technology. This recalls what Jasanoff labels the *constitutive* tradition in coproduction, which she says goes back to Latour.[196] As a second broad stream of coproductionist thought, she identifies work in an *interactional* tradition, which she says "is less overtly concerned with metaphysics and more with epistemology", in which research examines boundary conflicts between scientific and social knowledges.[197] My research describes how regulators' practices materialized estrogen as a potent and malleable object, and analyzes how estrogen sparked new regulatory logics and techniques centered on product labelling; coproduction is a natural fit with these processes. Thus, while this research takes an elementally constitutive approach, in focusing on conflicts between Committee members (and departmental lawyers) in deciding how to understand estrogen and how to regulate it, it also engages certain interactional concerns.

Scholars have recently reclassified the ways in which STS is engaged specifically by socio-legal studies. In reviewing law and society scholarship that draws on STS, Cole and Bertenthal identify two distinct avenues in the literature: *interaction* and *analogy*.[198] As they use it – which differs somewhat from Jasanoff's formulation – interaction involves areas "in which there actually is interaction between law and science", including law in laboratories, intellectual property, controversies that are simultaneously scientific and legal, and law's response to scientific expertise and uncertainty. In such contexts, legal scholars can use STS to ensure

[195] *Ibid* at 42.

[196] As Jasanoff notes, Latour introduced the term coproduction in *We Have Never Been Modern*, an extended essay that "linked constructivist themes from S&TS with themes of political philosophy"; Jasanoff 2004 at 22.

[197] Jasanoff 2004 at 19. For an example of a generally interactional approach, see Roger Brownsword & Karen Yeung, eds *Regulating Technologies: Legal Futures, Regulatory Frames and Technological Fixes* (Oxford: Hart Publishing, 2008).

[198] Cole & Bertenthal 2017 at 355. For another theorization of the relationship between STS and legal studies, see Cloatre & Pickersgill 2015. The introduction to this volume largely follows a constitutive (Jasanoff) or analogy (Cole & Bertenthal) tradition. The editors challenge distinctions between "law", "society" and "science" inherent to the "interactional" formula, and instead propose the expression "social studies of law" to reflect STS-inspired work in legal studies.

nuanced understanding of scientific knowledge.[199] Analogy, in contrast, refers to legal research that approaches law analogously to how STS approaches science, as a social phenomenon or epistemic institution. While this arguably describes most socio-legal research, legal scholars have analogically borrowed STS concepts, including from ANT, and methods to examine reflexivity and materiality.[200] Law and STS can swap "tools, methods and concepts, in order to study their respective objects of inquiry",[201] though often the trade is unidirectional as legal scholars adopt STS methods (if not its theoretical traditions).[202] The leading or at least earliest proponent of this adaptation might be Mariana Valverde, who has long urged borrowing STS methods and promoted ANT to socio-legal scholars.[203] If, as Valverde urges, rather than study static categories of scientific or non-expert, legal or lay knowledge, one tries to trace "the dynamics of knowledge processes" in socio-legal-technical networks, then "one sees new things".[204]

Materiality is a pervasive theme in socio-legal research proceeding analogically from STS,[205] inspired by growing theoretical attention to matter and materialization in feminist science studies,[206] posthumanist philosophy,[207] and political theory.[208] Studying materiality in and of law requires considering how things shape legal processes, how law is entangled in material forms, and "how materials become sites that produce, stabilize, and perpetuate particular kinds of

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[199] Cole & Bertenthal 2017 at 355, and 356-359. At 359, the authors place coproduction as one of seven thematic groups *under* their interaction umbrella, while conversely Jasanoff describes interaction as a type of coproduction.

[200] *Ibid* at 359-364.

[201] Valverde 2005 at 421.

[202] It has been noted that STS functions less like a theoretical intervention and more like an *antitheory* in socio-legal work, as it tends to focus "even greater attention on the contingent details of specific legal and scientific practices in specific places at specific times, at the expense of abstract theorizing"; Cole & Bertenthal 2017 at 364.

[203] Valverde 2005; Levi & Valverde 2008; Mariana Valverde, "Jurisdiction and Scale: Legal 'Technicalities' as Resources for Theory" (2009) 18:2 *Soc Leg Stud* 139; and Mariana Valverde, Ron Levi & Dawn Moore, "Legal Knowledges of Risk" in Law Commission of Canada, ed, *Law and Risk* (Vancouver: UBC Press, 2005) ["Valverde, Levi & Moore 2005"]. For a recent study using legal and STS approaches to regulatory knowledge, see Alex Faulkner & Lonneke Poort, "Stretching and Challenging the Boundaries of Law: Varieties of Knowledge in Biotechnologies Regulation" (2017) 55:2 *Minerva* 209 ["Faulkner & Poort 2017"].

[204] Valverde 2005 at 421. Abandoning such categories also tends to open up questions about what, if anything, distinguishes law and science, returning socio-legal scholars to the question of what "law" is; Cloatre & Pickersgill 2015 at 3. In these authors' view, in their Introduction at 8: "[i]f the insights of STS are taken seriously…law seems to become a set of fluidly defined associations within shifting networks, even though its language, institutional landscapes, and modes of deployment may appear specific … In other words, law can be reimagined as co-constituted rather than presupposed, in the way that social relations and objects are more generally".

[205] Cole & Bertenthal 2017 at 362.

[206] Works cited herein from this field include e.g. Haraway 1991; Murphy 2006; Roberts 2007; and Mol 2002.

[207] See e.g. Barad 2003; and Rosi Braidotti, *The Posthuman* (Cambridge: Polity Press, 2013).

[208] See e.g. Coole & Frost 2010; and Jane Bennett, *Vibrant Matter: a political ecology of things* (Durham, NC: Duke University Press, 2010).

power".[209] Analytic tools from STS include apprehending things as socio-legal objects, in which legal, technological and social relations are inscribed. Such objects are performative – they *do* things in the world, with potentially powerful effects that enact socio-techno-legal realities.[210]

An oft-cited example is Javier Lezaun's compelling ethnography of the European agency that creates "reference materials" for the many substances enumerated in EU law.[211] He asks how law comes to matter: "[b]y what strange alchemy is a legal obligation transformed into a material constraint?"[212] Also called reference standards – such as in the Sex Hormone Regulations – reference materials instantiate legal categories; they are things which "the law would be unable to find in the world if it were not for the availability of an official, stable version of the material in question".[213] Resulting from ontological practices of certification, documentation, and technical handling, reference materials render law and matter indivisible. In approaching standards as material rather than as texts or rules, Lezaun shows how, within a set of broader practices and relations, legal scripts get embedded in matter. Thinking with this "strong case" of legal ontology,[214] I likewise approach law's materialization through estrogen.[215]

Though inspired by ANT and investigating the textual, handling, machinic, and physical practices that materialize law, Lezaun does not explicitly draw on Mol. Yet other socio-legal scholars have recently have done so, demonstrating the utility to legal studies of evaluating how realities are enacted in practice. In *Brewing Legal Times,* Emily Grabham brings together philosophical work on time, literatures on law and time, social and legal history, and ANT-inspired literature that engages questions of materiality.[216] She does so to explore relationships among time, matter, and law. Following Mol, she aims to move beyond the idea that time has many representations, to think about how practices enact "multiple legal ontologies of time" or the "more-than-oneness of time".[217] In the context of a case study on HIV activism, for example, she shows how new temporalities result from law's entanglements with clinical knowledge, tests and drugs. Other case studies review practices that do things with law to "trace the provisional,

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[209] Cloatre & Pickersgill 2015 at 7-8.

[210] Cole & Bertenthal 2017 at 362.

[211] Specifically, the Institute for Reference Materials and Measurements, in Belgium.

[212] Lezaun 2012. For other scholars' discussions of Lezaun's study as exemplifying research into law and materiality, see Cole & Bertenthal 2017 at 362; Cloatre & Pickersgill 2015 at 6-7; and Grabham 2016 at 41-44.

[213] Lezauan 2012 at 38.

[214] Grabham 2016 at 44. Lezaun's study is especially generative in light of how legal responsibility for the creation of reference materials for estrogenic drugs was delegated to industry in Canada in the 1940s; see chapters 4 and 5.

[215] See e.g. Alain Pottage, "The Materiality of What?" (2012) 39:1 *J Law & Soc* 167 ["Pottage 2012"] (arguing for analysts to begin with materiality rather than with law, to understand what becomes materialized as law). See also Chapter 2, section 1.

[216] Grabham 2016 at 6-8.

[217] *Ibid* at 16, 23.

and thing-related, enactment of legal temporalities as they constitute new legal worlds".[218] Thus, by applying Mol's praxiographic approach to temporalization, Grabham argues that objects and humans together enact and sustain multiple legal temporalities, and materialize law.[219]

In *Pills for the Poorest*, Emilie Cloatre also draws on Mol's scholarship on the ontological multiplicities performed by knowledge-making and technical practices.[220] Cloatre's theoretical vocabulary and her ethnographic methods are both heavily guided by a traditional ANT approach, and her study into localized public health practices surrounding TRIPS and pharmaceutical patents in Dijoubiti and Ghana are framed around ANT-inspired research questions, including how legal texts are "black boxed" and stabilized through ongoing translations, how controversies settle into beliefs, how nonhuman actors contribute to these shifting relations, processes and events. The main object of her study is the performance of TRIPS as a socio-legal assemblage. Building on a nascent literature that employs ANT to explore the constitution of law, Cloatre asks what practices create effects that come to be known as "legal", how legal objects like patents materialize, and how legal texts become entangled in broader sociotechnical assemblages.[221] In particular, guided by Andrew Barry, pharmaceutical drugs are characterized as being inscribed with and carrying multiple events and legal scripts, which may or may not travel cleanly. "[I]n their most material form, in their packaging, in their labelling", including the differences between brand and generic forms, Cloatre argues that drugs are "influential and symbolic actors".[222] Effectively, drugs are "legal things" shaped by socio-legal relations and materializing regulatory practices.[223]

Guided by Mol's praxiological ontology, and its resonances in the sociology of standards and in work by socio-legal scholars, in the next chapter I describe my own practices, detailing my historical research methods and how they materialized this account of toxic enactment.

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[218] *Ibid* at 176.

[219] Grabham 2016 at 21, 31, 171-173.

[220] Cloatre 2013.

[221] *Ibid* at 7-18.

[222] *Ibid* at 20.

[223] With others, Cloatre has also deployed ANT to study the co-emergence of nicotine gum, regulatory regimes, and knowledge of tobacco addiction; see Catriona Rooke, Emilie Cloatre & Robert Dingwall, "The Regulation of Nicotine in the United Kingdom: How Nicotine Gum Came to Be a Medicine, but Not a Drug" (2012) 39:1 *J Law & Soc* 39 ["Rooke, Cloatre & Dingwall 2012"].

Chapter Two

Legal history, in theory: historical approach and research methods

> "These conjoined insights—that nonhuman stuff can have some sort of determinative influence on (or agency in relation to) humans, and that "the material" is a cultural construct—have particular implications for how we understand law in both past and present societies. … In different times and places, then, legal processes formed one of the means by which "objects" were created and policed. The particular material forms that law inhabited (hedge, slave, deodand) were culturally variable. Law projected a certain kind of materiality, and these projections manifested in material things." – Tom Johnson (2015)

This study adopts historical methods to critically examine how estrogenic drugs emerged together with new regulatory practices in Canada in the 1940s. While this project's methods are historical, however, it does not simply narrate one past. Without attempting to expound any general theory of the relationship between law and toxicity, let alone law and matter, this study still gestures towards a broader concept of toxic enactment. Conceptually, toxic enactment rejects purely positivist conceptions of legal rules that respond (or fail to respond) to an already fixed and stable matter, of governance techniques that try to control toxic substances or technological innovations already fully formed in the real world. It also departs from strongly constructivist accounts, in which social or legal norms, rules, and powers dictate the existence or form of substances and technologies. Instead, inspired by praxiological and performative ontology, toxic enactment theorizes an active and ongoing process in which toxics regulations and legalized toxins become together. Yet, despite gesturing towards this general abstraction, the history told here is of course not universalizable. Rather, using legal history methods, this study gives a detailed empirical account of the intersections between estrogen and regulation in mid-century Canada – of how regulatory practices enacted estrogen as drugs, as potent, as unstable, as multiple; and how estrogen triggered new regulatory techniques, namely new types of delegation and labelling, with implications for social relations and women's health. Potent though they were, these estrogenic enactments were the contingent and even peculiar results of specific actors' performances on particular institutional stages, done in their own time and place.

1. An historical approach – but, to what?

While this study adopts an "historical approach", identifying "to what exactly" this approach applies demands further articulation. Does this project take an historical approach only in service of a more abstract account of enactment, leveraging archival evidence to illustrate how regulatory practices can materialize different versions of reality? It is true that this narrative of

the activities of regulators and estrogen is conceptually driven, however it does not attempt to elucidate a general meaning of or parameters for the concept of "enactment". Is this study better understood, then, as legal history? After all, it seeks to describe temporally bound and shifting approaches to drug regulation, their evolution with new scientific practices for sex hormones, forgotten and abandoned regulatory directions, and unintended and unpredicted regulatory effects. Further, in recounting how estrogen was enacted, it examines alternative practices embedded in different lawyers' assessments of the validity of subordinate legislation and sub-delegation under the *Food and Drugs Act,* in the context of administrative law ideas at the time.

While these questions lack simple resolution, they are clarified in scholarship grappling with how legal theory and legal history do, or should, relate to one another. In *Law in Theory and History: New Essays on a Neglected Dialogue,* Maks Del Mar and Michael Lobban assemble explorations of the interdisciplinary space of legal theory and legal history, a space they deem to be "very young". [1] In Del Mar's contribution, after contrasting different cognitive and affective modes embraced by historians and philosophers, and arguing that historical work must be understood as always theorizing law, he advocates a strategy of entangling history in theory and *vice versa*, by abandoning claims to universality in theory and to particularity in history. The goal of this cross-disciplinary entanglement should be scholarship that "models the variability of law across time and space".[2] Similarly, a 2015 special edition of the *Virginia Law Review* explores commonalities in philosophical and historical inquiries into law. The introductory essay reminds us that a primary use of history in legal scholarship is to cast doubt on current concepts and values; in the same vein, Nicola Lacey's contribution argues that the power of historical scholarship lies in its ability to reveal the contingency of and denaturalize current legal practices, especially when viewing law as a structured social practice embedded in specific institutions.[3]

Accepting that historicizing law need not and perhaps cannot be disentangled from theorizing law, and that legal history can powerfully destabilize concepts viewed as "natural", perhaps the better question is whether this study is properly characterized as *legal* history? Is the object of study law – or is it estrogen? As my research details how regulators' practices fabricated a potent, changeable estrogen, and how estrogen catalyzed new governance techniques for such

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[1] Maks Del Mar & Michael Lobban, "Preface", in Maksymilian Del Mar & Michael Lobban, eds, *Law in Theory and History: New Essays on a Neglected Dialogue* (Oxford: Hart Publishing, 2016) at vi.

[2] Maks Del Mar, "Beyond University and Particularity, Necessity and Contingency: On Collaboration between Legal Theory and Legal History", in Maksymilian Del Mar and Michael Lobban, eds, *Law in Theory and History: New Essays on a Neglected Dialogue* (Oxford: Hart Publishing, 2016) at 25-26 and 34.

[3] Dan Priel & Charles Barzun, "Jurisprudence and (Its) History" (2015) 101:4 *Va L Rev* 849 at 853-856; and Nicola Lacey, "Jurisprudence, history, and the institutional quality of law" (2015) 101:4 *Va L Rev* 919 at 931-935.

substances, a more apt realization of my object might be "*law in estrogen*" or "*estrogen in law*", or better yet, both of these descriptors. Unlike "law and estrogen", these phrases refuse to render law and estrogen as wholly distinct phenomena. They challenge legal historians' traditional approach of exploring law by putting it in (political, economic, social) context, and its classic division "between law and what is extrinsic to it".[4] Instead, methodologically, they let me compound my object as essentially conjugated – as "more than one and less than many".[5]

Part of the challenge in pinpointing the precise object being approached historically is that few legal historians frame their inquiries around "law and matter" or within new materialisms.[6] In his work, Christopher Tomlins proposes "materiality" as an alternative methodology. However rather than "historicism", which, after Walter Benjamin, he describes as an approach which futilely attempts to see the past by differentiating law from its context, Tomlins argues for a historical materialism that "stresses the formal intersection between law and legal thought and technologies, artefacts and material practices; it considers how law might be expressed as technology and artefact, how law as a differentiated category of action is fabricated".[7] While legal historians engaging with materiality would surely also endorse moving away from law primarily as discourse, autonomous from the "real" world yet bestowing meaning upon it, they need not jettison the idea that something called "law" can be apprehended in history. As put by Tom Johnson, one of the few legal historians to have taken up materiality,[8] the material turn allows us "to conceive 'law' as a quality that can inhabit physical stuff, as well as legal treatises and social practices".[9] As Johnson concedes, in identifying law and the material world as analytical realms, we perform "precisely the kind of ontological partition…that we are purporting

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[4] Christopher Tomlins, "After Critical Legal History: Scope, Scale, Structure" (2012) 8 *Annu Rev Law Soc Sci* 31 at 31 ["Tomlins 2012a"].

[5] Mol 2002 at 55, 82. Mol uses this phrase to capture how different practices enact multiple objects. As she discusses at pages 78-82, the phrase originally derives from Marilyn Strathern's conceptual work on partial connections.

[6] Excluded from this claim is the materialism of Marxist historiography, a tradition in which Tomlins' writing is partly situated.

[7] Christopher Tomlins, "Historicism and Materiality in Legal Theory" in Maksymilian Del Mar & Michael Lobban, eds, *Law in Theory and History: New Essays on a Neglected Dialogue* (Oxford: Hart Publishing, 2016) ["Tomlins 2016"] at 59. See also Christopher Tomlins, "What is left of the law and society paradigm after critique? Revisiting Gordon's 'Critical Legal Histories.'" (2012) 37:1 *Law Soc Inq* 155 ["Tomlins 2012b"].

[8] Tom Johnson's forthcoming chapter brings legal history into conversation with literatures on materiality, proposing various new research avenues. Johnson identifies legal and historical geographers such as Nicholas Blomley and legal anthropologists such as Javier Lezaun whose research engages materiality. He also identifies socio-legal scholars who have explored materiality using historical methods, like Marianna Valverde and Alain Pottage. However, he cannot identify much existing work that positions itself as "legal history". Two exceptions are Teresa Sutton, "The deodand and responsibility for death" (1997) 18:3 *J Legal Hist* 44; and Cornelia Vismann, *Files: Law and Media Technology*, trans. Geoffrey Winthrop-Young (Stanford, CA: Stanford University Press, 2008). See "Legal History and the Material Turn," in Christopher Tomlins & Marcus Dubber (eds), *The Oxford Handbook of Historical Legal Research.* Oxford University Press (forthcoming) ["Johnson, forthcoming"].

[9] Johnson 2015 at 410.

to refute".[10] Still, this philosophical difficulty can help to ensure that legal historians' turns to matter are empirically and conceptually well-grounded.[11] Thus, following Johnson methodologically, this thesis conjoins legal history methods with the insights of ANT and performative approaches to materiality, so as to apprehend law's imbrication with matter.

2. Research methods – or, how practices enact realities

Having situated this study in historiographies of sex hormones and drug standardization, and having set out the conceptual and methodological issues at stake in this study, this section now details the research methods that were adopted to answer these questions. Or rather: that sentence is what I might write if it were entirely accurate to characterize my methods as flowing in a smooth and linear progression from the methodology, the methodology as flowing inevitably from the concept of toxic enactments, and that concept springing to life from the literature. I might write that first sentence if I wished to create the impression that research practices, habits, and methods were separate from, and subordinate and subsequent to, ideas, concepts, and theories – if thinking were distinct from doing, if concepts dictated practices.

To avoid severing the relations between discursivity and materiality, that sentence can be set aside. Rather than imply that my evidence-gathering practices were an afterthought to reading theory and history (which implication may be unfortunately solidified by following, as I do here, the standard practice of presenting methods after the literature review, almost as a postscript), these practices were vital in conjuring my object of study. That object – law in estrogen, estrogen in law – was not fully formed, waiting to be discovered in the archives. To the contrary, estrogen and law have been performed together in an ongoing intra-action, to use Karen Barad's term,[12] through a specific combination and sequence of legal and archival research.

Besides, a more candid account would be that I began this project with different research questions in mind. Originally, I was interested in assembling an intellectual history of "estrogenic substances" in Canadian food and drugs law, in light of present debates about that concept's meaning. However, as documented below, when I started searching for, wading through, and comparing the contents of archival files from the 1940s – initially conceiving of this material as "context" for regulations – the records took me by surprise. A cast of human actors and active substances were engaged in a plethora of competing and ostensibly incommensurate

[10] Johnson, forthcoming, at 7.

[11] As Johnson says "[w]hat works for enclosure and deodands may not add much that is useful to the history of trusts"; *ibid* at 8.

[12] Barad 2003.

discourses, professional traditions, representational strategies, and practices. This was not a story of regulatory texts constructing estrogenic substances as a static legal concept through which matter was corralled and disciplined. These actors were actively performing multiple kinds of estrogen – through experimental regulatory techniques, chaotic scientific knowledges, stalling industry practices, intransigent laboratory animals, and highly potent molecules. In the archives, estrogen was never one thing. The archival material revealed that the regulations I had traced were not the only or even core object of interest, and certainly not a representation of a fixed and stable substance, but were the *effects* of scientists, physicians, pharmacists, bureaucrats, and solicitors' practices in trying to know, measure, and standardize estrogenic substances.

In this way, my research practices transformed my questions and the theoretical literature guiding them, animating more elemental questions about the entanglement of law and materiality. Likewise, my methods triggered the realization that the feminist historical and STS literature addressing sex hormones, while foundational, was insufficient to understand how estrogens materialized as drugs – as, with noted exceptions, this literature largely studies laboratories, clinicians, patients, and industry, yet typically disregards regulators. This process led me to histories of drug enumeration, standardization, and regulation in the mid-20th century.

Out of order though it seems, then, the archival evidence raised, in large part, the questions that this study turns to answer. Still, stating that I "started with the evidence" is not quite right. Only by reading Nelly Oudshoorn and Celia Roberts on sex hormones, Annemarie Mol and Michelle Murphy on multiple ontologies, Sheila Jasanoff on co-production and Emily Grabham on law and materiality, could I bring to those materials an awareness of estrogen's history and with questions beginning to brew. So perhaps there is some truth in that first sentence, too.

2.i. Legislative and regulatory sources

I began my research by working to assemble the complete regulatory history of "*estrogenic substance*" in regulations under the *Food and Drugs Act* prior to 1977. To do this, I searched the *Canada Gazette,* primarily using the electronic database. Where there were gaps in digitization, I consulted the hardcopy volumes in various libraries in Toronto. Additionally, knowing that Health Canada's interprets "estrogenic substance" as referring to sex hormones,[13] I researched the full legislative and regulatory history of "*sex hormones*" under the *Food and Drugs Act.*

In doing this research, I was able to start from some existing, albeit incomplete, attempts by students and law librarians to help me piece together a regulatory history of "estrogenic

[13] Health Canada 2011.

substances" and "sex hormones".[14] Those efforts mistakenly identified one or the other of two orders-in-council amending Schedule B, both made in 1949, along with a 1949 amendment to Division II of Part C of the *Food and Drug Regulations*, ("the Sex Hormone Regulations"), as the first time that "sex hormones" had been addressed in the scheme.[15] Eventually, I located the original version of the Sex Hormone Regulations, dated May 18, 1944, and a corresponding earlier order-in-council adding sex hormones to Schedule B, dated May 4, 1944.[16] Having found the earliest enactments, I then mapped out a full history of all revisions and repeals, tracing the evolution of the Sex Hormone Regulations and Schedule B to the *Act*, until 1980. As amendments to these enactments were made by orders-in-council, my method was searching electronic versions of the *Canada Gazette* and, where necessary, returning to bound volumes.

To ensure statutory context for Schedule B and the Sex Hormone Regulations, I researched legislative history as well. Here my aim was to identify the genesis and evolution of statutory sections authorizing these two enactments and their provisions, with especial focus on sections authorizing the 1944 enactments (and authorizing their predecessors, like the biological products regulations). The *Food and Drugs Act* was amended many times between 1920, when it was first enacted, and 1953, when it was overhauled.[17] For this research, I used the Table of Public Statutes, and annotations in and appendices to the Revised Statutes of Canada (1953).

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[14] While only one name appears on the front of this thesis, the author is, of course, just one actor within the assemblage that enacted it. Many other actors who have materialized this thesis are credited in the Acknowledgements. This footnote identifies the people who helped me with legislative research. Prior to commencing my LLM program, as a staff lawyer at Ecojustice Canada and working with staff scientist Dr. Elaine MacDonald, I supervised articling student Ian Arnold and University of Ottawa law student Sally MacKinnon in their efforts to help us begin to map out a partial history of "estrogenic substances" and "sex hormones" in regulations under the *Food and Drugs Act*. Three law librarians also assisted this effort, first at the University of Ottawa and the Great Library in Osgoode Hall, and, once I began this LLM research in fall of 2016, at Osgoode Hall Law School.

[15] The students and librarians noted, *ibid,* all identified either the April 5, 1949 order-in-council amending Schedule B (PC 1949-1537), or the November 8, 1949 order-in-council amending Schedule B (PC 1949-5643), as the first time "sex hormones" were addressed in the *Act*. Yet upon reading those two orders, on their face, it was evident those conclusions could not be correct. The April 5, 1949 order expressly *removed* the term "sex hormones" from the Schedule, replacing it with the word "hormones" (although this was reversed shortly thereafter, with an order reinserting "sex hormones"; see PC 1949-3483 (13 July 1949)). Thus, it was evident that sex hormones must have been listed on Schedule B prior to April 1949.

[16] Professor John Davis of Osgoode Hall Law School resolved the confusion. Through creative searches for terms included in the 1949 versions of Schedule B, he located the earlier May 4, 1944 order-in-council (PP 1944-3308) that added "sex hormones" to Schedule B; while this order is located within the electronically archived *Canada Gazettes,* it is not indexed or searchable by the term "sex hormone" or "hormone". Ultimately, even this May 4, 1944 order proved not to be the first time that sex hormones were added Schedule B, although this only became apparent through archival research. The first time that sex hormones were added to Schedule B was on January 11, 1944 (PC 1944-96) but this order-in-council is not searchable in the electronic *Gazettes.*

[17] Whenever the *Food and Drugs Act* or the *Act* is mentioned in the body of the text, reference is made to the 1927 consolidated statute, *An Act Respecting Food and Drugs,* RSC 1927, c 76 ["*Food and Drugs Act*" or "*FDA*" or "the *Act*"]. Whenever a later amendment is relied upon, reference is made, in the footnotes, to the amending statute as well. The amending statutes include: RS 1930, c 23; RS 1930, c 30; RS 1934, c 54; RS 1939, c 3; RS 1945, c 7; RS 1946, c 23; and RS 1950, c 50. In 1953, the legislation was revised significantly; see *Food and Drugs Act,* RS 1952-1953, c 38. The 1953 Act was assented to on May 14, 1953, and it came into force on July 1, 1954; see SOR/54-293.

2.ii. Archival research

Concurrently, I searched the Library and Archives Canada ("LAC") database for materials regarding the 1944 Sex Hormone Regulations, Schedule B, and associated enactments. Two files on the Sex Hormone Regulations were open: a lawyer's file maintained by Elmer Driedger, who provided advice on the draft regulations;[18] and a file maintained by the Department of Pensions and National Health ("National Health").[19] I obtained similar files, of either solicitors or National Health officials, on the development of the 1944 amendments to Schedule B,[20] and the 1944 Parenteral Regulations.[21]

As explained, using my legislative and regulatory research to inform my archival research, and *vice versa*, redirected the project's focus. Preambular recitals in the above-mentioned regulations referenced the Canadian Committee on Pharmacopoeial Standards. As I soon learned, the Committee was established in 1942 to advise – in practice, sometimes to decide, sometimes to simply sign off – on many of Canada's first drug standards. Based on the preambles, I obtained LAC archival materials documenting the Committee's activities. As these Committee files were numerous and voluminous, I initially limited my review to late 1942 to May 1944,[22] expecting to find "context" for the Sex Hormone Regulations. Context soon became centre, and the scope expanded,[23] after I learned in the archives that the Committee and Department had enumerated four estrogens – *oestrone*, *oestradiol benzoate, stilboestrol,* and *stilboestrol diproprionate* – in Schedule B,[24] and had standardized these drugs in the Canadian

[18] Library and Archives Canada, "Pensions and National Health – Food and Drugs Act – Regulations Respecting Sex Hormones", RG13-A-2, volume/box 2116**,** file no. 146937, reproduction copy number e011193404 ["EA Driedger's Sex Hormone Regulations File, 1944"].

[19] Library and Archives Canada, Department of Health fonds, RG 29, "Canadian Committee on Pharmaceutical (sic) Standards – Proposed Regulation – Sex Hormones", 1944/03-1945/03, volume 250, file no. 339-4-3, reproduction copy number e011193404 ["National Health's Sex Hormone Regulations File, 1944-1945"].

[20] Library and Archives Canada, "Food & Drugs Act Part V – Proposed Amendment to Schedule B of the FDA Adding Certain Drugs to Part II & Adding a New Part V", RG 13, volume 2619, file no. 6-146115 (Part 1) ["EA Driedger's Schedule B File, 1943"]. This file was released to me under the *Access to Information Act,* under LAC file no. A201700062, on May 19, 2017.

[21] Library and Archives Canada, Department of Health fonds, RG 29, "Canadian Committee on Pharmaceutical (sic) Standards – Proposed Regulation – Parenteral Drugs", volume 250, file no. 339-4-6, reproduction copy number I-106866 ["National Health's Parenteral Drug Regulations File, 1943-1944"].

[22] Library and Archives Canada, Department of Health fonds, RG 29, "Canadian Committee on Pharmacopoeial Standards – Correspondence", 1942/09-1943/06, volume 250, file no. 339-4-7 (Part 1), reproduction copy number e011193405 ["Davidson's Committee Materials, 1942-1943"]; Library and Archives Canada, Department of Health fonds, RG 29, "Canadian Committee on Pharmacopoeial Standards – Correspondence", 1943/06-1944/01, volume 250, file no. 339-4-7 (Part 2), reproduction copy number e011193406 ["Davidson's Committee Materials, 1943-1944"]; Library and Archives Canada, Department of Health fonds, RG 29, "Canadian Committee on Pharmacopoeial Standards – Correspondence", 1944/01-1944/05, volume 251, file no. 339-4-7 (Part 3), reproduction copy number e011193404 ["Davidson's Committee Materials, 1944"]. All files under file no. 339-4-7 were files maintained by the Committee's Secretary A. Linton Davidson, of the Department's Food and Drug Division.

[23] An additional 15 files were reviewed in person at LAC offices in Ottawa; see the list of archival sources in the Bibliography.

[24] PC 1944-96 (10 January 1944), *Canada Gazette*, Vol LXXVIII, No 4, at p 354 (January 22, 1944).

Supplement.[25] These two enactments had not appeared in my *Gazette* research. The archival files raised new ontological questions, causing me to apprehend estrogen as legally multiple.

Further LAC holdings reviewed included two files containing newspaper and magazine advertisements for food and drugs, along with related compliance discussions and activities, maintained by National Health staff in 1938-1940 and 1949-1953.[26] I also reviewed prosecution and inspectors' records from 1950-1953, to determine if estrogenic drugs or cosmetics were ever the target of enforcement activities (and specifically if, in the process, the nature, composition or identity of these products had ever been contested).[27]

2.iii. Other primary historical sources

Building upon my regulatory and archival research, I reviewed all articles addressing Canadian food and drug law published in the 1940s and 50s in the *Food Drug Cosmetic Law Quarterly* and, later, the *Food, Drug, Cosmetic Law Journal.*[28] Many are authored by National Health officials, including Robert Curran, Dr. Leonard Pugsley, and Dr. Clare Morrell; some are by American officials and counsel. A pamphlet and book published in 1949, authored by Linton Davidson, a departmental official and the Secretary to the Committee, coupled discourses of nation-building and Christian fervor with key developments in the growth of the Food and Drugs Division (later the Directorate) and details on the Committee.[29] In more restrained bureaucratic prose, historical reviews by Pugsley and Dr. Gordon Cameron provided factual detail on the Department's evolution,[30] and a book summarizing food and drugs law in Canada by Curran gave insight into legal preoccupations.[31]

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[25] The Canadian Supplement, 1944, to the British Pharmacopoeia, Being Division III of the Regulations under the *Food and Drugs Act,* enacted through PC 1944-2515 (11 April 1944), *Canada Gazette,* Vol LXXVIII, No 30, at p 2983 (July 22, 1944).

[26] Library and Archives Canada, Department of Health fonds, RG 29, "Food and drugs - Articles taken from newspapers magazines & newspaper advertisements", 1938/12-1940/05, volume 258, file no. 347-1-6 (Part 2) reproduction copy number e011195705 ["Food and Drug Newspaper Clippings, 1938-1940"]; Library and Archives Canada, Department of Health fonds, RG 29, "Food and drugs - Articles taken from newspapers magazines & newspaper advertisements", 1949-1953, volume 259, file no. 347-1-6 (Part 4), reproduction copy number I-115336 ["Food and Drug Newspaper Clippings, 1949-1953"].

[27] Library and Archives Canada, Department of Health fonds, RG 29, "Monthly Reports of Completed Prosecutions and Seizures", volume 261, file no. 347-6-4; ["Monthly Prosecutions and Seizures Reports, 1950-1953"] and Library and Archives Canada, Department of Health fonds, RG 29, "Inspectors Reports", 1950-1953, volume 261, file no. 347-2-9 ["Inspectors' Reports, 1950-1953"]. Both of these files were reviewed in person at the LAC building in Ottawa.

[28] In 1992, this journal was again renamed, as the *Food and Drug Law Journal*.

[29] Davidson 1949a; and Davidson 1949b.

[30] Leonard I Pugsley, "The Administration and Development of Federal Statutes on Food and Drug Legislation" (1967) 23 *Med Serv J Can* 387 ["Pugsley 1967"]; and GDW Cameron, "The Department of National Health and Welfare" (1959) 50:8 *Cdn Jour Pub Health* 319 ["Cameron 1959"].

[31] Robert E Curran, *Canada's Food and Drug Laws,* Food and Drug Law Institute (Chicago: Commerce Clearing House Inc, 1953) ["Curran 1953"].

With little history on estrogenic drugs or drug standardization in Canada, and needing further insight into the background views likely held by the Canadian physicians, pharmacists, drug manufacturers, and scientists on the Committee, I did some targeted research in medical journals, relying most heavily on the Vancouver Medical Association Bulletin.[32] This research aimed to determine what estrogenic products were on the market in the late 1930s and 1940s in Canada, what "diseases" were being associated with estrogenic therapies and medical views on the therapies' efficacy, and how estrogenic drugs were being advertised. Similarly, I did targeted searches in endocrinology, pharmacology, and pharmaceutical journals, for studies examining reference standards and assay methods for biological substances, including estrogens, including for scientific studies published in the 1930s and 1940s by Pugsley and Morrell.

Finally, to situate departmental solicitors' requests for advice and Driedger's legal opinions on the validity and form of enactments including the Sex Hormone Regulations, Part V of Schedule B, the Canadian Supplement, and the order creating the Committee, I identified leading administrative law scholarship and judicial decisions, in this period, addressing statutory interpretation and (sub)delegation.[33] I also reviewed some of Driedger's own scholarly work.[34]

2.iv. Secondary historical sources

In addition to the historical literature already introduced, I researched secondary sources for further historical context and information regarding: scientific knowledge, at different times in the last 90 years, on the composition, production, clinical uses, marketing, potencies, and effects of substances including DES, Premarin, estradiol, and estrone; trends and controversies regarding hormone replacement therapy; the politics of menopause and its medicalization; the evolution and function of pharmacopoeias; and comparative developments in drug regulation in the US.

Having set out my methodological framework and my research methods, I now turn to Part II of this thesis. In the next three chapters, I describe how law materialized estrogen and how estrogen sparked new legal techniques in Canada in the 1940s and early 1950s.

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[32] This journal has been digitized and made searchable as part of an open collection on the history of nursing at the University of British Columbia; see https://open.library.ubc.ca/collections/historyofnursinginpacificcanada.

[33] Including John Willis, "Delegatus Non Potest Delegare" (1943) 21:4 *Can Bar Rev* 257 ["Willis 1943"]; John Willis, "Statutory Interpretation in a Nutshell" (1938) 16 *Can Bar Rev* 1 ["Willis 1938]; *Reference as to the Validity of the Regulations in Relation to Chemicals Enacted by Order in Council and of an Order of the Controller of Chemicals Made Pursuant Thereto,* [1943] SCR 1.

[34] Elmer A Driedger, "Subordinate Legislation" (1960) 38 *Can B Rev* 1 ["Driedger 1960"]; and Elmer A Driedger, "The Preparation of Legislation" (1953) 31 *Can B Rev* 33 ["Driedger 1953"].

Chapter Three

Delegating standards, assembling regulators: new ways of regulating drugs in Canada at the start of the 1940s

> Delegation, as that word is generally used, does not imply a parting with powers by the person who grants the delegation, but points rather to the conferring of an authority to do things which otherwise that person would have to do himself … If it is correct to use the word in the way in which it is used in the maxim as generally understood, the word "delegate" means little more than an agent. – *Huth v. Clarke* (1890) 25 QBD 391 at 395, *per* Wills J.

> Incompatibilities between objects enacted are no obstacle to medicine's capabilities to intervene – as long as the incompatible variants of an object are separated out…Distributions separate out what might otherwise clash. – Mol 2002.

This chapter begins my historical account of how estrogen co-emerged with new regulatory practices and techniques in Canada, between 1939 and 1953. It starts to demonstrate methodologically and empirically what was set out more theoretically and conceptually in Part I. Before describing the multiple ways in which Canadian regulators performed estrogen, however, it is necessary to give some shape and definition to the regulatory assemblage in which estrogen was enacted. As a prelude to showing how estrogen is a historically contingent artefact of multiple regulatory practices, it is necessary to constellate my regulatory network.

Thus, this chapter draws together some critical legal formations that had assembled by 1940. To insist on a rigid distinction between "regulations" and "regulators" can be artificial and unproductive – both are actors, after all – and like regulators, regulations "both shape and are shaped by the networks of which they are part".[1] Despite this, the chapter begins by setting forth statutory and regulatory provisions and amendments under the *Food and Drugs Act*, from the late 1920s to late 1930s, that, as will be shown in later chapters, would ground understanding and action in the standardization, regulation, and multiplication of estrogen. Trying to avoid toggling back and forth between something conceived as statutory "context" or "structure", on the one hand, and human "agents" or "actors", on the other, some of the humans entangled with these regulatory events, such as National Health officials A. Linton Davidson and Harry Mills Lancaster, are also introduced in this first section. More specifically, the first section outlines the distinct modes or ways of standardizing drugs under the *Act,* particularly pharmacopoeial standards and delegated legislation, and how these modes relied on a growing turn to increased

[1] Rooke, Cloatre & Dingwall 2012 at 56.

delegation. In the case of the Biologicals Regulation, these delegations were often unlawful, as National Health officials in the Food and Drug Division and the Laboratory of Health developed a deeply entrenched habit of delegating themselves power without statutory authority. This section also examines how National Health excluded estrogen from the ambit of the Biologicals Regulation, despite the original intention behind their empowering statutory provision, finding that the ambiguous legal status of sex hormones in the 1930s did not simply *reflect* estrogenic substances' apparent lack of therapeutic action, but *performed* estrogen as a marginal therapy. As estrogen was also an ingredient in cosmetics, the section ends by briefly noting the legislative amendments covering cosmetics in 1939, which were passed but not brought into force at that time.

The second and shorter section of this chapter describes the formation of a new regulatory community for drug standards in Canada, one that expanded beyond and overlapped with some departmental regulators. It details the inconsistent, contested advocacy efforts by senior Departmental officials and academic scientists that lead to the establishment of the Canadian Committee on Pharmacopoeial Standards ("the Committee"). Canvassing the political and legal concerns with delegating drug standards to non-governmental scientists, the section shows how National Health officials' habit of legally doubtful delegation would be central to cementing the Committee. After two years of debate and confusion, the Committee was created in the summer of 1942 and its members appointed that fall. Reviewing this assemblage in the making, and the activities through which interests and knowledges were aligned, will give a richer understanding, in later chapters, of the regulatory practices that enacted estrogen-in-law and law-in-estrogen.[2]

In demarcating this socio-technical-legal assemblage, through this chapter, certain choices have been made, and some of these choices are exclusionary. Most obviously, excluded from the assemblage defined here are women – whether as patients, consumers, participants in clinical trials, National Health officials, physicians, pharmacists, or citizens. When one begins with regulatory practices in the 1930s, it is easy to lose sight of those not invited to the table.[3] From the boardroom tables around which the Committee members would soon gather, in their letters preceding and following those gatherings, in their deliberations about estrogen, women were almost entirely absent (except for all the unnamed stenographers whose transcriptions formed the basis for the Committee's meeting minutes and thus for some of this research).[4] As

[2] Levi & Valverde 2008 at 811.

[3] See e.g. Star 1991.

[4] Only four women are mentioned more than once in the archival files consulted: Dr. Morrell's and Mr. Davidson's wives; Miss A. Dixon, the Associate Private Secretary to Minister Mackenzie, and Rebecca Lee Scott. In 1943, Scott worked as a secretary to

will be seen, only one Committee member expressed any concern about the safety of estrogenic drugs, and his concern was ignored. While the archival evidence relied on admittedly tends to render women invisible,[5] it remains the case that, in most every way, women were excluded from efforts to regulate and standardize estrogen in Canada in the 1940s.

Another implication of choosing to focus on the Committee's and related Departmental actors' regulatory practices in standardizing estrogen in the 1940s is that earlier events become characterized as "context". Of course, "context' can all too quickly be regarded as sufficient explanations of what is happening."[6] As Woolgar and Lezaun emphasize, in ontological analyses, "the invocation, construction, and constitution of 'the context' are intimately implicated in the situated determination of what the object is."[7] Thus, in beginning this history with an account of regulations and regulators, apprehending estrogen as an object embedded in and enacted by regulation is arguably rendered more straightforward. While it is impossible to abstain from context, whether characterized as legal, political, bureaucratic, or economic, this chapter endeavours to "set the scene" in a way that does not reduce the reason for subsequent events to statutory frameworks, regulatory dynamics, or the identity or interests of Committee members enlisted in the "estrogen regulation network" that I have chosen to assemble here.

Finally, throughout this chapter, certain regulatory practices are highlighted that were pivotal to the emergence of new approaches to drug standardization in Canada. Generally, these practices can all be understood as examples of delegation. Delegation, here, is experimented with in two distinct though overlapping registers. In a sense straightforward to legal readers, delegation refers to the practice of one body conferring its powers to a subordinate body, whether this takes the form of a legislature conferring to the executive its powers to legislate, or a minister conferring to her officials (or committees) her powers to make statutory decisions,

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Dr. Cook of Ayerst, McKenna, & Harrison Ltd. She had "attended McGill, the only woman in her class, graduating in 1937 with a BA in Economics and Political Science" (despite the opposition of Stephen Leacock, the Chair of the department, to women studying economics, but with the support of her tutor Eugene Forsey). In the summer of 1943, when Cook had been stalling on providing input on two draft monographs for DES, Davidson approached Scott to enlist her help in securing Cook's reply. She died in Toronto in 2015 on her 102nd birthday. See Davidson's Committee Materials, 1943-1944; and Deaths: Rebecca Lee Taylor (nee Scott)", *The Globe and Mail* (7 March 2016), online: <http://v1.theglobeandmail.com/servlet/story/Deaths.20150307.93357518/BDAStory/BDA/deaths>.

[5] This thesis endeavours to bring women into the network, if in a limited way, by examining how they were represented and targeted in advertisements for estrogenic drugs and/or estrogenic cosmetics, and how National Health responded to those ads.

[6] Steve Woolgar & Javier Lezaun, "The wrong bin bag: A turn to ontology in science and technology studies?" (2012) 43:3 *Soc Stud Sci* 321 [Woolgar & Lezaun 2012"] at 327.

[7] *Ibid*.

subject to doctrinal constraints in administrative law, such as limitations on sub-delegation.[8] In another register, delegation alludes to technological practices that assign or distribute a task, action, or activity from one actor, human or nonhuman, to another.[9] While this could include legislators delegating the power to regulate to Cabinet members, as in the sense of delegated legislation, it is a much broader concept that also captures, for example, how socio-technical objects can serve as delegates.[10] This second sense of delegation is developed in subsequent chapters, as National Health materialized a potent estrogen by delegating responsibility for its safety to other humans and nonhumans, and as that object in turn sparked new regulatory practices. Yet it is introduced here as a reminder that National Health's practices of delegation were not merely legal but also socio-technical in nature, and to keep in sight that these regulatory practices had material effects.

1. Delegation and standard-setting under the *Food and Drugs Act* prior to 1940

The regulatory practices that brought estrogen to life in Canada were enacted with the *Food and Drugs Act.*[11] In this section, I set out the statutory backdrop to my regulatory history of estrogen. In the 1930s, National Health officials practiced multiple regulatory modes of standardizing drugs. All these modes of drug standardization relied on significant delegation, not all were lawfully authorized, and, though they could have been, none were applied to estrogen.

Passed in 1920, the *Food and Drugs Act* is one of Canada's oldest statutes. Its origins stretch back to the *Adulteration Act*,[12] which had targeted dishonest and fraudulent trade practices, particularly through offences against adulteration and misbranding. By the early twentieth century, with this focus challenged by the "age of advertising", the law's failure to protect public health with food and drug standards was viewed as increasingly outdated.[13] At that time, the

[8] Common law doctrine governing both such forms of delegation has changed remarkably little, over time, in Canada. However, as addressed in Chapter 4, the year 1943 witnessed a significant appellate decision, in the form of the *Chemicals Reference,* that was interpreted as further empowering the delegation of legislative powers and of ministerial powers respectively.

[9] See Chapter 1, section 2.i.

[10] *Ibid.* Latour introduced the concept of "delegation" to ANT, deploying it to study technology in a way that arguably tended to reinforce the stability of the technological object; see Latour 1992, Latour 1999a. See also Akrich 1992.

[11] Whenever the *Food and Drugs Act* or the *Act* is mentioned in the body of this text, reference is made to the 1927 consolidated statute, *An Act Respecting Food and Drugs,* RSC 1927, c 76, as amended ["*Food and Drugs Act*" or "*FDA*" or "*Act*"]. Whenever a later amendment is relied upon, the amending statute is also referenced. In the period addressed in this thesis, the *Food and Drugs Act* was often amended, including through the following enactments (excluding, from this list, the various amendments to the *Act*'s two Schedules made by orders in council): SC 1927, c 56; SC 1930, c 23; SC 1930, c 30; SC 1934, c 54; SC 1939, c 3; SC 1944-1945, c 22; SC 1945, c 7; SC 1946, c 23; and RS 1950, c 50.

[12] *An Act to Impose License Duties on Compounders of Spirits, Amend the Act Respecting the Inland Revenue, and To Prevent the Adulteration of Food, Drink and Drugs*, SC 1874, c 8.

[13] Robert E Curran, "Canada's Food and Drugs Act" (1946) 1 *Food Drug Cosm LQ* 492 ["Curran 1946"] at 492-3, 497-8.

federal government's jurisdiction to legislate in relation to food and drugs was not obvious, as the provinces had been assigned significant authority to legislate in relation to health and to the medical professions.[14] Thus, it was federal legislative authority over criminal law that provided the necessary foundation for the *Food and Drugs Act*.[15] In 1933 the British Columbia Court of Appeal confirmed as much, holding in *Standard Sausage Company v. Lee* that the *Act* was validly authorized by the federal criminal law power; the concurring opinion held that it was also sustained by the federal legislative power over peace, order, and good government.[16]

By 1939, the *Act*'s purpose was seen as twofold: to protect public health and the consumer's pocketbook. As put by Departmental legal adviser Robert Curran,[17] the *Act*, "as a consumer's statute, is concerned with the protection of the public, both as to safety and honesty".[18] By the start of the 1940s, this twofold purpose was increasingly pursued through setting and enforcing standards for food and for drugs, although these purposes were also promoted through labelling requirements prescribed in regulations under the *Act*.[19] As will be explained, drug standards were set through various means, including pharmacopoeial standards and delegated legislation.

Canada's turn to standards was generally consistent with American regulatory trends, as the 1920s and 1930s saw increased effort by the US FDA to lead, or influence, the development of drug standards.[20] Calls for uniformity came from many directions. US drug manufacturers wanted standards to make it easier to compete for wholesale buyers, while consumers wanted assurances of consistency and quality.[21] The *Pure Food and Drugs Act*, passed by Congress in 1906, had provided American administrators with only an anemic ability, however, to make delegated legislation; instead, it "in essence required all drugs and drug products listed in the USP and the NF to conform to the specifications and standards" set out in these two pharmacopoeial works.[22] In 1933, a bill was introduced to reform that act, though it took five

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[14] *British North America Act, 1867*, 30-31 Vict, c 3, ss 92(7), (13), and (16).

[15] *Ibid,* s 91(27); see also Robert E Curran, "Drug Legislation in Canada" (1956) 11 *Food Drug Cosm LJ* 590 ["Curran 1956"] at 593.

[16] [1933] 4 DLR 501 (BCCA) at 505-507 *per* Macdonald JA; and [1934] 1 DLR 705 (BCCA) at 716, 722 *per* Martin JA. At 723-725, Martin JA explicitly left open whether the *Act* might also be sustained under the trade and commerce power in s. 91(2). Neither judge facially limited his holdings to the constitutionality of certain provisions but appeared to uphold the *Act* on a global basis.

[17] Curran became the Department's in-house legal adviser in 1945; see Curran 1953 at 5.

[18] Curran 1946 at 494. The BC Court of Appeal endorsed this view of the *Act*'s twofold purpose; [1933] 4 DLR 501 (BCCA) at 507.

[19] Curran 1946 at 492-493, 498.

[20] Richard H Parrish II, "Negotiating Reality: The Construction of Enforceable Pharmaceutical Standards" (2002) 57 *Food & Drug LJ* 457.

[21] Gwen Kay, *Dying to be Beautiful: The Fight for Safe Cosmetics* (Columbus, OH: Ohio State University Press, 2005) ["Kay 2005"] at 59-60.

[22] Martin L Blake, "The Role of the Compendia in Establishing Drug Standards" (1976) 31 *Food Drug Cosm LJ* 276 ["Blake 1976"] at 288; see also William W Goodrich, "The Canadian Approach to Enforcement Problems" (1950) 5 *Food Drug Cosm LJ* 667.

years – and the Elixir Sulfanilamide crisis in 1937 – before the *Food, Drug, and Cosmetic Act* ("US FDCA") was passed in 1938.[23] The US FDCA generally maintained the existing focus on misbranding and adulteration, and more strongly affirmed the role of pharmacopoeias in supplying standards for drugs.[24] The most notable distinction, then, between Canadian and US legislation was that, under the US FDCA, US drug companies were required to provide information showing the safety of a new drug before it could be sold in interstate commerce.[25] The new drug approval process was first put to the test in a contested application to market DES.[26] By contrast, in Canada new drugs did not need approval, and DES and Premarin were marketed here before the US FDA approved them. This absence of pre-market approval for drugs in Canada markedly sharpens the significance of standards. To use a Premarin-inspired metaphor: with no legal ability to close the barn door before the horse bolted, Canadian regulators could nonetheless determine what a "horse" should be – and as will be seen, under the *Food and Drugs Act,* there was more than one way to standardize a horse.

In Canada, drug standards were not set out in the *Act*. Rather, they were delegated. Indeed, the *Food and Drugs Act* was, and remains today, a scheme heavily premised upon delegation. Delegated authority to make regulations – by 1927, confirmed to have the same force and effect as the *Act*'s provisions[27] – was a relatively new,[28] and sometimes controversial,[29] feature of the country's legislative landscape. From the outset, the *Act* granted the Governor in Council (in effect, Cabinet) broad powers to make regulations.[30] Such regulations were often issued in the form of orders in council and, depending on the source of authority, were published in the *Canada Gazette.*[31] In the 1930s and early 1940s, National Health officials routinely conceived, drafted, and submitted regulations and orders to Cabinet, with a review by their departmental

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[23] *Food, Drug, and Cosmetic Act of 1938,* c 675, 52 Stat. 1040 ["US FDCA"]; see also David Cavers, "The Food, Drug and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions" (1939) 6 *L & Contemp Probs* 2 ["Cavers 1939"]. With respect to the role of the Elixir Sulfanilamide crisis, see e.g. Kay 2005 at 103-14; and Cavers at 20, 40.

[24] See e.g. Blake 1976 at 288; Kay 2005 at 96-97; and Cavers 1939 at 27-30 (food) and 32-38 (drugs).

[25] Cavers 1939 at 20, 40; Watkins 2007 at 26-29. Another distinction is that, as of 1939, the US FDCA applied to cosmetics and the *FDA* did not.

[26] Langston 2010.

[27] *Food and Drugs Act*, s 3(3), as added by *An Act to Amend the Food and Drugs Act,* SC 1927, c 56, s 9.

[28] Other federal and provincial schemes relied on delegation, although none so foundationally as the *Food and Drugs Act.* The *Adulteration Act* had been amended in 1890 to give the Governor in Council authority to make standards; and in the *Act* in 1920, this power was enlarged and formalized to encompass delegated legislation. See Curran 1953 at 157; and Pugsley 1967.

[29] The literature, in the 1920s-1940s, on the merits or deficiencies of delegated legislation to democratic governance, in which realists pitted themselves against formalists, is far too large to summarize here. As late as the 1950s and 1960s, *Food and Drugs Act* administrators felt it necessary to defend the use of delegated legislation; see e.g. Curran 1953 at 158-159; Pugsley 1967.

[30] *Food and Drugs Act*, s 3. As will be discussed, statutory powers to make regulations were expanded in the next two decades.

[31] Subsection 3(2) required all regulations made under ss 3(a) and (b) to be published in the *Gazette.* In 1939, this provision was replaced by a requirement that *all* regulations made under *any* provision of the *Act* shall be so published; SC 1939, c 3, s 6.

solicitor, and sometimes also by Department of Justice counsel, for legal validity and form. In this period, National Health created a burgeoning suite of regulations aimed at standardizing the quality, purity, and, importantly for this history, the potency of drugs. Further, in this period, the development and adjustment of drug regulations started to become a constant, ongoing, and iterative process. The approach to delegated legislation under the *Food and Drugs Act* revolutionized Canada's approach to public health and to public administration more generally, becoming "very much the pattern and trend of legislation in Canada".[32]

By 1939, the *Act* and its administrators had come to embrace multiple modes – both lawful and unlawful – of delegating drug standards. Three key modes of delegation are summarized here: pharmacopoeial standards, regulated drug standards, and regulated standards specific to biologics. Pharmacopoeial standards were an ancient, traditional mode of governing the safety and composition of drugs. Texts prepared by physicians (sometimes jointly with pharmacists) to guide drug-making,[33] pharmacopoeia can colloquially be thought of as "recipe books" for drugs and therapeutic substances, originally for the benefit of druggists, with each drug identified and described in a monograph through various technical specifications – that is, through standards.

While the *Act* did not endorse or adopt any pharmacopoeia, the default drug standards were those set forth in the British Pharmacopoeia. One of the oldest, most respected pharmacopoeia, the British Pharmacopoeia was the only pharmacopoeial work that was, or had ever been, expressly referenced in the *Act*.[34] To be clear, the *Act* did not require manufacturers or pharmacists to comply with the British Pharmacopoeia; rather, the *Act* made it a default pharmacopoieal authority for determining if drugs were adulterated. Section 6 deemed drugs to be adulterated if they were sold under a name recognized in a pharmacopoeia or another authoritative work on drugs, yet they differed "from the standard of strength, quality or purity laid down therein". While manufacturers or pharmacists could pick any pharmacopoeia to which their drugs could conform,[35] if they wished a drug's quality to be judged under an authority other than the British Pharmacopoeia, they were required to name that authority when selling the drug. If they did not do so, then unless their drug conformed by default to the British

[32] Leonard I Pugsley, "Food Laws and Regulations in Canada" (1964) 19 *Food Drug Cosm LJ* 374 at 376; and Curran 1953 at 157.

[33] Glenn Sonnedecker, "The Founding Period of the US Pharmacopoeia: European Antecedents" (1933) 35:4 *PhH* 151 at 158-159. At 151, Sonnedecker provides a general definition of pharmacopoeia as a work that "contains pharmaceutical specifications that are intended to secure uniformity in the composition, quality, and therapeutic activity of medicines and that are made obligatory within a political unit by legally effective authority".

[34] *Food and Drugs Act*, ss 6(a) and 6(2). For interpretations by National Health staff of the nature of the priority given by s 6 to the British Pharmacopoeia, see e.g. Robert E Curran, "Canada's Food and Drug Regulations" (1949) 4 *Food Drug Cosm LQ* 391 ["Curran 1949"]; and Clarence A Morrell, "Administration of the Canadian Food and Drugs Act" (1950) 5 *Food Drug Cosm LJ* 656 ["Morrell 1950"].

[35] *Food and Drugs Act,* s 6(1).

Pharmacopoeia standard, it was deemed to be adulterated.[36] Canada was not unique in relying on pharmacopoeias in this way. Subject to institutional and statutory nuances, Britain and the US also relied on pharmacopoeias to supply presumptively official standards, likewise applying and enforcing those standards through adulteration or misbranding claims.[37]

The second way that the *Food and Drugs Act* contemplated the imposition of drug standards may seem more "standard", at least from a current vantage point. Paragraph 3(a) of the *Act* delegated to Cabinet the power to make regulations prescribing "standards of quality" for food and drugs.[38] This authority was rarely invoked though, as by the 1930s, it had effectively been overtaken and replaced by a new, third way to standardize drugs under the *Act*. This third mode is especially significant to this story. In 1927, the *Act* was amended to create new regulatory authorities for biological drugs. These amendments authorized standards that took precedence over any other standards contemplated by the *Act*,[39] and "for practical purposes, replace[d] the necessity for the authority in section 3(a)."[40] To achieve this, beyond widening the definition of drug,[41] the 1927 amendments authorized the standardization and control of biologics.[42]

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[36] *Food and Drugs Act,* s 6(2).

[37] Walton M Jr Wheeler, "Validity of Official Drug Standards" (1946) 1 *Food Drug Cosm LQ* 588; DM Dunlop & TC Denston, "The History and Development of the 'British Pharmacopoeia'" (1958) 2:5107 *BMJ* 1250 ["Dunlop & Denston 1958"] at 1251-1252.

[38] Relatedly, s 3(b) of the *Act* empowered regulations requiring that drugs be labelled. In 1939, this was replaced by a new s 3(b) which broadened powers over labelling and packaging, including for cosmetics; see SC 1939, c 3, s 3. The new s 3(b) was proclaimed into force as of August 1, 1939 *except* for the part of it related to cosmetics; Proclamation, 22 July 1939, *Canada Gazette,* Vol LXXIII, No 8, p 509 (August 19, 1939).

[39] For an articulation of this view that standards authorized by s 6(3)(a) took precedence over standards authorized by s 3(a), which turned on the phrase "not otherwise prescribed by this Act" in s 3(a) and on s. 6(4), see Curran 1953 at 176-177.

[40] *Ibid.* It is not wholly clear what the Department perceived as the central limitations of s 3(a). In this period, it continued to sometimes provide a source of authority for certain drug regulations, as noted here by Curran.

[41] *Food and Drugs Act*, s 2(c), as amended by SC 1927, c 56, s 1(2)(c).

[42] *Food and Drugs Act,* ss 6(3) and (4), as amended by SC 1927, c 56, s 2, and providing:

> (3) Notwithstanding anything contained in subsections one and two of this section, the Governor in Council may make regulations respecting any or all of the drugs mentioned or described in Schedule B to this Act, –
>
> (a) prescribing standards of quality and potency
>
> *(b)* defining official methods for biological testing which methods shall permit manufacturers to have biological tests made in any laboratory;
>
> *(c)* providing for the licensing of manufacturers preparing drugs mentioned or described in Parts II and III of Schedule B;
>
> *(d)* providing for the inspection of premises, equipment and technical qualifications of the staff of manufacturers preparing drugs mentioned or described in Parts II and III of Schedule B;
>
> *(e)* requiring that manufacturers of drugs mentioned or described in Part IV of Schedule B submit test portions of each and every batch of such drugs to be tested in the laboratories of the Department of Health, and requiring that only approved batches may be imported, sold or offered for sale;
>
> *(f)* prescribing a tariff of fees for inspection, licensing and biological testing.

Following legislative developments in Britain,[43] and in the US,[44] these 1927 amendments were specifically intended to facilitate the standardization and control of antitoxins, vaccines, viruses, sera, insulin, and other substances positioned as biologics. Given the centrality of potency to defining and standardizing biological drugs, and to ensuring their safety, potency was addressed for the first time in the *Act,* which now empowered regulations prescribing potency standards for drugs.[45] Furthermore, the 1927 amendments envisioned that bioassays – official methods for biological testing, by which potency was measured – would also be prescribed by regulation.[46] As explained in 1949 by A. Linton Davidson, long-serving Dominion analyst in the Food and Drug Division and unofficial chronicler of the history of the Department,[47] these amendments were intended to allow "for the standardization of which animals had to be used".[48] The amendments also empowered the government to impose regulatory controls on the manufacture of biologics, through licensing and inspections,[49] as well as through batch testing. Schedule B was also added to the *Act* through these amendments, or at least it was in intention, if not in the legally required form.[50] This made the regulations that followed, in 1928, technically

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> (4) Any drug mentioned or described in Schedule B to this Act shall be deemed to be adulterated if it has not been manufactured, tested and labelled in accordance with regulations made by the Governor in Council under this section, or if it differs in quality or potency from the standard for such drug established by such regulations.

[43] In Britain, biologicals were controlled under the *Therapeutic Substances Act, 1925*. Similar to Canadian law, the British statute did not limit the sale of biological drugs (i.e. through prescription requirements), but instead sought to control purity and potency of drugs through scientific testing and manufacturing controls; see Stuart Anderson, "From 'bespoke' to 'off-the-peg': community pharmacists and the retailing of medicines in Great Britain, 1900 to 1970" (2008) 50:2 *PhH* 43 at 49.

[44] In the US, biologics were not regulated under the 1906 *Pure Food and Drugs Act*. They were regulated under the 1902 *Act to Regulate the Sale of Viruses, Serums, Toxins and Analogous Products in the District of Columbia, to Regulate Interstate Traffic in Said Articles, and for Other Purposes,* Pub. L. No. 57-244, 32 Stat. 728, 42 U.S.C. §§ 141-48 (informally, the "Biologics Act" or the "Biologics Control Act"), and an act creating the US Public Health Service and its Hygienic Laboratory (later the National Institute of Health). In the 1930s and early 40s, these acts formed a biologics regime focused on testing, standardization, licensing, and inspection, aimed at ensuring products' purity and potency. See Von Schwerin, Stoff & Wahrig 2013 at 3-9; and Terry S Coleman, "Early Developments in the Regulation of Biologics" (2016) 71 *Food & Drug LJ* 544 ["Coleman 2016"].

[45] *Food and Drugs Act,* s 6(3)(a).

[46] *Food and Drugs Act,* s 6(3)(b).

[47] According to an obituary in 1950, Davidson had been "one of the best known members of the staff". Born in Montrose, Scotland in 1888, he received his pharmaceutical chemistry degree from the University of London in 1909. Emigrating to Canada after WWI, he worked briefly in industry and joined government in 1925. In the late 1940s, in association with the Department, he "produced an extensive history of the Food and Drug Divisions and was the author of the departmental book *Canada Pioneers in Food and Drug Control*, issued to mark the 75th anniversary of Canada's first such regulations. He launched, and continued to edit, the division's publication 'Food and Drug News – Canada.'" See Ministry of National Health & Welfare, "Davidson Obituary" (1950) 4:2 *The Food and Drug News (Canada): 75th Anniversary Issue* 1 ["Davidson Obituary 1950"].

[48] Davidson 1949b.

[49] These controls were only permitted for drugs on Parts II and III of Schedule B. Moreover, the amendments empowered but did not require licensing. This will be illustrated, in the next two chapters, by sex hormones, which were first enumerated on Part II (but were never made subject to any licenses for Part II drugs) and then, intriguingly, were moved to Part I in 1949.

[50] SC 1927, c 56, s 14. Due to an apparent drafting error, it was denoted in the consolidated Act later that year as "Schedule" rather than as "Schedule B"; see RSC 1927, c 76, Schedule. The drafting error was corrected legislatively in the next amendment to the *Act* in 1934; SC 1934, c 54, s 4. The fact that no "Schedule B" *existed* did not stop Cabinet, on the Department's request,

ultra vires, and just the first example of the many (often unlawful) delegations through which National Health would standardize and enact biological drugs in the coming decades.[51]

As envisioned in the 1927 amendments, Schedule "B" comprised Parts I through IV. One can cavalierly characterize these four parts as containing drugs derived respectively from vegetable, animal, bacterial, or mineral sources. More accurately characterized, Part II – the part arguably applicable to sex hormone products in the 1920s and 1930s – listed "Preparations of Pituitrin, Thyroid, Adrenalin and any other animal tissue preparations".[52] When Part II was first drafted in 1927, the few estrogenic preparations available were all made from animal tissues, typically ovarian extracts.[53] Indeed, it seems that Part II may have been intended originally to cover sex hormones. This view is bolstered by Davidson's views on the origins of the 1927 amendments, which drew upon his close working relationship assisting Harry Lancaster throughout their long careers at National Health. Lancaster was the Chief Dominion Analyst from 1923 to 1945,[54] head of the Food and Drug Division, and deeply involved in preparing the 1927 amendments. These amendments, according to Davidson, were motivated by rapid changes in pharmacology, biologics, and endocrinology in the 1920s, and challenges in standardizing existing biologics like digitalis and ergot; overall, he felt that the "real reason for amending the Act" in 1927 was that:

> "Again, drugs of animal origin, for example, pituitary, epinephrine and sex hormones were coming into vogue and called for special legislative treatment. The great field of viruses, serums, toxins, vaccines and other bacterial products were engaging increased attention in the medical world … the need for control of such remedies in Canada was considered a matter of urgency."[55]

Though nothing suggests these developments did not motivate the bill, the amendments also served to build the bureaucratic machinery at National Health. Davidson himself notes that the bill received "much criticism" in the House of Commons and some opposition in the Senate. Delegated legislation was a new feature of governance in Canada, and Parliamentarians were apprehensive to extend these powers as they "raised the spectre of a still wider bureaucracy".[56]

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from purporting to exercise its authority in relation to "Schedule B drugs", by making regulations governing the "Schedule drugs", in 1928. To avoid confusion, the remainder of this chapter refers to the 1927 Schedule to the *Act* as "Schedule B".

[51] While I have not obtained any solicitor-client advice sought or received by National Health on this issue, any departmental legal advisors, who were tasked with reviewing the form and validity of regulations, likely would have advised National Health officials that they lacked jurisdiction to make regulations for any "Schedule B" drugs until something called Schedule B existed.

[52] Part I listed "Preparations of Strophanthus, Digitalis, Ergot and any other vegetable preparations for which biological tests are deemed necessary"; Part III listed "Serums, Viruses; Toxins, Vaccines; Analogous biological preparations"; and Part IV listed "Organic compounds of arsenic and analogous preparations prepared for parenteral medication".

[53] See Chapter 1, section 1.ii, particularly some of the content associated with notes 11-15, 87-89, and 95-96.

[54] Cameron 1959 at 321.

[55] Davidson 1949a at 67; and Davidson 1949b.

[56] *Ibid.*

After the 1927 amendments were enacted, National Health officials immediately began to draft the requisite regulations. Davidson, Lancaster, and Dr. Harris – the latter, as the Chief of the Laboratory of Hygiene,[57] would assume new responsibilities for researching and testing biologicals – together "spent many afternoons on this in the late summer and early fall of 1927".[58] What became known as the "Biological Products Regulation", or simply the "Biologicals Regulation", was made on February 6, 1928, as part of the wider Food and Drug Regulations.[59]

No provisions of the 1928 Biologicals Regulation referred specifically to sex hormones. However, understanding how the 1928 Biologicals Regulation defined and standardized the quality and potency of biological drugs is critical to appreciating the divergent approach that would later emerge in the mid-1930s, and that would transmogrify yet further in the 1944 Sex Hormone Regulations. The first part of the 1928 Biologicals Regulation addressed three plant-based drugs mentioned on Part I of the Schedule – digitalis, strophanthus, and ergot.[60] These plant-based drugs were legally defined according to their source material – for example, the leaves of the digitalis plant – as well as according to the means by which they were extracted therefrom. For each of these drugs, the Biologicals Regulation fixed standards of quality by identifying a standard reference material, kept by the Laboratory of Hygiene and obtainable on application. Furthermore, as envisioned by the *Act,* for these drugs, the Biologicals Regulation also explicitly prescribed both quantitative potency standards and specific biological test methods for measuring potency. Thus, for digitalis, the regulations prescribed detailed bioassay methods set out in Appendix A to the regulations; for strophanthus, the regulations adopted the bioassay methods used in the tenth revision to the US Pharmacopoeia ("USP X"); and for ergot, the method prescribed for biological testing was either that described in Appendix B or that in

[57] In the 1920s and 1930s, the Food and Drug Division and the Laboratory of Hygiene were organized as separate units in the Department. As stated by Curran, "[t]he Food and Drug Division is responsible for the administration and enforcement of the Act", while the "Laboratory of Hygiene is by administrative arrangement, responsible for the biological control of the products mentioned in Part III of Schedule B", and "undertakes the inspection of premises, equipment and technical qualifications of the staff of manufacturers preparing drugs mentioned or described in Parts II and III of Schedule B, and it is also responsible for special services in relation to the enforcement work of the Food and Drug Division, such as the identity of certain drugs". Until 1945, Lancaster administered the Food and Drug Division as the Chief Dominion Analyst; see Curran 1953 at 193. The Laboratory of Hygiene was established in 1921. It was envisioned to operate as a national public health laboratory. It hired its first pharmacologist in 1923 and its second in 1928. See Pugsley 1967; Davidson 1949b; and Cameron 1959 at 321, 330.

[58] Davidson 1949a at 67.

[59] PC 1928-127 (6 February 1928) (Regulations for Fixing Standards of Quality and Potency, and Defining Official Methods of Biological Testing of Drugs mentioned or described in Schedule, Part 1 of the Food and Drugs Act, RS 1927; Proposed Regulations for the Licensing, Manufacture and Sale of Drugs listed in Schedule B, Part II of the Food and Drugs Act, RS, 1927, hereinafter referred to as Biological Products; and Regulations for Fixing Standards of Quality and Potency, and Defining Official Methods of Biological Testing of Drugs mentioned or described in Part IV, of the Schedule of the Food and Drugs Act, RS 1927) [together, the "1928 Biologicals Regulation"], in *Canada Gazette,* Vol 61, Supp, pp 15-26 (February 18, 1928).

[60] At this time, Part I stated "Preparations of Strophanthus, Digitalis, Ergot and any other vegetable preparations for which biological tests are deemed necessary".

the USP X.[61] This same approach to prescribing identity and potency was taken for most of the animal-based drugs and bacterial drugs described respectively in Parts II and III of Schedule B – such as pituitary extract, thyroid, epinephrine, and antitoxins for diphtheria and tetanus – with the regulations defining these drugs by source material, prescribing quality and identity through standard reference materials, and prescribing biological methods for testing their potency either by incorporating scientific test methods or referring to methods in existing pharmacopoeias.[62]

Within a few years of the Treaty of Westminster, in July 1934, National Health secured from Parliament a further delegation of authority to create Canadian drug standards. In 1933, Lancaster had unsuccessfully advocated, in tandem with academic pharmacologists, that the *Act* should be amended to allow Cabinet to add any drug to Schedule B at the request of a new committee comprising representatives of the Canadian Medical Association, the Canadian Pharmaceutical Association, and the Canadian Pharmaceutical Manufacturers Association. Their goal had been to incorporate, *holus bolus* into the *Act,* the 1932 addendum to the British Pharmacopoeia prepared by Canadian academic physicians and pharmacists.[63] While this proposed amendment was rejected before reaching Parliament, the *Act* was amended to better enable ready use of Schedule B. Specifically, substances could now be added to or removed from Schedule B by regulation, rather than by legislation, where the Minister of Pensions and National Health deemed that addition or removal to be "necessary in the public interest".[64]

On the heels of this amendment, the Biologicals Regulation was repealed and replaced, in August 1934.[65] In a move that, a decade later, would be rejected as unlawful sub-delegation in the specific – and the limited – context of sex hormone products,[66] National Health officials changed their regulatory approach to measuring the potency of biological drugs. For the three

[61] 1928 Biologicals Regulation, at pp 15-16 and 25-26.

[62] *Ibid* at pp 19-23. For the arsenicals and organic chemicals in Part IV, the 1928 Biologicals Regulation defined these substances by chemical name rather than source material, and rather than bioassays for potency, they prescribed tests for toxicity.

[63] EA Driedger's Schedule B File, 1943 at 71-75. See also the content associated with *infra* notes 113-115.

[64] *Food and Drugs Act,* s 3(i), as amended by SC 1934, c 54, s 1. The 1934 amendments also added a prohibition against import or sale of any remedy represented as a treatment for the diseases listed in a new Schedule A to the *Act,* which included, for example, cancer, diabetes, tuberculosis, alcoholism, influenza, and sexual impotence; *Food and Drugs Act,* s 6A, as amended by SC 1934, c 54, ss 2 and 4. Additionally, the drafting error in the 1927 amendments was corrected, such that the heading "Schedule" was now properly revised to "Schedule B"; *Food and Drugs Act,* Schedule B, as amended by SC 1934, c 54, s 4.

[65] PC 1934-123/1852 (16 August 1934) (Regulations for Fixing Standards of Quality and Potency, and Defining Official Methods of Biological Testing of Drugs Mentioned or Described in Parts I and II of Schedule B of the Food and Drugs Act, RS 1927; Regulations for the Licensing, Manufacture and Sale of Drugs Listed in Parts II and III, Schedule B of the Food and Drugs Act, RS 1927; and Regulations for Fixing Standards of Quality and Potency and Defining Official Methods of Biological Testing of Drugs mentioned or described in Part IV, of Schedule B of the Food and Drugs Act, RS 1927) [together, the "1934 Biologicals Regulation"] in *Canada Gazette,* Vol LXXV, No 3, Supp, pp 16-27 (September 28, 1934).

[66] See Chapter 4, section 2, particularly that content associated with notes 98-135.

plant-based products on Part I,[67] and for some animal hormone products such as thyroid, pituitary extract, and epinephrine on Part II,[68] while they continued to prescribe quantitative potency units,[69] the 1934 Biologicals Regulation no longer set forth any official biological test methods. Despite that paragraph 6(3)(b) of the *Act* contemplated that regulations would define the official methods for biological testing, for these drugs, the 1934 Biologicals Regulation instead subdelegated the selection of test methods to departmental scientists, providing that official bioassay methods would be whatever methods were employed in the Laboratory of Hygiene, details of which could be obtained upon application to the Chief of the Laboratory.[70]

As in 1928, none of the provisions of the 1934 Biologicals Regulation expressly applied to sex hormones. Did National Health officials ever apply the general provisions of these regulations to estrogenic products? Despite Davidson's view that the "real reason" for the 1927 amendments empowering these regulations included a need to regulate sex hormones, it appears not. In governing the license, manufacture, and sale of animal-based drugs, the 1934 Biologicals Regulation included a newly broadened licensing provision, requiring a license to manufacture products that were "a virus, serum, toxic, antitoxin, a preparation of pituitrin *or other animal tissue preparation, or a product analogous thereto, and of established value in the prevention or treatment of diseases of man, and intended for parenteral administration*".[71] This echoed US regulations, in 1934, that required satisfactory evidence of therapeutic efficiency before a license could be granted to a new biological product, driven by concern to not bestow "worthless drugs with the imprimatur of a governmental license".[72] Indeed, as historians have shown, in the 1930s, estrogenic products were arguably not of "established value" in treating diseases in man (let alone in women).[73] Leaving that important point aside, as of 1934, many estrogenic products were clearly injectable "animal tissue preparations", made from ovaries, and had they wished to National Health officials could have required their manufacturers to obtain licenses.

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[67] 1934 Biologicals Regulation at pp 16-17. While the three plant-based drugs remained digitalis, strophanthus and ergot, the 1934 regulations expanded their coverage to include additional types of products derived from these plants.

[68] *Ibid* at 17 and 21-26.

[69] *Ibid* at 17 (with the exception of ergot, for which the potency standard prescribed by the regulations was instead a material standard of activity: "whatever is equal to the specific activity of the standard preparation when tested biologically").

[70] *Ibid* at 17 (thyroid) and 21 (pituitary and epinephrine).

[71] 1934 Biologicals Regulation (specifically, the Regulations for the Licensing, Manufacture and Sale of Drugs Listed in Parts II and III, Schedule B of the Food and Drugs Act, RS 1927), s 1 at p 18 (emphasis added).

[72] Coleman 2016 at 595, and also see 594.

[73] See Chapter 1, section 1.i., particularly that content associated with notes 39-44.

By this time, some estrogenic products were not made from ovarian extracts but from urine.[74] Furthermore, materializing estrogen from urine, whether expelled by women or horses, was a particularly Canadian undertaking. In 1930, McGill University endocrinologist Dr. James Collip, in partnership with the new Canadian drug company Ayerst, McKenna & Harrison Ltd.,[75] first extracted estrogen from pregnant Canadian women's urine. By 1933, Ayerst was marketing Emmenin, one of the "first orally active estrogens, distributed in the palatable form of sugar-coated tablets", for clinical uses.[76] Did National Health officials consider urine-based estrogenic drugs like Emmenin to be animal tissue preparations, or "a product analogous thereto",[77] for licensing purposes? Again, it appears not. Digging into National Health's licensing practices, it does not seem that the Department ever issued a license under the 1934 Biologicals Regulation for any sex hormone product. From time to time, the Department would publish, in the *Canada Gazette*, lists of those firms that were licensed to manufacture drugs listed in Parts II and III of Schedule B, accompanied by an identification of the types of preparations for which each such firm was licensed. [78] While sex hormone manufacturers such as Ayerst, Abbott, and Parke, Davis & Co. appeared on these lists, sex hormone preparations did not.[79]

Whatever was restraining National Health from applying the regulations to estrogenic drugs, it does not appear to have been the statute. Admittedly, Schedule B of the *Act* was limited, in Part II, to animal tissue products, and drugs like Emmenin were made from human urine. However, National Health did not otherwise let this statutory wording limit its regulatory practices. For example, in another instance of endemically unlawful delegation typifying Canada's regulation of biologics, the 1934 Biologicals Regulation were amended in 1942 to purport to cover not just animal tissue preparations as authorized by Part II, but also human tissue preparations.[80]

Nor was this regulatory restraint reflective of satisfaction with the situation amongst Canadian medical professionals. By the late 1930s, Canadian physicians were frustrated by the failure to

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[74] See *supra* note 53.

[75] Ayerst was founded in 1924; see Raison 1969 at 15. It was granted letters patent in January 1925; see Government Notices, *Canada Gazette,* Vol LVIII, No 81, p 2257 (January 25, 1925).

[76] Li 2002 at 103; Haraway 2012 at 308, 314 (fn 5).

[77] The 1934 Biologicals Regulation, in further defining "biological products", appeared to consider analogous products as analogous only to a virus, serum, toxin or antitoxin; see 1934 Biologicals Regulation (specifically, the Regulations for the Licensing, Manufacture and Sale of Drugs Listed in Parts II and III, Schedule B of the Food and Drugs Act, RS 1927), s 11 at p 18. While s 1 of this part of the regulations required licenses for products of established value in treating disease, in defining analogous products, s 11 used a lower threshold of "*applicable to* the prevention or treatment of diseases".

[78] These notices do not appear to have been required by any provision of the 1934 Biologicals Regulation.

[79] See e.g. Government Notices, List of Firms Licensed for the Manufacture of Drugs Mentioned in Parts II and III, Schedule "B", Food and Drugs Act, *Canada Gazette,* Vol LXXV, No 3, p 173 (July 19, 1941).

[80] 1942 Biologicals Regulation, s 11 at p 2172; see Chapter 4 at note 126.

standardize estrogenic products, writing in journals about how much "confusion has arisen from the many and varied trade names under which the oestrogenic preparations are dispensed, and the fact that there are two international units of different potency complicates the picture".[81]

National Health's apparent indifference to estrogen in the 1930s was also not the result of any lack of pharmacological expertise or knowledge of bioassay methods amongst its staff. In the latter half of the 1930s, under Dr. Harris, the Laboratory of Hygiene was steadily expanding its research activity, including through new research on the standardization and control of biologics.[82] Its pharmacological section was led by Harvard-trained pharmacologist Dr. Clare Morrell,[83] who had expertise in bioassays, including plotting and calculating dose-response curves with statistical techniques.[84] Morrell developed official methods of assay that could be distributed to manufacturers and used to test their products, and collaborated on scientific subcommittees of the British Pharmacopoiea Commission and the US Pharmacopoeia Revision Committee.[85] In 1936, Dr. Leonard Pugsley, a biochemist who had trained at McGill, joined the Laboratory to do work on sex hormones. Sex hormones were at the center of much of the Laboratory's growing activity; according to Davidson, "[b]y the time the Second Word War broke out, extensive work was being done on vitamins, liver oils and extract, and sex hormones."[86]

Nor did Canadian regulatory inaction wholly track American approaches. Admittedly, in the US, sex hormones (and other glandular preparations) had long been carved out of the legislative and licensing regime that existed for biologics; legally speaking, hormones were not biologics in the US.[87] This did not diminish American compliance activities, however. In the second half of the 1930s, the US FDA was busily enforcing the US FDCA and its predecessor statute against estrogenic preparations. As explained by two scientists with the US FDA's

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[81] EA Trites, "The Treatment of Functional Menstrual Disorders" (Jan 31, 1940) XVI:4, *The Bulletin of the Vancouver Medical Association* 97 ["Trites 1940"] at 100, in UBC Open Collections, History of Nursing in Pacific Canada, online: <https://open.library.ubc.ca/collections/historyofnursinginpacificcanada>.

[82] Dr. GDW Cameron succeeded Dr. Harris as the new Chief of the Laboratory of Hygiene in 1939; see Cameron 1959 at 322.

[83] One of two divisions within the Laboratory of Hygiene in the late 1930s, after WWII, the pharmacology section was incorporated into the new Food and Drug Directorate; see Davidson 1949b.

[84] For some of his research, see CW Chapman and CA Morrell, "On the biological assay of strophanthus" (1931) 4 *Quart J Phar & Pharm* 195; CW Chapman & CA Morrell, "On the biological assay of digitalis and strophanthus" (1932) 45 *J Pharm & Exp Thera* 229; CW Chapman & CA Morrell, "The potency and standardization of digitalis in Canada" (1934) 31:3 *Can Med Assoc J* 400; CA Morrell & CW Chapman, "Recent developments in pharmacology", (1934) 53:21 *Chemistry and Industry* 467; and Leonard I Pugsley & Clarence A Morrell, "Variables Affecting the Biological Assay of Estrogens" (1943) 33:1 *Endocrinol* 48.

[85] By the early 1940s (and perhaps earlier), Morrell was an auxiliary member of the USP Subcommittee on Biological Assays, and by early 1943, he was a member of the USP Advisory Committee on the Standardization of Insulin; see January 12, 1943 memorandum from Morrell to Cameron, in Library and Archives Canada, Department of Health fonds, RG 29, volume 248, file no. 339-4-1 (Part 5) 1940 to Oct 1943 ["Lancaster's File, 1940-1943"].

[86] Davidson 1949a at 82, and see also at 77-81; Davidson 1949b; and Cameron 1959 at 350.

[87] Coleman 2016 at 577-578, 598-600, and 604-606.

Division of Pharmacology, a sex hormones unit had been established in 1935 "for the purpose of making investigations of these products by use of the recognized methods available for some of them and for the purpose of the investigation of new methods for the assay of others."[88] Ensuing prosecutions enforced misbranding and adulteration prohibitions against estrogenic products. Many preparations, particularly those in oil solutions, were found to have a potency that was "quite high". However, the most common legal allegation was essentially that estrogenic preparations had a *lower* potency than labelled.[89] For example, a prosecution involving Follicovar, which "contained approximately 25 percent of the number of International Units of ovarian follicular hormone declared on the label", alleged adulteration as the product's strength fell below the professed standard under which it was sold.[90] Apparently unimpeded by the variance in manufacturers' potency units and test methods, these prosecutions targeted sex hormone preparations the potency of which was expressed in everything from "International Units", to "mouse units", to "Rat Units Standardized by the vaginal smear method".[91]

At base, National Health's inaction simply reflected – and performatively enacted – the fact that, in the 1930s, estrogenic drugs were neither very prevalent nor demonstrably effective for identified diseases. This challenges conventional wisdom that if a technology is unregulated, its sale and use will increase. As will later be seen in the context of the Sex Hormone Regulations, however, National Health officials were concerned that extending regulation to sex hormone products would equate to an *endorsement*. The same concern had driven, for three decades, the US Public Health Service's resistance to licensing hormonal products derived from glands "because it thought that most of them were worthless, although basically safe, and that a license would be seen as a governmental determination that they were effective."[92] Recognizing

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[88] Jack M Curtis & Ewald Witt, "Activities of the Food and Drug Administration in the Field of Sex Hormones" (1941) 1:4 *J Clin Endocrinol* 363 ["Curtis & Witt 1941"] at 363.

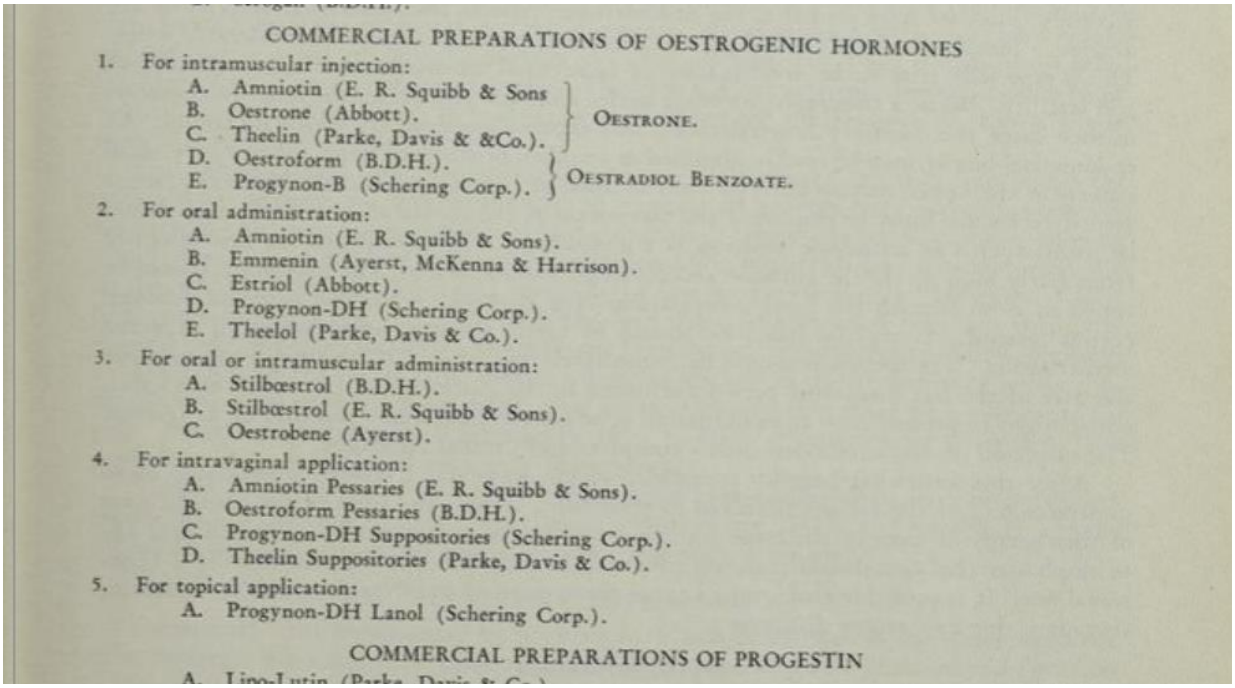
[89] *Ibid* at 364, also stating that "[l]egal action has been concluded against a number of the preparations found to be deficient in their labelled potency". For examples of prosecutions alleging that potency was lower than claimed, see *U.S. v 174 Boxes of Cristallovar*, Notices of Judgment under the Food and Drugs Act, No. 28698 (S.D.N.Y., October 13, 1937); and *U.S. v. 2 Packages, 2 Packages and 8 Packages, each containing six 1-ec Ampuls of Thelestrin Ovarian Follicular Hormone*, Notices of Judgment under the Food and Drugs Act, No. 27268 (D. Mass., May 17, 1937).

[90] *U.S. v Hypo-Medical Corporation,* Notices of Judgment under the Food and Drugs Act, No. 30321 (S.D.N.Y., January 11, 1939).

[91] See e.g. *U.S. v 353 Boxes, et al of Endofolllicolina*, Notices of Judgment under the Food and Drugs Act, No. 28325 (S.D.N.Y., October 13, 1937); and *U.S. v 5 Packages of Ampacoid Estrogenic Hormone,* Notices of Judgment under the Food and Drugs Act, No. 26973 (E.D. La., January 6, 1937).

[92] Coleman 2016 at 577. As an early example of this concern to not endorse hormonal products, he quotes from a 1909 PHS memo opposing licensing: "[M]ost of these organo-therapeutic preparations are in the experimental stage; but few of them are really useful and but a few of them are occasionally harmful; with the exception, perhaps, of adrenalin, these glandular extracts cannot be standardized; to license them would give respectability to a class of drugs some of which are on the borderline of being non-ethical; to license these preparations would serve little or no useful purpose, and it is doubtful if they may be properly considered as either viruses, serums, toxins or analogous products under the Law of July 1, 1902"; at 577-578.

through regulation that a substance was a drug served as official sanction. Critically, from this perspective, regulation as was much about enacting estrogen – calling it into action – as constraining it. Despite repeated delegations of authority to standardize biologics between 1927 and 1942, National Health did not deploy these delegations to sanction sex hormones as therapeutically effective drugs, and, in partial consequence, estrogen remained marginal.



COMMERCIAL PREPARATIONS OF OESTROGENIC HORMONES

1. For intramuscular injection:
   - A. Amniotin (E. R. Squibb & Sons
   - B. Oestrone (Abbott).
   - C. Theelin (Parke, Davis & &Co.). } Oestrone.
   - D. Oestroform (B.D.H.).
   - E. Progynon-B (Schering Corp.). } Oestradiol Benzoate.
2. For oral administration:
   - A. Amniotin (E. R. Squibb & Sons).
   - B. Emmenin (Ayerst, McKenna & Harrison).
   - C. Estriol (Abbott).
   - D. Progynon-DH (Schering Corp.).
   - E. Theelol (Parke, Davis & Co.).
3. For oral or intramuscular administration:
   - A. Stilbœstrol (B.D.H.).
   - B. Stilbœstrol (E. R. Squibb & Sons).
   - C. Oestrobene (Ayerst).
4. For intravaginal application:
   - A. Amniotin Pessaries (E. R. Squibb & Sons).
   - B. Oestroform Pessaries (B.D.H.).
   - C. Progynon-DH Suppositories (Schering Corp.).
   - D. Theelin Suppositories (Parke, Davis & Co.).
5. For topical application:
   - A. Progynon-DH Lanol (Schering Corp.).

COMMERCIAL PREPARATIONS OF PROGESTIN

Figure 1: List of 18 estrogenic preparations commercially available in Canada as of 1940

From EA Trites, "The Treatment of Functional Menstrual Disorders" (1940) XVI:4 *Bulletin of the Vancouver Medical Association* 97 (UBC Open Collections, History of Nursing in Pacific Canada)

Indeed, by early 1940, according to a contemporaneous account, only 18 estrogenic products, prescribed mostly for menstrual disorders, were available commercially in Canada. Most of the 18 preparations were based on estrone or estradiol benzoate. Yet as the list above shows, a couple were new creatures – not animal, vegetable, bacterial, or mineral, but stilboestrol.[93] Within less than a year of the synthesis of DES, these new DES products, developed for parenteral and oral use, had arrived.[94] In two years, Premarin would join them.

[93] Stilboestrol was the British name for what was referred to in the US as DES; see the Introduction at notes 46-48.

[94] The first ad in Canada for DES that I have located is dated April 30, 1939. However, my search was not exhaustive, and it is possible that DES was marketed somewhat earlier. See British Drug Houses Ltd advertisement, (April 1939) XV:7 *The Bulletin of the Vancouver Medical Association* at 191, in UBC Open Collections, History of Nursing in Pacific Canada, online: <https://open.library.ubc.ca/collections/historyofnursinginpacificcanada>.

Turning away from drug standards and to other statutory provisions relevant to estrogen, in 1939, cosmetics arrived on the legislative agenda. In 1938, US food and drug law had been extended, for the first time, to cover cosmetics.[95] In response to the US FDCA, in the spring of 1939, Parliament hastily passed amendments to the *Food and Drugs Act*, including a new definition of drug (making "any cosmetic" a drug), a definition of cosmetics, a provision related to cosmetic packaging, and a provision empowering the licensing of cosmetics manufacturers.[96]

While many of the 1939 amendments were proclaimed into force as of August 1, 1939, the cosmetic provisions, which comprised half of the bill, were not.[97] Davidson and others argued, implicitly, that masculine war efforts were more important than feminine beauty products, claiming that the reason the government refused to bring the cosmetic legislation into force was because of WWII. Ironically, Davidson then continued his account by writing that "[t]he outbreak of the Second World War in September 1939, had little immediate effect upon the Food and Drug Division since its work is equally essential in war and in peace".[98] Cosmetics were surely not the highest priority of the Canadian government in August 1939, yet the same could be said of matters addressed by the amendments that *were* brought into force that month (like preconditions to customs entry, or misleading advertisements).[99] The better explanation may be that, before the bill passed, there had been murmurs that its cosmetic provisions might not be constitutional.[100] Indeed, Davidson acknowledged that "questions of validity loomed" regarding

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[95] The US FDCA provisions applicable specifically to cosmetics did not come into force until July 1, 1939 (except for a provision relating to coal tar dyes used in mascara, eyebrow dyes, etc); see Kay 2005 at 105.

[96] SC 1939, c 3, ss 1, 2, 3 and 5. In 1939, the Dominion Council of Health expressed concerns over the unrestricted sale of potent drugs to the general public; see Curran 1953 at 130, citing Grant L Kalbfleish's article entitled "Prescription Drug Legislation" in the February 1952 issue of the *Canadian Pharmaceutical Journal.* In response to these concerns, the 1939 amendments also empowered regulations prohibiting the sale or defining the conditions of sale of any substance which may be injurious to health when used as drug – allowing certain drugs to be sold only on prescription – and restricting use of injurious substances as drug ingredients; *Food and Drugs Act,* s 3(k), as added by SC 1939, c 3, s 5. Paragraph 3(k) came into force on August 1, 1939; Proclamation, 22 July 1939, *Canada Gazette,* Vol LXXIII, No 8, p 509 (August 19, 1939). Regulations setting out prescription drugs were not made under this power until 1941; see Chapter 4, section 1.i., particularly content associated with notes 24-26.

[97] For the Proclamation, see *ibid.*

[98] Davidson 1949b. Similarly, Pugsley attributed the failure to bring these provisions into force to "the outbreak of the war and the difficulties encountered in obtaining qualified personnel to enforce the cosmetic regulations", and he incorrectly claimed that "the portion of the Act dealing with cosmetics was not brought into force until 1946"; Pugsley 1967. He likely relied on Curran's book, in which Curran had likewise argued that the cosmetics provisions were held up due to the war, and likewise erroneously claimed the provisions were brought into force in 1946; see Curran 1953 at 155. Curran did go on to acknowledge that "[b]ecause of the constitutional decisions respecting attempts in federal legislation to regulate particular trades and industries through forms of licensing or other devices, doubt might well be cast on the validity of such a provision", at 155.

[99] SC 1939, c 3, ss 7 and 8.

[100] Library and Archives Canada, "Powers to License Manufacturers of Cosmetics if Section 3(j) of Food & Drugs Act is Unconstitutional", RG 13, Vol 2635, file no 9-150108. This file was partially released under the *Access to Information Act,* LAC file no. A201700062, on May 19, 2017, and after a complaint to the Office of the Information Commissioner, fully released on January 29, 2018 ["EA Driedger's Cosmetics Regulation File, 1946-1947"]. In January 1946, Driedger opined that section 3(j), the cosmetics licensing provision in the bill, was unconstitutional. His opinion indicates that, in 1938, the provision "was reviewed in this Department in its draft stages and although the constitutionality of the provision in question does not appear to have

the bill in the House and Senate.[101] Moreover, the government declined to proclaim another provision, unrelated to cosmetics, which one suspects may have attracted legal concerns.[102]

By 1939, estrogenic cosmetics were on the Canadian market.[103] As Parliamentarians were debating the cosmetics bill, departmental officials were discussing whether to act on estrogenic preparations advertised for breast enhancement. In March 1939, Davidson brought his supervisor's attention to an advertisement for S-8 Brand Hormone Preparations, a product represented as "restoring the breasts to the graceful contours and firmness of youth". [104] While characterizing the product as a cosmetic and not a drug – landing it outside the Department's statutory jurisdiction – Davidson nonetheless proposed investigatory efforts. In response, Aime Valin, the Assistant Chief Dominion Analyst, advised Davidson to take "no action for present".[105]

The start of the 1940s was a turning point in Canadian drug regulation. Despite the economic depression of the previous decade, the pharmaceutical industry in Canada had been expanding. New Canadian drug companies had opened in Toronto and Montreal; and British, American, and even Swiss companies had set up subsidiary operations in Canada.[106] With demand high and supply low, drug manufacturing would expand in Canada during WWII.[107] Relatedly, the 1940s would also witness a major expansion of National Health's ambitions and activities. In the wake of the Treaty of Westminster, senior officials seized the moment to make Canada-specific food and drug regulations. Though there had been little regulatory activity under the 1934 amendments and Schedule B in the 1930s, this was about to change. During WWII, National Health took further opportunities to distance Canadian drug regulation from

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been considered at any length, the then Deputy Minister of Justice did state in his letter of December 30, 1938, with respect to this amendment that "the breadth of the field of "jurisdiction sought here may occasion contention but "I am not prepared to object to the form of the paragraph "as drafted"." See also Chapter 5, section 1, content associated with notes 7-8.

[101] Davidson 1949a at 81.

[102] Only one provision, unrelated to cosmetics, was not proclaimed to come into force on August 1, 1939. It purported to permit a sub-delegation of federal powers to provincial officials, empowering regulations "for designating as Dominion analyst …upon the request of any province, city or other municipality, any duly qualified analyst then and for such time as the said analyst shall remain so employed by the said province, city or other municipality…"; SC 1939, c 3, s 4.

[103] Beginning in 1931, Toronto newspapers carried occasional advertisements for consultation sessions or for hormone facial treatments, in person, at the Helena Rubinstein salon at 126 Bloor Street West. While my search was not exhaustive, the earliest advertisement located which offered a hormone "beauty aid" product for sale, rather than a salon treatment, dated to 1938; see *The Globe and Mail (1936-Current)* (27 May 1938), p 11, ProQuest Historical Newspapers: The Globe and Mail.

[104] "Venus de Milo" advertisement (March 1, 1939), in Food and Drug Newspaper Clippings, 1938-1940.

[105] Analyst's Report from AL Davidson to JGA Valin (March 22, 1939), in Food and Drug Newspaper Clippings, 1938-1940.

[106] Raison 1969 at 17.

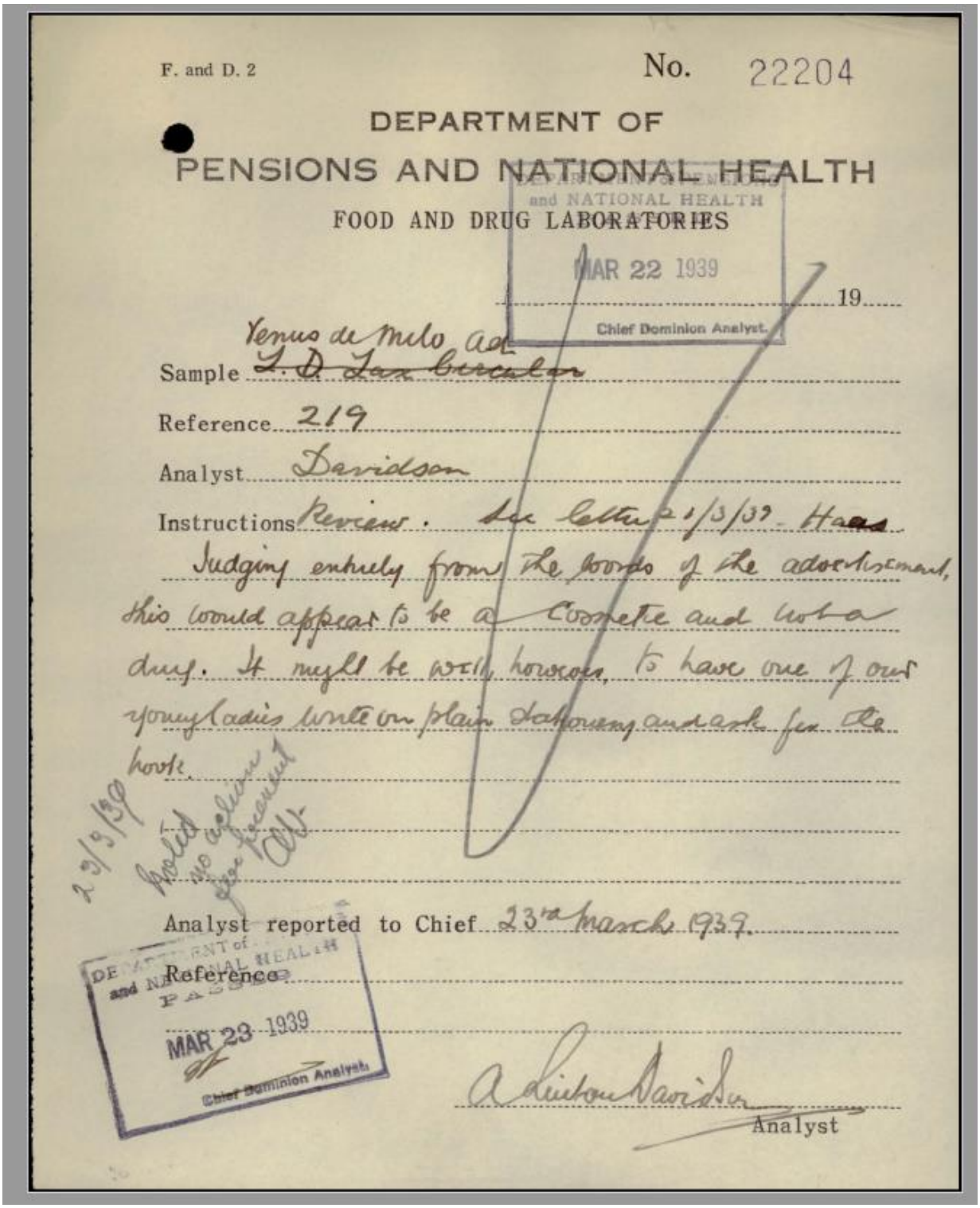
[107] Davidson 1949b.

Britain, and expanded its workload and its bureaucratic machinery significantly; as just one example, the sampling done by the Laboratory of Hygiene tripled between 1938 and 1944.[108]

Figure 2: "Venus de Milo" advertisement for S-8 Brand of Hormone Preparations, *The Montrealer,* March 1, 1939

Library and Archives Canada, RG 29, Vol 258, File 347-6-6 (Part 2), reproduction copy number e-011195706

[108] *Ibid.*



F. and D. 2

No. 22204

DEPARTMENT OF

PENSIONS AND NATIONAL HEALTH

FOOD AND DRUG LABORATORIES

and NATIONAL HEALTH
MAR 22 1939
Chief Dominion Analyst.

19

Sample Venus de Milo and L.D. Tan Circulan

Reference 219

Analyst Davidson

Instructions Review. See letter 21/3/39. Haas

Judging entirely from the words of the advertisement, this would appear to be a Cosmetic and not a drug. It might be well, however, to have one of our young ladies write on plain stationery and ask for the booklet.

2/3/39 Booklet received and placed on file

Analyst reported to Chief 23rd March 1939.

Reference

DEPARTMENT of and NATIONAL HEALTH PASSED
MAR 23 1939
Chief Dominion Analyst.

A Linton Davidson
Analyst

Figure 3: Analyst's Report on S-8 Brand Advertisement, Linton Davidson, March 22, 1939

Library and Archives Canada, RG 29, Vol 258, File 347-6-6 (Part 2), reproduction copy number e-011195706

Indeed, by 1950, Dr. Clare Morrell, by that time the Chief Dominion Analyst and Director of the Food and Drugs Divisions, would comment that, to avoid the confusion of drugs being put on the Canadian market under "a great variety of names and strengths", the drugs on Schedule B had "been considerably increased in the last few years".[109] This situation would not materialize, however, through any abstract power of the Canadian pharmaceutical industry nor through some bureaucratic master plan. Rather, this growth in Canadian drug standards began in 1940 with messy, laborious, and contested activities to create the Canadian Committee on Pharmacopoeial Standards. In the process, National Health deployed regulatory techniques – in particular, questionable delegations of power supported by erasures of evidence of the invalidity of those delegations – that would later characterize the regulatory enactment of estrogen.

2. The formation of the Canadian Committee on Pharmacopoeial Standards, 1940-1942

Having described the legal dynamics, this section introduces many of the human regulators that would come to enact estrogen in Canada in the mid-1940s. Before estrogen could be enrolled into different regulatory regimes, these actors first needed to assemble. The Committee's formation was bitterly contested, controversial, and confused, and as time would show, the Committee itself would prove to be unstable. Yet, for a brief time in the mid-1940s, it enacted socio-material realities in Canada – and when it came to estrogen, some of those realities would be more durable. Uncovering the regulatory techniques that enacted the Committee, and the interests of its future members, will ensure greater insight into the regulatory players, practices, and techniques that later together enacted estrogen.

If one reads closely, one can identify three stories that have been told about the Committee. The first is the "wartime shortages" story. One finds this explanation for the Committee's formation and its activities in articles and books by National Health officials, beginning in the late 1940s with Davidson's accounts, in the 1950s and 1960s with sporadic articles by other officials, and in the prefaces to Canadian pharmacopoeial or pharmaceutical works.[110] A second story also comes through, if more subtly, in these accounts, celebrating the Committee as one weapon in a swelling arsenal of departmental machinery and regulatory prowess at National Health. Sometimes this story is less subtle, as in the occasionally nationalistic, triumphant, and Christian tones of Davidson's work (including visual narratives of nation-building through

[109] Morrell 1950 at 659. Indeed, by 1946, standards of quality and potency had been established for over 200 drugs, contained in the Canadian Supplement to the British Pharmacopoeia; see Curran 1946 at 500-501.

[110] See e.g. Davidson 1949a, Davidson 1949b, Curran 1953, and Pugsley 1967.

pharmacy, as illustrated below). Finally, recent work in legal and policy history has touched upon the Committee, summarily suggesting its formation reflected something akin to regulatory capture of National Health by the pharmaceutical industry.[111]

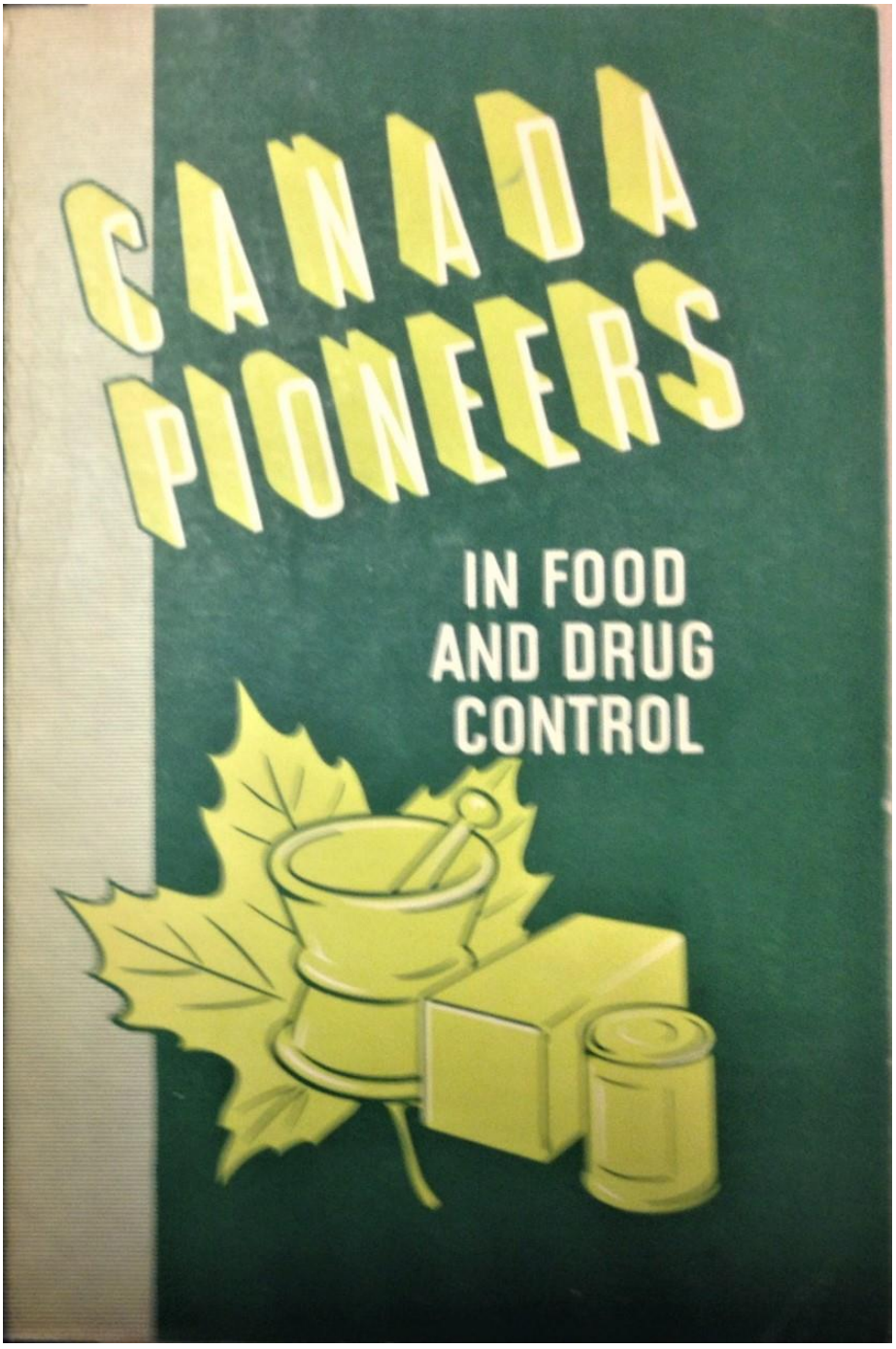


Figure 4: Book cover for AL Davidson's *Canada Pioneers in Food and Drug Control,* 1949.

[111] Herder 2015 at S112-S114; and Lexchin 2016 at 17-18.

The story narrated here, about the Committee, has not been told before. I follow certain scientists, regulators, and lawyers, within and outside the Department, as they schemed to form (or deflate) the Committee and to shape its powers. This involves tracing relations among departmental officials, physicians and pharmacists and their professional associations, and representatives of the Canadian Pharmaceutical Manufacturers Association ("CPMA"). In particular, this section traces the vigorous, year-long debate that occurred within National Health, and between National Health officials and stakeholder associations, regarding the political and legal validity of delegating authority to the Committee and the scope of that authority. In the process, it introduces the idea that disputed delegation practices would be central to how certain drugs were standardized and materialized in Canada.

In tracing these associations, this chapter also shows that, while the human actors were influenced by forces of the interwar period, with its declining British colonial influence, and by the outbreak of WWII, with its declining drug standards in Britain, and furthermore while these actors drew on wartime exigencies and Canadian nationalism where rhetorically productive, WWII did not cause the Committee to come into being. Nor was the formation of the Committee, in its structure or duties, reflective of a successful "capture" of the Department by any person, profession, or industry. Rather, archival evidence and other primary sources suggest that the better metaphor to describe the Committee's formation is a regulatory experiment. The actors who generated the Committee did not begin with any overarching vision of its structure, powers, or purposes, but were trying to move beyond failed attempts in the 1930s to create a meaningful role for Canadians in drug standardization. Like many experiments, it had unintended and ambiguous effects. Significantly, the creation of the Committee contributed to novel enactments of power and legitimacy within National Health and the drug industry, and, ultimately, to a diminished role for pharmacopeias as a way of regulating drugs. Furthermore, it would lead to other innovations as, through and with its later activities, estrogen would become multiple.

Two people were most influential in establishing the Committee – Dr. Velyien Henderson, a professor at the University of Toronto and Harry Lancaster, the Chief Dominion Analyst. Henderson and Lancaster were long-time collaborators, and they seem to have been friends. By 1940, they had known each other for at least thirty years, going back to time studying and teaching at the University of Toronto's Faculty of Medicine. From 1908 to 1923, Lancaster had been a demonstrator in that faculty, a professor of chemistry at the College of Dental Surgeons,

and a Director of the Provincial Board of Health.[112] About five years older, Henderson joined the faculty in 1904, becoming a full professor of pharmacology in 1909.[113] A recognized expert on pharmacopoeial standards, he had many years of experience drafting pharmacopoeial monographs in consultation with British scientists. Through the late 1920s and 1930s, Henderson served in leadership roles with the Canadian Medical Association ("CMA").

The two men's interests in establishing distinctly Canadian drug standards originated long before WWII, entangled with the decline of British colonialism in the interwar years. In 1925, Great Britain communicated officially with academic faculties and licensing bodies in the Dominion (and in other colonies) to seek suggestions on upcoming proposed revisions to the British Pharmacopoeia; in 1927, the British Pharmacopoeia Commission also asked the Dominion government to collaborate on these revisions. To coordinate a unified response, leading professors of medicine and pharmacy decided to form a "Canadian Committee on Pharmaceutical Standards", which was chaired by Henderson and joined by Lancaster, and this informal committee was the channel through which Canadian pharmacologists and pharmacists assisted with the monographs for the 1932 revision to the British Pharmacopoeia. Over time, and fuelled by nationalism, committee members became concerned that British revisions were not meeting Canadian needs, as drugs still used in Canada were deleted from, or not added to, new editions. Emboldened by the preface to the 1932 revision,[114] this committee prepared a detailed Canadian "addendum" to the British Pharmacopoeia, which was published as part of the *Canadian Formulary*.[115] Its legal status under the *Act* was ambiguous, and its effects on Canadian medical practice were underwhelming. However, its more lasting impact was the idea that such supplements or addenda were a direct means to Canadian-specific drug standards.[116]

While WWII was not the cause of new Canadian drug standards, it was a catalyst. Henderson became especially agitated by a series of changes to the British Pharmacopoeia that began in

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[112] Davidson 1949b. He served in some of these roles simultaneously. It is not entirely clear if Lancaster's degree was a B.Sc. or an M.Sc. Davidson says the former as does the Canadian Formulary 1948; Cameron says the latter. Davidson likely knew better, as he worked with Lancaster for 20 years. See Davidson 1949a at 62; Canadian Formulary 1948 at 7; and Cameron 1959 at 321.

[113] JH Gaddum, "Obituary: Prof. Velyien Henderson" (December 8, 1945) 156:3971 *Nature* 638 ["Henderson Obituary 1945"].

[114] Canadian Formulary 1948 at 5, citing the 1932 revision to the British Pharmacopoeia at xii-xiii: "where it is desired that official recognition should be given in any part of the Empire to local drugs or local substances, we suggest that this should be left to the Governments concerned, which by means of Supplements or Addenda to which they may accord the necessary sanction, can meet any local requirement or introduce any modifications or alternatives desired."

[115] Davidson 1949a at 85; and Pugsley 1967. For contemporaneous accounts by pharmacists, see Canadian Conference of Pharmaceutical Faculties, *The Canadian Formulary* (Toronto: The Canadian Pharmaceutical Association, 1949) at vi-vii; and Canadian Committee on Pharmaceutical Standards, *The Canadian Formulary,* 4th ed (Toronto: University of Toronto Press, 1948) ["Canadian Formulary 1948"] at 5-6.

[116] For a window into Henderson and Lancaster's earlier effort, in 1933, to revise the *Act* to enable the addition of such addenda to Schedule B, see EA Driedger's Schedule B File, 1943 at 71-75. See also the content associated with *supra* notes 63-64.

1936 and continued at a greater frequency during the war.[117] Due to wartime shortages in Great Britain of various chemicals, such as glycerin, alcohol, and vitaminized oils, the British had been substituting certain drug ingredients, through "wartime addenda" to their Pharmacopoeia. Canada, by contrast, did not suffer shortages of these ingredients. Furthermore, the British were no longer consulting the Canadian committee on these weakened drug standards. For Henderson, these deficiencies were intolerable. Legally, the situation was lowering drug standards in Canada (as explained, British Pharmacopoeia monographs had a default official status in determining drug adulteration under Canadian law, except where replaced by Canadian standards in regulations). Henderson wanted to create new standards in a Canadian Supplement to the British Pharmacopoeia, and he insisted to Lancaster that new standards be legally binding. Though the desire and groundwork for Canadian drug standards stretched back to 1925, Henderson and Lancaster leveraged the wartime addenda to justify more urgently a new, official Canadian Committee.[118]

Together the two men began to cook up a new way of regulating drugs in Canada. After meeting together in Toronto, they started to refine their ideas over the fall of 1940.[119] Henderson felt it would be easy to enlist pharmacists' support through the Canadian Pharmaceutical Association and possible to obtain support of the medical profession, though "the question remains – is it worthwhile making a fight and forcing the Department to put the Canadian Formulary and its Addendum Section particularly on a more official basis?" Lancaster quietly egged on the fight, promising backup by stressing how "it would be quite within the powers of the Food and Drugs Act to establish both name and standard of quality" for drugs in Canada.[120]

Henderson was insistent that any reconstituted committee should have legal standing. A decade later, Davidson suggested legal standing was needed to "enable the Government to pay out-of-pocket expenses in connection with meetings".[121] Expenses were no doubt a relevant factor, yet Henderson sincerely viewed making a committee legally official as a precondition to

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[117] Henderson's correspondence with Lancaster and Davidson could tend toward condescension, pedantic clarification, and exaggeration; further, he often took a "kitchen sink" approach that argued from multiple angles. Put another way, his letters vividly convey his concerns and are useful to understanding challenges with drug standardization in Canada in the early 1940s.

[118] By the time the order establishing the new Committee was made in June 1942, five such addenda had been officially added to the British Pharmacopoeia. Henderson's former committee, the Canadian Committee on Pharmaceutical Standards, had been permitted to comment on the first addendum in 1936, but not on the subsequent four addenda. Not only were shortages an issue, but the Commission's offices were destroyed during the war and it lost many of its documents. See Lancaster's File, 1940-1943; Davidson's Committee Materials, 1943-1944; and Davidson 1949a at 85-86. See also Worthen 2004 at 7, 93-98.

[119] In 1940 and early 1941, some of Henderson's letters were sent on behalf of himself and the other two Toronto-based members of the informal committee. Over 1941 he increasingly began to correspond with Lancaster on his own behalf.

[120] September 24, 1940 letter from Henderson to Lancaster, and September 28, 1940 letter from Lancaster to Henderson, in Lancaster's File, 1940-1943.

[121] Davidson 1949a at 85; and November 24, 1941 letter from Lancaster to Wodehouse, in Lancaster's File, 1940-1943.

making new drug standards legally binding. In January 1941, he made a lengthy pitch to the CMA, drawing on nationalist sentiment and pragmatism. Taking a kitchen sink approach, he claimed that the existing addendum in the *Canadian Formulary* was already legally binding and that National Health had always intended it be an official work under paragraph 6(c) of the *Act*, yet simultaneously advocated that the CMA should support a new official committee to make standards which would need to be "officially published in the Gazette" in order to be binding.[122]

As Henderson enlisted allies, Lancaster worked to identify a statutory basis for any standards created by a new committee, that would award such standards legal precedence – as any new pharmacopoeial work, whether or not published in the *Gazette,* would be trumped, by default, by the British Pharmacopoiea.[123] Drawing from his failed effort, in 1933, to incorporate *holus bolus* the earlier committee's addendum into the *Act,* he resurrected the idea that new standards by a new committee could be incorporated through Schedule B, although he felt "only in exceedingly important cases should this procedure be invoked".[124] Lancaster did not seek legal advice on the idea, and did not always seem confident that the *Act* provided the requisite authority.

Nonetheless, by March, this idea had crystallized into a plan. By June, Henderson was urging the CMA to support an official committee to make new drug standards that if "concurred in by the Government, could be made legally binding by notification in the Gazette, under powers now *probably* possessed in the Act".[125] That same month, Lancaster set about trying to persuade Dr. Robert Wodehouse, the Deputy Minister,[126] and his chief executive assistant, Dr. John Heagerty.[127] Presenting the use of Schedule B as the easiest option, he cautioned that rather than give a new committee all of the powers that the physicians appeared to be seeking, which would require an amendment to the *Act* – never a politically palatable option, especially as it had been amended only two years prior – the better way to replace the British Pharmacopoeia for drugs requiring Canadian standards would be to list those drugs on Schedule B. Within a few months, Wodehouse and Henderson were meeting directly to discuss the plan.

However, by November 1941, the plan had stalled, and the physicians were growing anxious. Lancaster attempted to assure senior departmental officials that the new committee would just

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[122] January 6, 1941 memorandum from Henderson to the CMA committee on pharmacy, in Lancaster's File, 1940-1943.

[123] See also the content associated with *supra* notes 34-36.

[124] January 25, 1941 letter from Lancaster to Henderson, in Lancaster's File, 1940-1943.

[125] March 24, 1941 letter from Lancaster to Henderson, in Lancaster's File, 1940-1943 (emphasis added).

[126] Wodehouse had been appointed Deputy Minister of National health in 1932; see Cameron 1959 at 321.

[127] Heagerty was a physician who also had earned a doctorate in public health at McGill in 1912. He had been the head of a Departmental division on venereal disease control from 1921 to 1928, and in 1929, he had become the Chief Executive Assistant of National Health, as well as the Director of Public Health Services. See *ibid*; and also Lancaster's File, 1940-1943.

be advisory, though he had a very robust notion of what qualified as advice. He clarified that the committee's decisions should not be given the force of law, *except* that the committee would decide which drugs to list on Schedule B, and those drugs could then be the subject of special regulations.[128] The proposal had clearly evolved to encompass greater delegation. Earlier that year, the proposal had envisioned that the committee's main duty would be to advise the British, through the Department, of proposed modifications to the British Pharmacopoeia; only as a secondary activity would the committee recommend which drugs to add to Schedule B. Further, in the earlier proposal, the committee was limited to recommending which drugs to *enumerate* on Schedule B; it had not been contemplated that it would advise how to *regulate* those drugs. Now, the proposal was that the committee would have the power to add drugs to Schedule B – under a new Part V to be candidly entitled "Any drug which the Canadian Committee on Pharmacopoeial Standards may designate for addition to the Pharmacopoiea, deletion from the Pharmacopoiea, or for modification of name or of composition" – and also advise on regulations.

This triggered a major debate amongst senior departmental officials on the appropriate nature and extent of delegation to the committee. Heagerty felt that the delegation contemplated was excessive and impermissible. In annotations in red ink scrawled all over a draft of the proposal in November, Heagerty wrote that "[t]his ties the hands of the department by giving the Committee the right to set up standards which are binding upon the department. I am opposed to this delegation of powers to vested interests."[129] The vested interests that concerned Heagerty were those of physicians and pharmacists. From his experience labouring to create a national health insurance program, Heagerty was strongly attuned to the excessive influence of medical practitioners on public health planning, and alive to labour and agricultural groups' concerns that physicians had too much political power in existing provincial health commissions.

Heagerty enlisted Mr. B.W. Russell, K.C., the Acting Departmental Solicitor. Russell opined that sufficient statutory authority existed to empower a committee, but he needed more detail about just what the committee was anticipated to do, before he could advise whether that mandate was valid. Therefore, in December 1941, Lancaster prepared a draft order-in-council empowering the committee. The draft order proposed that a committee would directly advise the British Pharmacopoeial Commission.It also proposed that the Committee would recommend what pharmacopoeial drugs to list in Schedule B, and would recommend standards of quality and potency. In a postscript, Lancaster flagged that it would "be necessary to pass a further

[128] November 24, 1941 memorandum from Lancaster to Heagerty and Wodehouse, in Lancaster's File, 1940-1943.

[129] November 1941, unattributed, "Proposed Addition to Schedule B to the FDA", and November 25, 1941 memorandum from Heagerty to Wodehouse, in Lancaster's File, 1940-1943.

Order in Council amending Schedule B to the *Act* so as to include a new Part V". His insistence on the need for Part V became a running theme in all his communications with Departmental officials regarding the committee.

Lancaster understood the legal interrelations between section 6 of the *Act,* Schedule B, and its Parts I through IV. His continued insistence on the need for a new Part V is therefore curious. He cannot have been unaware that Canada lacked statutory jurisdiction to regulate the licensing, manufacture, and sale of Schedule B drugs unless those drugs were listed on Parts II, III or IV. The only matters that could be regulated, for a Schedule B drug *not* on one of those Parts, were quality and potency – and yet the very *raison d'etre* of a new committee was that its members themselves would, in the process of recommending modifications to the standards in the British Pharmacopoeia, define these drugs' identity, quality, and potency. That is, in recommending any new, improved or Canada-specific "recipe" for any given drug, the committee would *already* have codified that drug's qualities and potencies. One rather unavoidable conclusion, therefore, is that Lancaster was contemplating Part V to be a separate "holding zone", a place where drugs newly defined by technical standards could be enumerated, without the Department being required then to divide up those drugs amongst the existing four Parts or to make any regulatory decisions about whether or how to control or license those drugs. However, Lancaster does not appear to have considered the potential problem of duplication; namely, what would occur if, as a result of the committee's additions to Part V, a drug ended up being mentioned *twice* in Schedule B? Was it not foreseeable that a drug might be listed on one of Parts I through IV for the purpose of a regulation under subsection 6(3), and then be listed again on a new Part V for the purpose of supplementing the British Pharmacopoeia? In that situation, which would take precedence? To this, a lawyer might respond that such a situation would never occur, because given the words and legislative history of subsections 6(3) and (4), Schedule B was not intended to contain anything but those biological drugs that might be standardized and regulated under subsection 6(3).

When Russell reviewed Lancaster's draft order, he flagged to Heagerty that the Chairman should be a National Health official and suggested that the committee be reduced in size. Disagreeing on both counts, Lancaster felt that a larger committee would "avoid any suggestion of domination by a small group"; despite his concern that the committee might be captured by narrow interests, in January 1942, Lancaster solicited revisions from Henderson alone on the

draft order and advanced the revisions to his superiors.[130] The revisions gave the committee the power to dictate additions, deletions, or modifications to Part V of Schedule B.

The Department's solicitors were having none of this. Russell and Gunn each reviewed the revised order, in early February, and they concurred that, in proposing to give the committee the right to add any drugs that it saw fit to Schedule B, the order was *ultra vires*. Russell, now the Departmental Solicitor, opined that "the proposed addition to Part V of Schedule B to the Food and Drugs Act is unconstitutional" as it amounted to allowing Cabinet to subdelegate. In his view, only the Governor in Council could add or remove drugs from Schedule B. Gunn went even further, opining that if the committee's input into the British Pharmacopoeia was intended to bind Canada, then he was "very doubtful if the method proposed would be constitutional".[131] This exemplified Departmental officials' practices, at this time, of consulting the legal division on the validity of a regulatory proposal only *after* consulting professional associations and industry representatives on the substance of that proposal. Predictably, one effect of this practice was that legal concerns with regulatory proposals were identified late in the process, and solutions focused on rendering the proposals technically valid rather than on substantive reconsideration.

Faced with his solicitors' opposition, the Deputy Minister intervened. He brought Lancaster, Heagerty, and Russell together for a meeting to review the draft order in council, and to address concerns with the invalidity of a new Part V to Schedule B. The group decided that, as long as the Department (and not the committee) made the decision to add drugs to a new Part V, and as long as each drug was added to Part V individually (and not by blanket incorporation of the committee's addendum), the textual reference to Part V could remain in the order-in-council.[132]

This agreement was short-lived, however. In the next draft of the order, in March, the decision was made to excise all textual reference to the anticipated Part V. The intention to employ a new Part V remained but, with continuing skepticism on its legality, the technique adopted was erasure – Part V was disappeared from the face of the order. The plan to allow the committee to enumerate this new list of drugs, outside the statute's existing structure, was made invisible.[133]

As the drafting challenges simplified, the external relationships got more complicated. Reflecting entrenched distrust between medical professionals and drug manufacturers, and suspicion of a proposal instigated by Henderson, the CMPA opposed the Committee. First their

[130] January 16, 1942 memorandum from Lancaster to Heagerty and Wodehouse, in Lancaster's File, 1940-1943.

[131] February 6, 1942 memorandum from Heagerty to Wodehouse, February 9, 1942 memorandum from Russell to Heagerty, and February 9, 1942 memorandum from Gunn to Heagerty, all in Lancaster's File, 1940-1943.

[132] February 11, 1942, memorandum-to-file by Lancaster, in Lancaster's File, 1940-1943.

[133] March 1942 draft of proposed order-in-council establishing the Committee, in Lancaster's File, 1940-1943.

leadership approached Lancaster; when that went nowhere, they set about lobbying other senior officials. On February 27, 1942, three CMPA members "dropped in" on Heagerty, who loaned them a receptive ear. Shortly thereafter, the President of the CMPA, Mr. Laverty, met with the Minister, Ian Mackenzie, to again oppose the committee, to support the existing department-lead process for drug standards, and to express "that the Committee would be an embarrassment" to drug manufacturers.[134] Faced with opposition, Lancaster and Henderson turned up the rhetoric of nationalism and emergency, stressing how wartime addenda were being made without regard to Canadian conditions and interests.[135]

Under the influence of the drug manufacturers, and cutting Lancaster entirely out of the loop, on March 12, 1942, Heagerty wrote to Wodehouse with his own advice for the Minister. While agreeing that a committee should be recognized the purpose of revising the British Pharmacopoiea, he strongly objected to allowing the committee to advise on what drugs should be listed on Schedule B or on new drug regulations. This he viewed as an unlawful delegation. In this respect, he particularly opposed the proposal to add a new Part V to Schedule B, that would include whatever drugs the Committee wished to add or remove. Heagerty had no love lost for Henderson; he referenced a past conversation in which Henderson had suggested National Health "was not competent to set up standards of food and drugs". He recommended that the Committee be authorized to draw up a Canadian Pharmacopoeia, which he felt would make Canada "independent" with respect to drug standards, but that it should not be authorized to advise the Department on drug standards under section 6 of the *Act*.[136]

Wodehouse advised Minister Mackenzie the next day. Ignoring the debate about delegation, his advice was pure political pragmatism – how to respond to wartime challenges, while keeping the most economically powerful actors happy. Sympathetic to physicians' desire to clarify standards, especially given the "peculiar" situation whereby multiple pharmacopoeias were statutorily recognized under Canadian law and the "tremendous" wartime modifications to the British Pharmacopoiea, Wodehouse nevertheless rejected the idea that Canada should "shoulder the expenses" of its own Canadian Pharmacopoeia. The real dynamic underlying the discord, in his view, was competition between retail pharmacists and drug manufacturers; in a

[134] February 28, 1942 memorandum from Heagerty to Wodehouse; March 5, 1942 letter from White to Mackenzie; and March 6 letter from Lancaster to Henderson, all in Lancaster's File, 1940-1943.

[135] The only concession that Lancaster made to the CMPA was to increase their membership from one to two members, reflected in the next draft of the order on March 6.

[136] When Lancaster learned a week later of Heagerty's advice, he told Wodehouse that Heagerty had "misunderstood and overemphasized" the alleged delegation, and that the current proposal left regulatory power "exactly where it is at the present time, in the hands of the Minister." Further, while in Lancaster's view a Canadian Pharmacopoeia was an excellent idea, it was "twenty-five years ahead of its time" and would be legally complex, diplomatically challenging, time-consuming, and expensive.

postscript, he added statistics showing that, despite massive economic growth in drug manufacturing in Canada between 1930 and 1940, pharmacists remained the larger constituency (not only did the number of retail pharmacies vastly exceed manufacturers, but investments and sales were higher).[137] Rather than bootstrap broader regulatory changes to wartime exigencies, Wodehouse suggested an alternative option of a temporary order in council under the *War Measures Act* to prevent revisions to the British Pharmacopoeia from being automatically effective in Canada. In any event, he recommended that the Minister convene a conference of the interested parties, to "see just how far we want to go to meet the changing war conditions". Mackenzie agreed, and the conference was scheduled for April 28, 1942.

At first blush, the conference seemed to resolve the discord. The next day, National Health revised the draft order in council, such that the Committee's proposed duties were twofold: to advise the Department "with regard to any modifications to the British Pharmacopoeia" thought to be "necessary in the public interest"; and, upon request of the Department, to advise it "with regard to regulations proposed to be made under section 6 of the *Food and Drugs Act* respecting any drug included or be included in Schedule B". Ironically, the revised draft went slightly *further* than earlier versions in delegating power. Yet perhaps because it addressed the concern that Schedule B should not be amended by the Committee, the drug manufacturers approved it.

Unexpectedly, the physicians advised that they could not support the order. While the order failed to give Henderson what he had long desired – the ability to dictate legally binding standards for drugs in Canada – the CMA had accepted for months that the trade-off for legally binding standards was that the Committee would be limited to recommendations. Rather, the CMA's objection was driven by Henderson's outrage at the appointment processes. Having anticipated that he would chair the committee, he was furious that the professional associations were not empowered to nominate members directly and the committee would not elect its own chairman. On these points, and on the advice of Gunn, National Health would not budge, as they felt the Minister required "absolute discretion" as to whether associations' nominees should be appointed. Dissenters also remained within the Department, including its legal division. However, Lancaster's idea survived. On June 5, 1942, an order in council was made authorizing the Committee, empowering the Minister to appoint its members, and fixing its duties.[138]

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[137] "The total investment in the manufacture of pharmaceutical products in 1930 was $18.433,000 and in 1940 it was $28,158,000, a tremendous increase. Investments in the retail trade (drugs stores) in 1930 was $36,000,000 being twice that of the manufacturing industry. Sales from the retail trade (drug stores) in 1930 was $76,848,000. Sales for 1940 were $75,473,000"; see March 12, 1942 memorandum from Wodehouse to Mackenzie, in Lancaster's File, 1940-1943.

[138] PC 1942-4739 (June 5, 1942); see Lancaster's File, 1940-1943. I could not locate this order in council in the *Canada Gazette.*

Appointed were four professors of medicine and pharmacology, and two deans of pharmacy, chosen by the Minister from nominees submitted by three professional organizations.[139] Bitterly disappointed that he had not been made Chair, Henderson accepted his invitation belatedly and petulantly, saying he had "reluctantly come to the conclusion that it is my duty to serve".[140] He had received the message – this was the Department's Committee and not his. In the Chair would be Lancaster.[141] Lancaster struggled with a serious illness in 1942, and he was often bedridden (and by 1944 occasionally hospitalized). His illness caused the inaugural Committee meeting, scheduled for November 1942, to be postponed twice. That postponement did not stop the Department from trumpeting to newspapers that Canada might soon achieve its own drug standards independent from Britain. The other departmental officials appointed were Aime Valin, the Assistant Chief Dominion Analyst, and Dr. Morrell, the senior pharmacologist with the Laboratory of Hygiene. Davidson, a Dominion analyst and pharmaceutical chemist, was appointed as the Committee's Secretary. He would serve diligently in that role until his untimely death in 1950.[142] No solicitor was assigned to the Committee, a fact that would later prove quite relevant to the practices of the Committee, and of the Department, in standardizing drugs.[143]

The Minister also appointed two industry scientists. The CPMA nominated four candidates but identified two as "by far best qualified to represent us". [144] One industry favourite was Dr. A. Stanley Cook, Director of Research and Biological Laboratories at Ayerst, McKenna & Harrison Ltd. At the time of Cook's appointment, Ayerst had been selling Premarin in Canada for over a year. The other favoured candidate, also appointed, was Mr. North of Canada Pharmacal Co.

In their negotiations over the Committee's formation, and in the approach that they later took when nominating members for the Minister to appoint to the Committee, CMPA officials consistently advanced the position that the role of "their" two members was to represent the CMPA. Unlike Henderson, who saw himself as independent of his nominating organization, the

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[139] In 1942, the six academic members appointed were Dr. D Sclater Lewis, Dr. VE Henderson, Dr. Ray F Farquharson, Dr. J Alfred Mousseau, Dean EL Woods and Dean RO Hurst. The three professional organizations asked to submit nominees were the Canadian Medical Association, the Royal College of Physicians and Surgeons, and the Canadian Pharmaceutical Association. These appointments were made by Minister Mackenzie on September 19, 1942; see Lancaster's File, 1940-1943.

[140] September 29, 1942 letter from Henderson, in Lancaster's File, 1940-1943.

[141] Lancaster was made the Chair, on the advice of the Department's solicitor and motivated by the desires of both the Deputy Minister and Minister to ensure Committee members accepted that the Committee's role was just advisory, at least officially.

[142] Davidson Obituary, 1950. Arising from his role as the Committee's Secretary, Davidson's correspondence files, and his files documenting the Committee's proceedings and meetings, are a substantial source of material for this thesis.

[143] In contrast, an analogous committee, the Advisory Committee on Health Insurance, also created in 1942 and chaired by Dr. Heagerty, included as a member the Departmental solicitor (presumably either Mr. Gunn or Mr. Russell). See Cameron 1959 at 322; and Canadian Museum of History, "Dr. John J. Heagerty", online exhibition, "Making Medicare: The History of Health Care in Canada, 1914-2007", online: <https://www.historymuseum.ca/cmc/exhibitions/hist/medicare/medic-3k06e.shtml>.

[144] See the two October 10, 1942 letters from Laverty to Wodehouse, in Lancaster's File, 1940-1943.

CPMA repeatedly would position Cook and North as representatives of drug manufacturers' interests. To be fair, National Health senior officials had initially implied, as part of their efforts to solicit CPMA's support for the proposed Committee, that the CMPA's appointed members would play precisely this representative role. Depending on the circumstances, National Health's position fluctuated on whether Committee members, especially the industry scientists, were appointed as independent experts or to represent their associations' interests. Left unresolved in the negotiations in the spring of 1942, the following year, the question flared up repeatedly. In the spring of 1943, Wodehouse advised Laverty that the CMPA should raise protests about Committee matters directly to the Committee through the two industry members rather than to him; yet, in the fall of 1943, when the CMPA tendered resolutions to the Committee through North, Wodehouse shifted gears, insisting that the CMPA should write to him personally about such "special interests" and arguing that Committee members were independent.[145] Much of the CPMA's concern with the Committee's activities, over 1943, was triggered by Henderson and other academic members' strong advocacy for establishing, through regulations, the proper or official names of drugs to appear on labels, and by the physicians' general hostility to patents and trademarks for drugs.[146] Arguably, these disputes about intellectual property rights would make it easier for Committee members to agree on matters deemed "technical" rather than regulatory – or at least, they agreed that they should be *able* to agree on technical matters.[147]

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In playing this prelude of the formation of the Canadian Committee on Pharmacopoeial Standards, I have offered an entry point to an integrated Canadian history of the standardization of estrogen. When studying drug regulation, as Cambrosio puts it, "the analysis of the different

[145] April 8, 1943 letter from Wodehouse to Laverty, in Lancaster's File, 1940-1943; and October 2, 1943 letter from Wodehouse to Laverty, in Davidson's Committee Materials, 1943-1944. The CMPA's position persisted, however. For example, on October 8, 1948, AK North resigned from the Committee as the firm that he worked for was no longer a CMPA member and he believed Committee members should be "representatives" of the CMPA; Library and Archives Canada, Department of Health fonds, RG 29, volume 249, file no. 339-4-1 (Part 8) Oct 1948 to Sept 1949 ["Unknown Committee Member's File, 1948-1949"].

[146] Space precludes discussing the growing trend towards increased intellectual property in drugs (and their names), as part of which vast numbers of new drugs (including Premarin) increasingly were introduced under proprietary names, during the 1920s-1940s. This "unsatisfactory position created by the issue of the same drug under a variety of such names by different manufacturers and the restrictions put upon their use is generally acknowledged and has been the subject of frequent comment"; Dunlop & Denston 1958 at 1252. As in other states, in Canada this trend was generally opposed by elite physicians, who advocated for non-proprietary names on product labels and in prescriptions, including through the Committee. By contrast the CMPA, sometimes through "its" Committee members, sought to blur the differences between patented and common drugs, and to protect brand names from encroachment in pharmacopoeias or regulations. The Committee "considered, on various occasions, proper names for drugs, so as to ameliorate the confusing situation arising from the multiplicity of trade names for new drugs"; Davidson 1949a at 85-86. In 1944, with the Committee's input and despite CMPA opposition, Cabinet made regulations prescribing common names, to be used on labels, for a limited subset of 18 drugs; PC 1944-1981 (21 March 1944), *Canada Gazette,* Vol LVXVIII, No 14, at p 1328 (April 1, 1944).

[147] See e.g. April 10, 1943 letter from Laverty to Wodehouse, in Lancaster's File, 1940-1943.

forms of regulation should not be separated from the analysis of the constitution of the entities, processes and activities that are the subject of regulation".[148] By reviewing recurring practices giving rise to the Committee – the pugnacious negotiation, drafting techniques that supported legally dubious delegations, a holding together of diverse ways of regulating drugs in hybrid configurations – one is better placed to grasp how estrogen was later enacted in practices.

Through the formation of the Committee, a new "way of regulating drugs" emerged in Canada.[149] What were formerly distinct practitioners, logics, and modes of standardization were, for the first time, lumped together in and around this new collective. Previously, elite physicians and pharmacists, associated with universities or other teaching institutions and represented by individuals like Dr. Velyien Henderson, had shaped the contents of the British Pharmacopoeia and other pharmacopoeial works. Through pharmacopoeia, these professional regulators determined the potency and dosage of drugs. In essence, elite physicians like Henderson had been the *sous chefs* helping to write the colonial cookbook, and they saw, in a new committee, a chance to become Canadian *chefs de cuisine.* Canadian drug manufacturers perceived this incursion by Henderson and his enlisted professional supporters as an embarrassment, as ethical manufacturers endeavoured to regulate drug standards through rigorous quality control of drugs, including through bioassay methods standardized within firms, if not within states. Rather than pre-scripted recipes that interfered with innovation, industry expected its pre-made products to be endorsed (or, for bad actors, rejected) through government-issued licenses.

Within National Health, regulatory practices had become ever more divaricated. On the one hand, National Health had emulated professional ways of regulating, as empowered by the 1927 statutory amendment, through efforts to codify drugs' identities and potencies in the Biologicals Regulation. Initially, this effort had involved the formal adoption of pharmacopoeial standards and bioassay methods directly into law. Later, in the 1934 Biologicals Regulation, this effort involved purporting to delegate to Departmental officials in the Laboratory of Hygiene the power to select their own methods for measuring and materializing drugs and their potencies. Fuelled by growing scientific capacity and bioassay expertise within the Laboratory of Hygiene, and less beholden to external professionals, the Department had shifted from endorsing the experts' cookbooks to adopting its own secret recipes (or more fairly, its own changing and unwritten recipes, apparently available upon request). On the other hand, again sparked by the 1927 amendments and effected through the Biologicals Regulation, National Health also began

[148] See Chapter 1 at note 107.

[149] For Gaudillière's and Hess' framework, see Chapter 2, section 1.ii, including the content associated with notes 106-117.

controlling drugs through licensing. In this mode, standards advanced a different logic; rather than a guide to drug compounding, standards were a means to test if a pre-made product measured up – although what pre-existing products should measure up *to* was not always clear.

These varying modes of regulating drugs in Canada were all embedded into the Committee's structure and mandates. The establishment of the Committee further naturalized the notion, still quite new in 1942, that Canada should enact its own drug standards. Just as notably, the structure of the Committee reinforced that manufacturers should have a say, though whether that "say" was to be voiced by members serving as scientific experts or industry mouthpieces was left open-ended. The Committee would also continue to advance professional modes of regulation through pharmacopoeia, though professional judgement was officially positioned as a merely advisory input to ministerial decision-making. Through its design and membership, the Committee would thus hold together multiple, overlapping modes of drug standardization.

The Committee clearly had other unintended political and structural consequences. In cooking up a new, official committee that would create uniquely Canadian drug standards, Henderson successfully secured the support of the CMA and the CMPA, and Lancaster similarly enlisted his Deputy Minister despite the objections of other senior Departmental officials. Yet, the resulting Committee was not what either had envisioned. Seemingly blind to the trade-offs in soliciting the state's imprimatur for scientific work, Henderson had sought to enlist governmental authority to empower a mode of professional regulation; yet, through interactions mediated by bureaucrats and lawyers, the ultimate outcome saw professional judgment and expertise officially subordinated to state control. With the anticipated Part V of Schedule B to be made subject to the Minister's decision, pharmaceutical fact would be proclaimed by the state – drugs would be what Canada said they were. Rather than *sous chefs* to the British, elite physicians and pharmacists would instead, increasingly, serve to legitimate the plans of National Health bureaucrats. Indeed, taking a broader view, one can argue that Henderson's efforts backfired spectacularly. The structure and functions of the Committee contributed not only to diminishing academic scientists' independence in drug regulation, but to augmenting drug manufacturers' regulatory influence. In part, this unintended outcome resulted from how Canadian medical elites had framed the problem – to return to the earlier equine metaphor, they continued to focus on what horses should be, yet displayed little interest in whether barn doors should be closed. Meanwhile the drug industry, focused on keeping barn doors open, took its seat at the table.

This chapter has also described the regulatory practices and techniques through which the Committee, with its myriad intended and unintended consequences, were accomplished. In a theme that will continue to resound within the next two chapters, the Committee was enacted

through various practices of delegation. A regulatory culture and ever-deepening habits of delegation permeated drug standardization in National Health, both within Lancaster's Food and Drug Division and within the Laboratory of Hygiene. The *Food and Drugs Act* itself was strongly premised upon the delegation of powers to standardize drugs. Statutory modes of delegation included the effective delegation to pharmacopoeial works with primacy given to the British Phamacopoiea, and the formal delegation to Cabinet to regulate standards of quality and potency for biological drugs. In performing these powers for biologics, National Health officials developed a long-standing habit of delegating themselves regulatory power without lawful authority. In 1928, they purported to standardize drugs listed on Schedule B before any Schedule B had been brought into existence; in 1934, they purported to supplant official tests authorized to be prescribed in regulations with the internal bioassay methods practiced by staff in the Laboratory of Hygiene; and in 1942, they purported to regulate human tissue preparations when only animal tissue preparations were listed on Part II of Schedule B. Notably, these practices of building bureaucratic power, without deferential regard to statutory constraints, were never extended to sex hormones. With licensing viewed as an endorsement, National Health regulators chose not to perform estrogen as a therapeutic substance. However, this habit of legally dubious delegation would prove central to the creation of the Committee. Despite opinions of the Department's solicitors that adding a new "Part V" to Schedule B, uncontemplated by the *Act*, would be an unlawful sub-delegation, Lancaster's insistence that drug standards created by the Committee should be housed in a new Part V prevailed.

Administrative lawyers past and present might, of course, reasonably disagree on the legality of the 1942 order-in-council that established the Committee and its duties. They might say that the intent, at least on the face of the order, was clear – the Committee would only give advice. In this chapter, however, the goal has not (simply) been to assess the legality of the order, nor of the Department's earlier enactments. For the purpose of establishing that National Health's drug standardization practices embraced routine delegation of a regularly unauthorized nature, it is enough to set out the legal concerns of the Department's own solicitors at the time. Rather, the objective is to describe the practices and techniques by which the Committee was achieved.

In this respect, the order performed several critical acts of "coordination". First, the suggestion that the Committee would serve an advisory role was essential in bringing together diverse actors. A careful read of the order, and its silences, would have raised questions about the nature, extent, and direction of such advice. Nonetheless, a nominally advisory role, with vagueness on the limits of delegation, allowed the Committee to cohere. Still, as will be seen with later actions on estrogen, the fragile understandings on the nature and extent of delegation

to the Committee, that had plagued negotiations, never settled. As Mol observes, in practice, controversies about an object are often dissolved or diffused, rather than stabilized or closed.

The order in council also performed multiplicity. Fundamentally, it held together two different ways of regulating drugs. On its face, it assigned the Committee two duties: the duty to advise the Department with regard to any modifications to the British Pharmacopoeia considered to be necessary in the public interest; and the duty, upon request of the Department, to advise it on proposed regulations respecting any drug included or to be included in Schedule B. The order made this multiplicity "hang together", in Mol's words. It did so through addition – by adding two modes of regulatory practice without regard to their overlapping aspects or potential tensions.

Finally, and critically, the order erased any traces of the legal dispute over Lancaster's plan to create a new Part V and allow the Committee to decide its contents. After months of internal debate, and without anybody within the Department mounting a coherent legal defence of the plan, National Health had little way to render the plan compatible with the *Act.* Therefore, the regulatory technique adopted, to ensure the plan and the statute could hold together, was to simply ignore and bracket out the incompatibility, by erasing any evidence of the plan from the face of the order in council. This erasure would preclude the raising of any red flags, at the Department of Justice or amongst stakeholders. Relatedly, another practice facilitating delegation to the Committee was National Health officials' habit of consulting Departmental lawyers only after solidifying their regulatory intentions, a practice which skewed advice away from developing legal options and towards finding ways to allow invalid proposals to proceed.

To conclude, this chapter has highlighted practices by which the delegation of drug standards was done at National Health. Rather than apprehend delegation solely as a doctrine, delegation can be considered a technological practice. The chapter has thus sought, tentatively, to bridge an analysis of delegation in its doctrinal sense, with a more STS-inspired approach to how realities are performed. Whether a committee born through a chain of translations initially sparked by two persons' desire to create national drug standards yet resulting in increased industrial and bureaucratic power, or the drugs themselves that were later the subject of standardization, new socio-material realities were done.

Indeed, by the fall of 1944, the Committee would effectively dictate standards of quality and potency for over 200 drugs in a Canadian Supplement to the British Pharmacopoeia, including for estrone, estradiol benzoate, and DES.[150] In exchange, National Health officials would secure the Committee's technical input – and importantly, its legitimacy – on their upcoming regulatory

[150] Curran 1946 at 501.

proposals, including its Sex Hormone Regulations. Many of the practices and techniques that had enacted the Committee would soon be revived to enact estrogen. Furthermore, the multiple ways of regulating drugs, reflected in the Committee's composition and mandates, would reverberate in how this new regulatory assemblage apprehended estrogen. Through diverse institutional, epistemic, and regulatory practices, estrogen would be materialized multiply.

Chapter Four

"At some loss as to the precise object you have in mind": enacting estrogen multiply, 1943-1944

> "The provision of reference standards for these preparations has been a difficult problem. At the time physiologically active sex hormone preparations were introduced for sale on the Canadian market most manufacturers appeared to be satisfied in expressing the potency of the product in terms of animal units, with little regard to the design of the test, dosage response relationships, precision, reference standard or any means of regulatory control of the activity of the product. Some manufacturers used small animals, others large animals, depending on the method of assay used, and possibly there was a competitive element for the greater number of units per dose. The chaotic state of affairs was well summed up by Professor Burn of Oxford University when he stated that "the field of tame laboratory animals has been nearly exhausted and it remains now for the bolder spirits to discover methods in which a lion or elephant unit may be described." – Leonard Pugsley (1951).
>
> "May they multiply." – toast given to pituitary hormones by Leonard Pugsley and others in Dr. Collip's lab, in the early 1930s.[1]

This chapter provides an account of how estrogen was standardized in Canada in the mid-1940s. It follows a group of scientist-regulators, from within and outside the Department of Pensions and National Health and centred on the Canadian Committee on Pharmacopoeial Standards, assembled in the preceding chapter. This chapter also adds to that network those government lawyers, in National Health and at the Department of Justice (DOJ), that joined this cast of actors late in 1943 and provided legal advice on proposed regulations throughout the first half of 1944.

When it came to standardizing estrogen, the Committee proceeded along two parallel – yet rarely intersecting – regulatory tracks. On the first track, its members were creating new drug standards in what would become the Canadian Supplement to the British Pharmacopoeia, continuing the long-standing professional way of regulating drugs discussed in the last chapter. On the second track, Committee members were simultaneously enlisted to review and comment on National Health's proposed Sex Hormone Regulations, part of an emerging administrative mode of regulating drugs in which government agencies rather than physicians or pharmacists would set standards. Section 1 of this chapter recounts disputes in and around the Committee, in 1943, detailing how academic physicians and pharmacists, representatives of drug manufacturers, and National Health officials debated the standardization of estrogen. The most

[1] As referenced in Li 2003b at 94.

sustained debate related to whether and if so what bioassay methods, aimed at testing potency, should be adopted to identify sex hormones. These actors also debated how to apprehend estrogens – as pure substances or as industry-made products – as well as questions of how estrogen should be standardized, by whom, at what point in time, and in what (if any) doses.

These two regulatory tracks led, by the summer of 1944, to a series of new enactments.[2] However, before each of the new regulations were made, National Health officials and government lawyers raised concerns about their legal validity. Section 2 of this chapter explores some legal techniques that were deployed by these regulators, and especially by DOJ counsel Elmer Driedger, to work through and around the *ultra vires* aspects of these regulations. In focusing on the details of technical practices that DOJ and National Health counsel regularly employed to render as valid those draft regulations that they believed were legally dubious, this thesis refuses the idea that drug regulation can be understood by reducing it solely to a reflection of the power or interests of dominant social and economic actors. Instead, by looking at the routine moves taken in the making of these regulations, one sees how socio-technical orders were also performed with, and inseparable from, the personal, institutional, and professional practices and habits of government lawyers. What estrogen would be and do, at this time in Canada, was contingent on these legal "techniques of validating", entangled as they were with the government's ability to purport to lawfully enact regulatory standards for estrogen.

Section 3 analyzes one specific enactment. Made in May 1944, the Sex Hormone Regulations were unique as an exercise in drug standardization. They delegated to drug manufacturers the power to choose assay methods, to prepare their own reference standards, and, crucially, to decide on the doses of estrogen products. Additionally, the regulations contained an unusual definition of "sex hormones"'; eschewing the usual references to biological sources, physiological effects, or therapeutic functions, estrogen was defined as a product "purporting" to have estrogenic properties. Perhaps the most historically noteworthy feature of the Sex Hormone Regulations, however, and an element that would ultimately travel to other regulatory areas such as cosmetics, was their novel approach to labelling. In devising new types of potency labels and caution labels, the Regulations effectively replaced standards with labels, aiming not to protect women consumers but rather to ensure that National Health was supplied with industry information on test methods while avoiding responsibility for unsafe use or dosage.

[2] Summarized here, the Canadian Supplement was dependent upon the creation of a new Part V of Schedule B to the *Act*, and was itself ultimately made Division III of the general Food and Drug Regulations, in 1944. The Sex Hormone Regulations were premised upon Part II of Schedule B to the *Act*, and would ultimately be made as part of Division II of those general regulations.

Throughout the chapter, estrogen is shown to have been enacted as multiple varieties of the same substance. Section 4 describes how this was most clearly realized and articulated by Esli Woods, the Dean of Pharmacy at the University of Saskatchewan, at the Committee's final meeting of 1944. At this meeting, members addressed other frustrations with the effects of their regulatory performances, including their concerns with drug manufacturers' unresponsiveness to National Health's proposed methods for standardizing sex hormones. Unsurprisingly perhaps, firms preferred the freedom to enact estrogen with varied and incommensurable potency tests.

Natural and synthetic, biological and chemical, pure substances and ready-made drug product, pills and injections, prescribed by doctors and purchased over the counter, valuable and worthless, safe and hazardous. As Dean Woods explained, these multiple varieties of estrogen were material. They were not (just) scientific, cultural, or legal representations of estrogen, but ontologically distinct entities, performed through legal-material practices with sensitive rodents' bodies, sticky caution labels, diverse dosage ranges, and deleted regulatory preambles. In becoming therapeutic, estrogen emerged not just in laboratories, pharmaceutical firms and clinics, but, in Canada in the 1940s, through regulators' performances of material distinctions in their efforts to define, enumerate, test, classify, and label estrogenic drugs.

1. The Committee attempts to standardize estrogen, 1943

In three meetings and much more correspondence, over 1943, the physicians, pharmacists, drug manufacturing researchers, and the Department's own pharmaceutical chemists and pharmacologist, aided by its sole endocrinologist, discussed dozens of new drug standards. No drug proved more contentious than estrogen, in its various forms and modes.

1.i. "Canadian Standards should specify methods of assay around which everything seemed to centre": the Committee meets, January 1943

The Committee members assembled for the first time on January 15 and 16, 1943, in the library of the now-demolished Daly Building in Ottawa. From the outset, National Health officials strategically centred the Department. With members gathering around a large U-shaped table, the Chief Dominion Analyst, Harry Mills Lancanster, took up his position as Chair at the base of the U. Lancaster was flanked by his assistant Aime Valin and by long-time analyst and Committee Secretary Linton Davidson. Dr. Wodehouse, the Deputy Minister, attended much of the meeting. On the Friday morning, he welcomed the Committee members with an assurance

that they would be free to make any motions or recommendations, without restriction, emphasizing that they were there because the Department sought the Committee's direction. Following Wodehouse's warm welcome, Lancaster reset the tone. He gave extended opening remarks in which he strongly intimated that members should defer to the Department on challenging regulatory issues, giving as his example the regulation of sex hormones. It would be necessary, he cautioned, "to avoid mistakes arising from the taking of snap judgments", and the Sex Hormone Regulations would call for the Committee's "careful and mature" consideration after it had heard from Dr. Pugsley.[3]

Pugsley was a biochemist who had worked with the Department's Laboratory of Hygiene since 1939. In the early 1930s, he had done master's and doctoral studies at McGill,[4] where he had specialized in endocrinology. His doctorate had been supervised by Dr. Collip – the acclaimed endocrinologist who, backed by Ayerst, had extracted and isolated the human and equine estrogens that lead to the development of Emmenin and Premarin respectively.[5] As the Department's only endocrinologist, in addition to conducting research,[6] Pugsley was charged with developing the Sex Hormone Regulations. In doing so, he worked closely with Dr. Clarence (Clare) Morrell, the Laboratory of Hygiene's senior pharmacologist.[7] Morrell had joined the Laboratory in 1930, after earning bachelor's and master's degrees from the University of Toronto and a Ph.D. from Harvard, including time spent at Yale and the University of London, and then working for two years with the West African Yellow Fever Commission in Nigeria.[8]

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[3] January 14-15 meeting minutes and materials, in Lancaster's File, 1940-1943 and Davidson's Committee Materials, 1943-1944.

[4] "Reports to the Reader: About the Authors" (July 1951) 6 *Food Drug Cosm LJ* 483 ["About the Authors, 1951"] at 483-484.

[5] Leonard I Pugsley, "Studies on Calcium and Phosphorus Metabolism" (PhD dissertation, McGill University, 1932) [unpublished]. Pugsley worked in Collip's lab during his graduate studies, publishing studies with him; see e.g. JB Collip, LI Pugsley, H Selye and DL Thompson, "Observation Concerning the Mechanisms of Parathyroid Hormone Action" (1934) 15:6 *Br J Exp Pathol* 335. See also Allison Li, "COLLIP, JAMES BERTRAM" in *Dictionary of Canadian Biography*, Vol. 19, University of Toronto/Université Laval, 2003–, online: <http://www.biographi.ca/en/bio/collip_james_bertram_19E.html>; and Li 2003b at 91. Allison Li tells a story about how Pugsley and other graduate students, travelling to a conference in the US during the prohibition era, filled a number of bottles of Scotch for the trip and labelled them "emmenin"; see Li 2003b at 94.

[6] After joining National Health, Pugsley published a number of scientific articles on hormones and bioassay methods; see Leonard I Pugsley & Clare Morrell, "Variables Affecting the Biological Assay of Estrogens" (1943) 33:1 *Endocrinol* 48; Leonard I Pugsley, "Application of the Principles of Statistical Analysis to the Biological Assay of Hormones" (1946) 39:3 *Endocrinol* 161; S. Bird, LI Pugsley & MO Klotz, "The Quantitative Recovery of Synthetic Estrogens from Tissues of Birds (Gallus Domesticus), the Response of the Birds' Testis, Comb and Epidermis to Estrogen and of Humans to Ingestion of Tissues from Treated Birds" (1947) 41:4 *Endocrinol* 282; CG Willis, SE Rampton & LI Pugsley, "Variables Affecting the Assay of Testosterone Propionate Using the Seminal Vesicle Response of the Juvenile Castrated Male Rat" (1949) 44:3 *Endocrinol* 251. He also published a law journal article on the regulation of endocrinal products; see Leonard I Pugsley, "Canadian Control of Endocrine Products" (1951) 6 *Food Drug Cosm LJ* 532 at 533-534 ["Pugsley 1951"].

[7] On Morrell's scientific work, see Chapter 3, section 1 at notes 84-85.

[8] "About the Authors" (1954) 9 *Food Drug Cosm LJ* 500 ["About the Authors, 1954"] at 500; and "Reports to the Reader: About the Authors" (October 1950) 5 *Food Drug Cosm LJ* 627 (1950) ["About the Authors, 1950"] at 628.

On the second day of the meeting, with Pugsley now also in attendance, the Committee members were presented with his complete draft of the Sex Hormone Regulations. In effect, members were being asked to comment on the Department's settled regulatory conclusions, rather than being invited to engage in any foundational or frank discussion about policy objectives or a range of potential regulatory approaches.[9] This effort to constrain and shape the Committee's input was not somehow justified by the simplicity of the regulatory task at hand. To the contrary, as summarized by Pugsley himself a few years later, as seen in this chapter's opening quote, in the early 1940s in Canada, the nascent market for sex hormones was in a "chaotic state of affairs". Estrogenic products were being manufactured using wildly variant means of expressing and testing potency, creating challenges for their regulatory control.

In briefing the Committee on the proposed regulations, Pugsley and Morrell explained that they would define "sex hormone" to include all products, synthetic or natural, purporting to have androgenic, estrogenic, gonadotrophic, or progestational properties. But how would National Health officials know whether a product that purported to have "estrogenic properties" actually did? In biological standardization, hormones were commonly defined by some characteristic biological activity in a biological system – in a snappier ontological version, hormones were what hormones did – so how would National Health know if a product *was* a sex hormone?

The solution presented by the draft regulations seemed, at least superficially, to reflect what was then a quite uncontroversial approach to characterizing, testing, and standardizing biologics, including estrogenic drugs. Pugsley had considered, in drafting the regulations, the two central questions: *how to measure if a substance was estrogenic,* and *what to measure this substance against.* Put more precisely, the draft regulations mentioned methods of assay for measuring and expressing in quantitative units a drug's estrogenic activity (also referred to as potency or strength), and they prescribed certain physical reference materials that would serve as standards of reference for measuring the potency of preparations.[10] The theory of estrogenic

[9] At this first meeting, Pugsley proffered no explanation as to why the Department proposed to regulate sex hormones separate from the Biologicals Regulation, most recently amended in 1942. At that time, for all other biologics regulated under the *Food and Drugs Act*, National Health had prescribed their standards of quality and potency in a substance-specific part of the existing Biologicals Regulation. By contrast, for sex hormones, the Department was proposing a discrete, standalone regulation.

[10] The standards referenced in the Sex Hormone Regulations were not textual standards but rather physical reference material. In biological standardization, the word "standard" has two meanings: "It usually refers to a batch of samples of a reference material – a 'biological standard' – with which other preparations of similar material are quantitatively compared. The properties on which comparison are made are various; usually it is one or more kind of response of biological activity in a biological test system – the biological assay. A measured amount of a biological substance is assigned to define a quantity of that activity, in terms of a number of 'units of biological activity'. In this sense, the International Unit (IU) to quantify biological activity is analogous to the metre as the physical unit of length… the other common, qualitative, meaning of 'standard' is a set of criteria or specifications to characterize quality, as in a monograph of a drug in a pharmacopoeia." Derek R Bangham, *A History of Biological Standardization: the characterization and measurement of complex molecules important in clinical and*

identity underlying the draft regulations was therefore consistent with a physiological and pharmacological conception of estrogen, namely that a product's "estrogenic properties" would be a function of bioassay testing for activity, rather than a chemical conception of estrogen in which analytical chemical assays confirm the purity and amount of a constituent compound. Combined, the reference material and the assay method would identify a sex hormone.

While in principle this was straightforward, Pugsley had struggled to prescribe potency standards and reference standards in the draft regulations. With respect to reference standards, as discussed further below,[11] while the pure substances had standardized in the 1930s through the League of Nations, finished drug products and mixtures had not been widely standardized.[12]

With respect to potency, the draft regulations became even less precise. Pugsley's draft stipulated that sex hormone products would be measured in "International Units, where those existed", to be estimated by test methods employed in the Laboratory of Hygiene. This potency provision went on to state that where "International or Canadian Standards have not been established and stable standards cannot be furnished by the manufacturer, the methods of assay and of expressing potency shall be acceptable to the Chief of the Laboratory of Hygiene".[13] As of 1943, endocrinologists understood that there were *two* International Units for estrogens,[14] which in manufacturing and regulatory practices had often been confused. As summarized by two US government pharmacologists in a 1941 article, the "existence of two international standards with the correlated two international units, not equivalent in biological potency, has caused misunderstanding and confusion in the minds of many individuals…The erroneous concept that an international unit of estrogenic potency is a single standard is widely accepted."[15] Confusion was augmented in Pugsley's draft by his slide away from biological units and towards chemical assay. This occurred in a labelling provision – dropped from the final regulation – that required packaging to state a product's potency expressed either in International Units *or* on a weight volume basis for pure products.[16] Furthermore, although by

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research medicine (Bristol: Society for Endocrinology, 1999) ["Bangham 1999"] at 7. See also Chapter 1, section 1.ii; and Lezaun 2012.

[11] See section 1.ii below.

[12] Bangham 1999 at 34-35.

[13] Draft Sex Hormone Regulations, January 15, 1943, in Library and Archives Canada, Department of Health fonds, RG 29, "Canadian Committee on Pharmacopoieal Standards", 1942/06-1943/10, volume 252, file no. 339-4-8 (Part 1) ["(Possibly) Morrell's Committee file, 1942-1943"].

[14] One for estrone and one for estradiol benzoate.

[15] Curtis & Witt 1941 at 364.

[16] Draft Sex Hormone Regulations, January 15, 1943, s 4(d), in (Possibly) Morrell's Committee file, 1942-1943. A unit measured through bioassays quantifies biological *activity* rather than chemical *mass*. For a helpful explanation, see Bangham 1999 at 7-9.

1941 the potency of estrogenic preparations was “almost universally estimated by some modification of the Allen-Doisy vaginal smear technique on rodents”, the regulatory control of estrogenic drugs involved modifications to this technique to reflect the fact that preparations, not pure substances, were being tested, and “to allow statistical evaluation of the results.”[17] Moreover, increasing uniformity in research and regulatory laboratories was not paralleled in manufacturing practices, where assay procedures remained diverse and even firms using the Allen-Doisy method often modified it. Finally, consistent with National Health’s approach since 1934 to many Part II biologics, Pugsley’s draft regulations did not attempt to stabilize methods directly in law. His draft was silent on the potency test methods that should be used to identify sex hormones, and subdelegated to departmental officials the power to decide on test methods.

Pugsley’s effort to address the potency of sex hormone products did not sit well with the Committee. Committee members felt that Canadian regulatory standards for sex hormones fundamentally would need to specify methods of assay, around which, in the words of the minutes, “everything seemed to centre.”[18] As experts in biological standardization understood, the measurement made the material: “the identity of certain hormones is virtually ‘defined’ by the reference material and the particular assay method used to quantify activity.”[19] A regulation purporting to govern sex hormone preparations, that failed to prescribe the methods by which sex hormones were identified and defined, was no sex hormone regulation at all. In Committee members’ minds, the chaotic diversity of estrogenic potency should be circumscribed through careful selection of assay methods, defined unitage, and reference materials.

The National Health officials strongly resisted the idea that test methods should be prescribed in the regulations themselves. With his 13 years of experience with the Biologicals Regulation and with the amendments made, in 1934 and 1942, allowing for sub-delegation of methods to bureaucrats, Morrell argued for departmental discretion. He characterized the Department’s concern as financial. Inevitably, he noted, methods of biological standardization would change, such that prescribing test methods in the regulations themselves would require constant and expensive regulatory amendments. To break the deadlock, he offered that the Laboratory of Hygiene could instead informally distribute its internal bioassay methods, upon application by universities or manufacturers. Their interests satisfied, the professors backed down. With a motion moved by Henderson and seconded by Cook, the Committee recommended that the Department multigraph its biological test methods and supply them

[17] Curtis & Witt 1941 at 364.

[18] January 15-16, 1943 meeting minutes and materials, in Davidson’s Committee Materials, 1942-1943.

[19] Bangham 1999 at 34-35.

loose-leaf form “to as large a group as necessary, including teachers in Colleges of Medicine and Pharmacy and University Libraries.”[20] This would not be the only time, in their discussions of standardizing estrogen, that in performing their mandate to provide advice on drug standards, the academics would conflate their teaching and research interests with the public interest. Always keen to ensure access to test methods, the professors frequently regarded regulations prescribing drug standards less as a means to protect public health and more as codified teaching aids. One member went so far, at the next meeting, to criticize the draft monographs intended for the future Canadian Supplement as too “cold and legalistic in their phraseology” and as not elaborate or detailed enough for teaching pharmacy students.[21]

Though methods of standardization received the most sustained attention at the meeting, they were not the only aspect of the draft regulations considered by the Committee. Shedding light on a perceived purpose of the regulations, Committee members also discussed the classes of products that the regulations should “recognize”.[22] Far from aiming to restrict the composition, manufacture, sale or use of sex hormone products, the regulations were premised on giving sex hormones official government *recognition*, in effect endorsing them as drugs. Revealing manufacturers’ support for the regulations, Cook advocated that their coverage be extended to apply to additional types of estrogenic drugs. With an eye to Ayerst’s strategy for differentiating Premarin from other estrogenic drugs, he suggested that the regulations should be amended to recognize hormone preparations into two distinct categories: one for oestrogenic substances, administered by injection; one for conjugated substances, given by mouth. With no dissention, Pugsley agreed to amend the draft regulations accordingly, thus ensuring greater regulatory recognition and market differentiation for Ayerst’s conjugated brew of equine estrogens.[23]

During this discussion of the draft regulations, only one Committee member expressed concern with the hazards of sex hormones. Wing Commander Dr. Ray F. Farquharson, of the University of Toronto medical faculty, took the position that sex hormone products should only be sold on prescription. Prescriptions were one of the few means, absent prohibition, by which dangerous drugs could be controlled in Canada. The idea that potentially injurious drugs should

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[20] January 15-16, 1943 meeting minutes, in Davidson’s Committee Materials, 1942-1943 and in (Possibly) Morrell’s Committee file, 1942-1943.

[21] June 10-11, 1943 meeting minutes, in (Possibly) Morrell’s Committee file, 1942-1943.

[22] January 15-16, 1943 meeting minutes and materials, in Davidson’s Committee Materials, 1943-1944.

[23] Similarly, with respect to gonadotrophins, Cook also successfully advocated that the regulations should require the *source* of this hormone to be identified, again allowing for product differentiation between gonadotrophins derived from humans and horses. See Davidson’s Draft “Report of Canadian Committee on Pharmaceutical Standards”, in Davidson’s Committee Materials, 1942-1943; and A Linton Davidson, “Report of Canadian Committee on Pharmaceutical Standards” (March 1943) 48 *Can MAJ* 266, online: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1827694/pdf/canmedaj01700-0146.pdf>.

be sold only on prescription was quite new in Canadian law;[24] the first regulation under the *Act* that enumerated a list of potent drugs, prohibited for sale to the public without prescriptions, was made in 1941.[25] As Davidson commented in his departmental history, drugs added to the 1941 prescription list either had "a narrow margin between an effective and a poisonous dose or may produce undesirable effects if taken for long periods without competent supervision."[26] Over a decade's worth of studies had suggested a correlation between estrogen dosage and toxicity, so Farquharson's recommendation was not scientifically controversial. However, no Committee member supported his recommendation, and the suggestion was never raised again.

At the very first meeting of the Committee, the ontological precariousness of estrogen thus came into view. Estrogen's status as socio-technical and legal object – rather than a purely natural object – is underscored by the debate on the need to regulate bioassay methods in order to apprehend estrogens.[27] From the outset, National Health and the Committee appear as a regulatory site where, beyond laboratories and clinics, estrogen would be materialized.

1.ii. "At some loss as to the precise object you have in mind": apprehending estrogen as pure substance or as ready-made drug product, early 1943

Over the course of 1943, and as anticipated by the order in council establishing it, the Committee was engaged in two parallel regulatory activities. On the one hand, the Committee was reviewing and providing comments on Dr. Pugsley's draft Sex Hormone Regulations. In entirely separate discussions, it was also developing a new Canadian Supplement to the British Pharmacopoeia. Both regulatory activities would immediately come to engage estrogen. Just as rapidly, it would become evident that the estrogen performed in the practices of bureaucrats, manufacturers, and professors of medicine and pharmacy was not the same estrogen.

After its first meeting, the Committee members continued to flesh out their list of candidate drugs for inclusion in the Canadian Supplement. As Davidson had responsibility for drafting all

[24] In the 1930s, provincial laws governing pharmacists and drug dispensing, and imposing prescription or other requirements on potent drugs, were highly inconsistent across provinces; see Curran 1956 at 595-596. The *Act* was amended in 1939 to allow drugs that may be injurious to health to be restricted to sale on prescription; Chapter 3, note 96. In 1946, this power was expanded – driven by concerns over resistance to penicillin – to allow drugs to be restricted to sale on prescription "in the interest and for the protection of the public health"; see SC 1946, c 23 and Appendix IV to the Food and Drug Regulations.

[25] PC 1941-8442 (31 October 1941), *Canada Gazette,* Vol LXXV, No 19, at p 1496 (November 8, 1941). See also Davidson 1949a at 84; and Davidson 1949b. Included were aminopyrine, barbiturates, Benzedrine, cinchophen, neocinchophen, dinitrophenols, sulphonamides, and thyroid (like sex hormones, also listed on Part II of Schedule B to the *Act*). In 1944, the list was extended to veterinary drugs; see PC 1944-2194 (27 March 1944), *Canada Gazette,* Vol LXXVIII, No 16, at p 1552 (April 15, 1944).

[26] Davidson 1949b.

[27] Von Schwerin, Stoff & Wahrig 2013b at 26-30; see also Chapter 1, section 1.ii, particularly that content at notes 72-77.

the monographs, in March, Henderson sent Davidson a revised list of drugs.[28] Newly on his list were estrone and estradiol benzoate,[29] as, at the end of 1942, both substances had been added to the US Pharmacopoeia ("USP").[30] After discussing the substances with Pugsley,[31] Davidson wrote back to Henderson. Pugsley, he advised, "seemed to be at some loss as to the precise object you have in mind".[32] Rather than see the two estrogens as drug entities appropriate for pharmacopeial monographs, Pugsley saw them as manufactured, pre-made, industry products. As estrone and estradiol benzoate preparations would be controlled under his forthcoming Sex Hormone Regulations, Pugsley saw no need for them to be included in the Supplement.

Henderson was befuddled. While he did not hold "any very strong brief" for including estrone and estradiol benzoate in the Supplement, and he appreciated that hormone products would be controlled by future regulations, he nonetheless felt that "surely it is advantageous to have a definition of such pure and active substances as these" included in Supplement. In his view, these definitions would "doubtless form the reference substances for hormonal testing and a complete description of their characteristics should be available for workers and practitioners".[33]

This was not reducible to divergent views on how these substances should be represented. Rather, multiple versions of estrone and estradiol benzoate were realized – made real – in relation to diverse scientific and regulatory practices. Oudshoorn has shown how divergent material practices, in different and networked disciplines, shaped concepts about sex hormones: "hormonal drugs are neither ready-made laboratory products that are subtly marketed to their audiences, nor are they compounds simply discovered in nature. The specific "nature" of the drug and the interests that become embodied in it are shaped in the networks of the different groups that called hormonal drugs into existence".[34] Gaudillière has similarly shown how divergent testing logics and practices existed within different manufacturing firms' laboratories.[35]

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[28] March 17, 1943 letter from Henderson to Davidson, in Davidson's Committee Materials, 1943-1944.

[29] The American spellings were estrone and estradiol benzoate. In the 1940s, Canadian regulators used British spellings. Estradiol benzoate is an ester of estradiol that had been synthesized by Schering, the German drug manufacturer, in 1933. It was often used in estrogenic preparations intended for intramuscular injection, typically combined with oil (peanut mostly).

[30] *The pharmacopoeia of the United States of America: twelfth revision, U.S.P. XII: official from November 1, 1942* (Easton: Mack Printing Company, 1942) ("USPXII").

[31] March 24, 1943 memo from Davidson to Morrell, in Davidson's Committee Materials, 1943-1944.

[32] April 5, 1943 letter from Davidson to Henderson, in Davidson's Committee Materials, 1943-1944.

[33] April 7, 1943 letter from Henderson to Davidson, in Davidson's Committee Materials, 1943-1944. On April 14, 1943, Henderson likewise proposed that diethylstilbestrol should be added to the Supplement, as it was then proposed for addition both to the USPXII and to the sixth addendum of the British Pharmacopoeia; see Davidson's Committee Materials, 1943-1944.

[34] Oudshoorn 1994 at 83.

[35] Chapter 1, section 1.i. and section 1.ii.

Likewise, within biological testing practices, difference was performed by testing done in regulatory control of drug products or in pharmacological characterization of pure substances.

Working in the Laboratory of Hygiene, which had regulatory responsibilities for controlling industry products by testing them on laboratory animals to determine if their activity and identity corresponded with their labels, Pugsley was occupied by whether an estrogenic preparation did (and therefore *was*) what its manufacturer claimed. As of 1942, when Pugsley first drafted the regulations, estrogenic preparations had emerged on the market in three basic forms: in oil solutions, in aqueous solutions, and as tablets, capsules, or powders. Of these, most preparations on the market were oil solutions with "quite high" potency intended for parenteral administration, while the various aqueous extracts by contrast tended either to have little activity or quickly deteriorated, and the oral tablets were only just appearing.[36] Not only did the product form change regulatory tests, but the specific formulants were also highly material. These nontherapeutic agents played many roles, whether "to emulsify, stabilize, suspend, preserve, dilute, solubilize or flavour",[37] and were essential partners in any dosage form or preparation. Indeed, these agents lived up to their names. They acted to sometimes radically change potency test results; as Doisy explained, "[d]epending on the solvent and on the division of the dose, estrone may be four or two hundred and sixty-six times as potent as estriol".[38] Thus, for Pugsley, estrone and estradiol benzoate only became "estrogenic" when mixed with nontherapeutic agents like oils, fats, or milk, presented in a liquid solution, tablet, or ointment, and delivered in various doses to various animals. In the Laboratory of Hygiene, an enforcement chemist was required to "rely entirely on the results of his analysis of the finished product", and to "use analytical procedures which give him accurate information on the amount of the drug present and assure him that the values obtained have not been influenced in any way by the presence of other substances in the formulation".[39] This challenge was pronounced with orally-administered conjugated estrogen products, for which there was no generally accepted assay method nor official reference standard, and which, when tested with existing methods, proved that labelled potencies were wildly imprecise.[40] For Henderson, a university-based pharmacologist, estrone and estradiol benzoate were estrogenic and could be known as such,

[36] Curtis & Witt 1941 at 364-365; and Trites 1940 at 100. Trites indicates that, as of January 1940, a single topical estrogen preparation, marked as "Progynon-DH Lanel" and manufactured by the German firm Schering, had appeared on the Canadian market. However, it is unclear whether this product remained available in Canada by 1943.

[37] Blake 1976 at 279; see also generally 279-84.

[38] Edward Doisy, "The Estrogenic Substances" (1941) 16:6 *JAMA* 501 ["Doisy 1941"] at 504.

[39] Frank H Wiley, "The Analysis of Drugs" (1961) 16 *Food Drug Cosm LJ* 733 ["Wiley 1961"] at 735.

[40] William Homer Lawrence & CW Chapman, "The Bioassay of Some Commercial Conjugated Estrogens" (1952) XLI:11 *J Am Pharm Assoc* 624 ["Lawrence & Chapman 1952"].

regardless of product mixtures. Not engaged in the regulatory practice of testing manufacturers' claims, his laboratory practice would primarily involve working with "pure" substances and extracts. In regulatory testing in the Laboratory of Hygiene, and in pharmacological research at the University of Toronto, estrone and estradioal benzoate were simply different things.

Though not put in such terms by Pugsley or Henderson, one might also reduce their dispute to the question, as much legal as ontological, of whether these two estrogens were "medicine", to be administered to patients, or were "drugs", a concept encompassing drug ingredients, substances, or materials. The *Act* was not particularly helpful in answering such a question. Legally speaking, after the 1939 amendments, "drugs" were defined as a broader category of substance than "medicines". A drug included *inter alia* "all medicine for internal or external use for man or animal" and "any substance, mixture of substances and any article that may be used for the diagnosis, treatment, mitigation or prevention of disease in man or animal". Medicine, on the other hand, was itself defined to mean "any substance or mixture of substances that may be used in restoring, correcting or modifying organic functions".[41] That is, a drug was defined to mean both a medicine ready for administration to humans and also a medicinal ingredient or article. Further, the *Act* simultaneously provided that "drugs" could be mentioned or described in Schedule B,[42] and that "any material" could be added to or removed from Schedule B.[43] When considered through the lens of the statute, estrone and estradiol benzoate were drug and medicine, substance and mixture, article and material.[44] When considered in the hands of practitioners, the laboratory practices and tests that performed these estrogens were multiple.

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[41] SC 1939, c 3, ss 1 and 2, which amended s 1(c) and added s 2(j) respectively to the *Food and Drugs Act.*

[42] *Food and Drugs Act,* s 6(3)(c).

[43] *Food and Drugs Act,* s 3(i).

[44] Debate engaging the question of whether estrone was a drug or an ingredient was not limited to the Canadian Committee on Pharmacopoeial Standards. In 1944, the US Customs Court considered the matter, in *Roche-Organon, Inc v United States*, 1944 Cust Ct LEXIS 25. Released on April 29, 1944, the decision did not seem to come to the attention of Committee members or National Health (nor would it, as a foreign customs decision, be likely to come to their attention). The matter involved whether imported "estrone crystals (urine concentrate)", consisting of about 90 percent oestrone, was a "medicinal preparation" or a "drug" for customs purposes (with medicinal preparations receiving less favourable tariff treatment). The Court applied an existing test, holding that if the imported estrone, when arriving in the US, possessed sufficient therapeutic properties to be used medicinally without the use of any other active agent, then it was a medicinal preparation and not a drug. The estrone was held to qualify as a medicinal preparation, regardless that to be administered to patients it needed to be further compounded, in the US, with various inert bases to form different manufactured products. Regardless of this, the estrone itself underwent "no chemical change" in the manufacturing process. Notably, the Court reached this conclusion without considering potency or dose, both of which are changed by combining pure estrone with inert bases. Roche brought a second case – not technically an appeal, but with the same intent and effect – in 1947. This time potency was considered. For this and other reasons, the opposite conclusion resulted in the second case; see *Roche v United States*, 1948 CCPA LEXIS 323.

Changing industrial dynamics were also at play. Henderson's understanding of the role of pharmacopoeia was that which had predominated in decades and indeed centuries past, when pharmacopoeia guided drug making. By the 1940s, at the beginning of what some would call the therapeutic revolution, the function of pharmacopoeia was evolving, as they increasingly became reference rather than recipe books, and as pharmacists increasingly became suppliers of pharmaceutical firms' products rather than drug makers.[45] Canadian pharmacists were not whipping up complex estrogenic drugs in pharmacy backrooms, yet nonetheless Henderson held to the principled position that all drugs should be defined in pharmacopoeia.

When the Committee gathered for its second meeting, in June 1943, and it turned to the draft list of drugs for the Canadian Supplement, the estrogens proved to be the most controversial. Their inclusion on the list triggered a deeper and sustained debate among Committee members, one that engaged fundamental epistemic and ontological issues of how to apprehend, construct, reflect, and respond to the troublesome and temperamental estrogens.[46] From the outset, Ayerst's scientist Dr. Cook challenged the proposed inclusion of estrone and estradiol benzoate. Resonant with Pugsley's earlier views, Cook felt that these standards simply were not needed. Of the commercially available drug products containing oestrone and oestradiol benzoate, 95% were manufactured in the United States to standards under the USP, arriving in Canada in ready-made, mass-produced dosage forms (whether tablets, capsules, suppositories, or single-dose injections). With Ayerst having just been acquired by a US drug firm in March 1943,[47] Cook adopted a discourse of Canadian regulatory impotence. He argued that Canadian regulators had no ability to influence potency standards embedded within imported drugs, or relatedly, the doses in which those drugs would be offered on the Canadian market.

The medical professionals, in contrast, insisted on the need for National Health to be as comprehensive as possible in its drug standardization efforts. Henderson insisted that these two substances be standardized to assist physicians, and Esli L. Woods, the young new Dean of the University of Saskatchewan's pharmacy faculty, also emphasized that the Supplement should be as complete a guide as possible for pharmacists. The discourse that Henderson and Woods leveraged hinged on a principle of "no special treatment" and on the assumed value of providing as much information as possible to practitioners – regardless of whether that information would, practically speaking, make any difference to Canadian physicians prescribing imported drugs.

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[45] Quirke 2005 at 177.

[46] June 10-11, 1943 meeting minutes, in (Possibly) Morrell's Committee file, 1942-1943.

[47] American Home Products Company acquired both Ayerst McKenna & Harrison Ltd. and its small US subsidiary; Mira Wilkins, *The History of Foreign Investment in the United States 1914-1945* (Cambridge, MA: Harvard University Press, 2004), at 547.

National Health officials slid between and combined discourses of futility and pragmatism. The department's senior pharmacologist, Dr. Morrell, agreed with Cook that, because estrone and estradiol benzoate were not administered "in pure form" but typically arrived on the Canadian market in ready-prepared dosages, that rather than try to standardize these substances through the Supplement, they could instead be controlled post-manufacture under the future Sex Hormone Regulations.[48] Intriguingly foreshadowing the shift from standards to labelling that would ultimately be achieved in the Sex Hormone Regulations,[49] Lancaster suggested that instead of promoting drug standardization *per se,* these new regulations would nonetheless ensure drug uniformity by requiring the use of proper names. When the Ayerst scientist doubled down, arguing that tethering manufacturers to standards would remove incentives to improve products, Morrell interjected to remind everyone that, unlike in the U.S., there was no process in Canada for regulators to test the safety of new drugs. In this way, National Health adopted industry's futility discourse while deploying that same message to stress, subtly, that Canadian regulators should still take whatever action was open to them to fill any gaps left by the US FDA. Unspoken in this debate, but surely hovering over it, was the fact that Premarin had been marketed in Canada before the US FDA ever deemed it to be safe.

Also unspoken in the debate, at least expressly, was women's health. Patients went unmentioned. So did consumer protection. Nobody expressed any views on the perceived value of these two estrogens to treat any disorders. The physicians and pharmacists emphasized that estrogens should not be exempted from standards; manufacturers asserted the realities of US market control and the underlying industrial standards built into imported drugs; and National Health officials accepted the difficulty of influencing manufacturers while identifying other regulatory avenues towards uniformity. All participants were concerned with standardization, if from diverse logics. Yet the women who would consume these drugs disappeared from view.

At a stalemate, the Committee members broke for lunch at the Chateau Laurier. That afternoon, without further discussion, they decided to include estrone and estradiol benzoate in the Supplement.[50] Rather than squarely resolve the dispute by forcing a decision as to which logic or practice of standardization should take priority when determining whether a drug should be added to the Supplement, the members appear to have bracketed their disagreement.

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[48] It is notable that, at the January meeting, Morrell took the opposite view with respect to vitamins. Despite that the USP then contained standards for vitamins, he argued that vitamin monographs should be included in the Canadian Supplement; *ibid.*

[49] See section 3 below.

[50] Technically, following the practice of the British Pharmacopoeia, the Canadian Supplement monographs would be headed by Latinate names. Thus, in addition to oestrone and oestradiol benzoate, the main headings of would be *oestradiolois benzoas* and *oestronum* respectively. None of the Committee members ever spoke of these substances using these stylized Latin names.

The same debate re-opened the next day. This time, though, it involved DES. Morrell queried whether stilboestrol and stilboestrol dipropionate should be included in the Supplement, as had been proposed by Henderson. Surprisingly, Cook reversed his position from that taken the previous day, and advocated that stilboestrol and stilboestrol dipropionate be included, although he advocated that the two monographs not be completed until the British Pharmacopoeia Commission finalized its next addendum. The Committee agreed, and Cook assumed personal responsibility for reviewing the draft DES monographs before the Committee's next meeting.[51] Thus Ayerst would have significant influence in determining what DES would be and would do.

Charged with advising on how DES should be enacted, Cook delayed giving any advice. Over the summer, Davidson persistently sought his input on the draft DES monographs. For stilboestrol, Davidson had based his work on the draft USPXII monograph, but for stilboestrol dipropionate, with little guidance material available, Davidson had prepared a "more or less skeleton draft", [52] and asked Cook to fill in the details.[53] To the great frustration of National Health officials, Cook ignored these repeated entreaties (including Davidson's effort to enlist Cook's secretary in securing his reply).[54] With the Committee's fall meeting approaching, Lancaster had to intervene, by making a long-distance phone call that spurred Cook to return the DES monographs with his revisions. However, they were not returned in time to circulate in the package of materials that Committee members were expected to review before assembling that fall. With no other members ever engaging in such non-responsive behaviour, National Health officials came to view Cook's delay as a deliberate tactic rather than an oversight. [55]

Premarin was being actively positioned by Ayerst as the main competitor to DES, yet nobody contemplated whether asking Ayerst's research director to draft standards for the quality, purity, and potency of DES might pose a conflict of interest. The technical details of these standards were by no means neutral – they had political, economic, and ethical consequences. DES had been characterized, in laboratories and in advertisements, as the most potent of the estrogenic

[51] June 10-11, 1943 minutes and materials, in (Possibly) Morrell's Committee file, 1942-1943.

[52] August 25, 1943 letter from Davidson to all Committee members, in Davidson's Committee Materials, 1943-1944.

[53] Letters from Davidson to Ayerst on July 5, 1943; August 5, 1943; August 16, 1943; August 31, 1943; and September 13, 1943; and letters from Ayerst to Davidson on August 30, 1943; September 14, 1943; and September 16, 1943; all in Davidson's Committee Materials, 1943-1944.

[54] This is the one of the only appearances by a woman in Canadian archival materials from the 1940s regarding sex hormones. In the summer of 1943, Mr. Davidson exchanged some letters with Rebecca Scott, the secretary to Dr. Cook, pleading for her help in enlisting Dr. Cook's reply; in Davidson's Committee Materials, 1943-1944. On Scott, see also Chapter 3 at note 4.

[55] Davidson was not naively trustful of Cook. For example, in September 1943, he exchanged correspondence with Mr. Hunter of the EB Shuttleworth Chemical Co., in which he shared information about the draft regulation to control variability in capsules, tablets and ampoules. On the expectation that Cook would consult Hunter about it, he asked Hunter to keep the exchange confidential from Cook; see September 15, 1943 letter from Davidson to Hunter, in Davidson's Committee Materials, 1943-1944.

drugs. When it came to potency, Premarin was at a competitive disadvantage. Yet Davidson advised Cook that, if Cook saw fit to exclude a unit of potency for stilboestrol in its monographs, then the Committee would surely agree with Cook's advice.[56] When Cook finally sent comments on the DES monographs, despite that they followed the USPXII monograph "rather closely", he nonetheless suggested changes. He recommended that the DES monographs should "omit the statement of potency in international units, as these standards are applicable strictly only to oestrone or to oestradiol monahenzoate (sic)".[57] Beyond concealing DES' potency, he also advocated to widen the dosage range, and to mention two modes of administration.[58] Sensitive to the greater potency of DES, Ayerst was working to brand its Premarin tablets, characterized by oral administration and flexible dosage, as more convenient and less nauseating.

The Supplement monographs were not the only matter of debate. Continuing to engage in the disjointed practice established at its very first meeting, at its June 1943 meeting, the Committee again considered the Department's draft Sex Hormone Regulations entirely separately from the question of whether to standardize estrogens in the Supplement. Not only did they address these regulations at different moments in their meetings, but in different terms. In contrast to their discussion of the Supplement, during which Committee members referred to estrone, estradiol, stilboestrol, or other such common names, when discussing the Department's Sex Hormone Regulations, they shifted to speak of "sex hormones" or "sex hormone preparations".[59] Their discussion of the draft regulations continued to centre heavily on what methods of assay should be adopted by National Health. That spring, Pugsley and Morrell had written down the bioassay methods then being used in the Laboratory of Hygiene to test three substances – the "male hormone", the "oestrus-producing hormones",[60] and chorionic gonadotrophins – and Davidson had circulated these methods documents to the Committee. While most members reviewed the internal test methods favourably, Cook claimed that the methods were not actually used by any manufacturers; if manufacturers were materializing estrogenic drugs using variant potency tests, that could undercut National Health's ability to test and control those products. Once again, the Committee's proceedings featured onto-epistemological divergence on the question of what "oestrus-producing hormones" were, what they did, and how to measure them.

[56] July 5, 1934 letter from Davidson to Cook, in Davidson's Committee Materials, 1943-1944.

[57] September 16, 1943 letter from Cook to Davidson, in Davidson's Committee Materials, 1943-1944. Cook's recommendation was consistent with some of the leading literature; see e.g. Doisy 1941. His recommendation was adopted both for stilboestrol and for stilboestrol dipropionate. Both prescribed the Doisy-Allen test but neither used International Units to express potency.

[58] In the final Canadian Supplement, the first of these two recommendations by Cook was rejected and the second accepted.

[59] For the historiography on the scientific shifts in the names assigned to the steroid "sex" hormones, see Chapter 1, section 1i.

[60] This was the collective name assigned in the Department's bioassay methods document for estrone and estradiol benzoate.

And once again, the debate was not resolved but rather deferred. Rather than counter Cook's claims about the industry's practices, a sex hormone sub-committee was formed. Comprised of Cook, Morrell and Henderson, the sex hormone sub-committee was tasked with consulting US commercial laboratories on their assay methods, and with reporting back at the next meeting.

1.iii. "It was not for the officers of the Department to take a stand …until they were satisfied that there was danger to the public": the Committee meets, October 1943

Perhaps over the summer of 1943 Cook was busily consulting US drug manufacturers on their bioassay methods; perhaps he had lacked the time to review the DES monographs; perhaps, as he said, it had been an unusually strenuous summer.[61] Or, perhaps, knowing that the Canadian Pharmaceutical Manufacturers Association ("CMPA") was planning an intervention, Cook's delay was meant to ensure that he acted consistently with the CPMA.

At the Committee's fall meeting, held over October 1-2, 1943, and without prior notice, the CPMA submitted four resolutions.[62] One resolution expressed concern that industry was not being afforded sufficient time to study the Committee's proposed recommendations that involved changes to regulations.[63] The CPMA intervention was less than well received. The Deputy Minister intervened swiftly and forcefully with the CPMA president. Wodehouse claimed that Committee members were not to lobby for industry interests, and that the CPMA should instead communicate with him. As mentioned, Wodehouse had taken largely the opposite position the previous year, when he was seeking the CPMA's support for the Committee.[64] With the Committee an ongoing site of struggle between medical professions, government, and industry, the ongoing tactical efforts to position industry scientists simultaneously as independent advisors and industry representatives were to be expected.

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[61] September 16, 1943 letter from Cook to Davidson, in Davidson's Committee Materials, 1943-1944. Cook's delay throughout the summer was not limited only to DES. He also failed to approve the June 1943 minutes or to give input on National Health's regulatory proposal for variability standards for tablets and capsules; see the correspondence cited at *supra* notes 53-55.

[62] The CPMA tendered its resolutions through Committee member A.K. North, and not through Cook.

[63] Two resolutions focused on intellectual property issues, which constantly arose in the Committee's deliberations (and would cause ongoing debate in the years to come). Another sought to separate "technical matters" from regulatory matters, through formation of a new technical committee; see October 1-2, 1943 meeting minutes and materials, in Lancaster's File, 1940-1943.

[64] See Chapter 3, section 2. See also "Report of Canadian Committee on Pharmaceutical (sic) Standards" that the Department wrote and published in the *Canadian Medical Association Journal* in March 1943, *supra* note 23, in which Committee members were identified as 'representing' the Canadian Medical Association (Henderson, Mousseau), the Royal College of Physicians and Surgeons of Canada (Farquharson, Lewis), the CMPA (Cook, North), or the Department (Morrell, Valin, Lancaster, Davidson).

Aside from this drama, this meeting in October 1943 proved pivotal in enacting estrogen. The first item up for discussion was bioassay methods in the Sex Hormone Regulations. On behalf of the sex hormones sub-committee, Cook provided an interim report, drafted on a Chateau Laurier notepad right before the meeting. He reported that he had now contacted U.S. commercial laboratories - and, as it turned out, there would be little criticism from US firms of the Department's bioassay methods for the estrogens. However, one US firm had suggested that more study was needed on the bioassay methods for gonadotrophins. Thus, reflecting Morrell's desire to avoid prescribing methods of assay directly in the Sex Hormone Regulations, Cook concluded his report by advising that the sub-committee would expedite its study of bioassay methods so that National Health could later publish a "book of official methods".[65]

By the October meeting, then, a clear question was emerging for the Committee's decision: ***who*** should decide how to measure the potency of sex hormones, and ***when*** should this occur? This question was squarely at issue when the Committee returned to the Sex Hormone Regulations on the second day of the meeting. Noting that it was "rather futile" to finalize regulations before settling on methods of assay, Henderson advocated that the Department should wait until the methods were ready before it made the regulations. At this point, a member shifted the discussion away from methods and towards reference standards, allowing Morrell to emphasize his long-favoured means by which sex hormone preparations could be standardized. Rather than wait for methods, Morrell suggested, National Health would create reference standards based on manufacturers' submitted samples of their hormonal products. Henderson agreed that where no reference standards already existed, the Department should accept a manufacturer's standard, however this did not resolve who should determine the test methods for potency, and whether this should occur before the regulations were made.

Discussion was shut down by the Deputy Minister. Robert Wodehouse was attending the meeting during the discussion of the Sex Hormone Regulations. He expressed his view that:

> "…the Department should not discourage, through lack of knowledge, any company or laboratory from continuing research and attempting to bring out new products so long as no harm was being done. It was not for the officers of the Department to take a stand, in any new field, until they were satisfied that there was danger to the public."[66]

[65] October 1-2, 1943 minutes (Appendix B), in Lancaster's File, 1940-1943; and Cook's report on Chateau Laurier stationary, in (Possibly) Morrell's Committee file, 1942-1943. On the "book of methods", see content associated with *infra* notes 195-198.

[66] October 1-2, 1943 minutes, in Lancaster's File, 1940-1943. Wodehouse's position strongly contrasted with the "precautionary" approach to DES taken by senior FDA officials between 1939-1941, before the FDA ultimately issued a new drug approval for DES; see Langston 2010 at chapter 3.

With this remarkable intervention by Wodehouse, who was merely a guest and observer, the Committee backed off any further scrutiny of the Sex Hormone Regulations. Immediately following his intervention, Committee members voted to defer the question of whether sex hormone products should be licensed. They would never return to this question. Furthermore, the Committee decided to give advance approval to the regulations, passing a motion that it would "agree in principle to the proposed Sex Hormone Regulations after they had been redrafted and received, but before being submitted to council". A few weeks later, in the course of routine correspondence seeking approval of minutes, Davidson enclosed the revised draft of the regulations, casually noting that he was "assuming" that members approved.[67] No member ever provided any further comments on the draft regulations.[68] The Deputy Minister had aligned with Ayerst's position that Canada should not standardize the potency of estrogenic drugs, which would be allowed to multiply with many doses, test methods, and standards. Estrogenic drugs could be as potent as industry preferred, manufactured in whatever doses it desired.

From here, estrogenic multiplicity snowballed even further. Maintaining its disjointed and bifurcated approach, the Committee considered, again separately from the Sex Hormone Regulations, the estrogens proposed to be listed on the Canadian Supplement. It gave final approval to all the monographs that would be included in the Supplement, and to the full list of drugs that it was recommending become Part V of Schedule B to the *Act*.[69] The monographs and the Part V list included estrone, estradiol benzoate, stilbestrol, and stilbestrol dipropionate. On the face of it, these estrogens were about to be standardized in Canada. Or were they? On closer review, the monographs embedded many ambiguities, delegations, and diversities. First, in the estrone and estradiol benzoate monographs, the assay method for potency was left to the discretion of the Laboratory of Hygiene. That is, while these monographs adopted International Units for *expressing* potency, they did not set out a method for *measuring* the potency of

[67] November 5, 1943 letter from Davidson to Committee members, in Davidson's Committee Materials, 1943-1944.

[68] Despite this, the Department continued to position the Sex Hormone Regulations as something that the government had endorsed on the Committee's recommendation, rather than a departmental initiative to which the Committee had acceded. As one official example, a preambular recital to the final regulations provided: "WHEREAS the Minister of Pensions and National Health reports that the Canadian Committee on Pharmacopoeial Standards constituted under the authority of Order in Council of the 5th June, 1942 (P.C 4739), has recommended that standards of quality and potency be prescribed, and labelling requirements specified, in respect of sex hormones mentioned or described in Part II of Schedule B to the Food and Drugs Act, and that officers of the Department of Pensions and National Health have concurred in such recommendation."

[69] October 1-2, 1943 meeting minutes and materials, in Lancaster's File, 1940-1943. As approved, the Canadian Supplement simply reinstated many *British Pharmacopoeia* monographs in their original form before the wartime addenda; MG Allmark, "The Pharmacopoeias and their Status under the New Canadian Food and Drugs Act" (1954) 9 *Food Drug Cosm LJ* 251 ["Allmark 1954"]. However, Davidson also drew heavily upon the USPXII monographs; see Davidson's Committee Materials, 1943-1944.

estrone and estradiol benzoate.[70] Furthermore, the stated dose ranges described were fairly wide. The monographs for stilboestrol and stilboestrol dipropionate were silent *both* on the unitage and the method of assay for potency. This silence on bioassay methods was atypical in pharmacopoeias, although it did align with the Department's (unlawful) approach to subdelegating to the Chief of the Laboratory the power to prescribe how potency would be expressed and tested for numerous biological drugs under the Biologicals Regulation.

Another ambiguity, also related to assay methods, was whether these four substances were biological substances or chemical compounds. At this meeting, members had debated whether to include any structural chemical formulae at all, in any of the monographs.[71] At Dean Hurst's motion, the diagrams were generally included. The monographs for the four estrogens enact these substances, to differing degrees, as both biological and chemical. Each featured a chemical diagram, and the DES monographs included chemical tests for identity and purity.

Finally, intriguingly, neither the estrone nor the estradiol benzoate monographs identify any "estrogenic properties" of the substances. By contrast, under the "tests for identity", the two DES monographs each state that these two substances produce "vaginal oestrus in ovariectomized adult female albino rats following the subcutaneous injection of 0.002 mg in oil". No such effects or properties are identified for estrone or estradiol benzoate (nor did the monographs identify any symptoms, diseases, or disorders that these estrogens were meant to treat). Yet, as will be discussed further, in the Sex Hormone Regulations, the definition of a "sex hormone", its very identity, was stated to hinge on its purported estrogenic properties. In the Regulations, what an estrogen was depended on what it was purported to do. Here, in the Supplement, the very place that Henderson originally envisioned would provide definition of these pure substances, the monographs declined to define these two estrogens by how they would act with bodies.

2. Techniques of validating: enacting Part V, the Canadian Supplement, the Parenteral Regulations, and the Sex Hormone Regulations

At its meeting in October 1943, the Committee ultimately endorsed a heterogenous group of laboratory, manufacturing, and enforcement practices that, taken together, served to materialize

[70] In these monographs, each milligram of estrone was prescribed to have a potency of 10,000 international units, and each milligram of estradiol benzoate was prescribed to have a potency of 10,000 international (benzoate) units.

[71] October 1-2, 1943 meeting minutes and materials, in Lancaster's File, 1940-1943. The primary reason for the debate was that some diagrams had been rendered erroneously or incompletely. Henderson, a pharmacologist, also suggested that they would be expensive; Dean Hurst, a pharmacist, wanted them included. The legal significance of the Committee's decision to enact these drugs both biologically and chemically is addressed below; see the content associated with *infra* notes 85-89.

estrogen in many different forms, potencies, and properties. However, legal vehicles were needed to drive these practices and potencies forward. Specifically, the government of Canada still needed to formally enact, as law, the Canadian Supplement (and a new Part V of Schedule B) and the Sex Hormone Regulations (and amendments to Part II of Schedule B). Before they could be made, National Health solicitors and DOJ counsel were required to perform these enactments as *intra vires*. This section describes the "techniques of validating" that were employed by these officials to materialize these enactments and their estrogens.

As described in the last chapter, Harry Lancaster, the Chief Dominion Analyst, had long insisted that the necessary precondition to enacting the Canadian Supplement was to amend Schedule B of the *Act* by adding an entirely new "Part V" to the schedule, only after which could legally binding drug standards of quality and potency, in the form of the Supplement, be made for those drugs.[72] As seen, however, his plan had received a rough ride from National Health's other senior officials and its solicitors Gunn and Russell, which was only resolved with the erasure of this plan from the order in council creating the Committee. Still, in 1943, the fact remained that on its face the *Act* spoke of Schedule B as comprising four discrete parts – Parts I through IV. It did not mention any Part V, nor did it explicitly authorize adding new Parts.

Moreover, National Health solicitors remained unconvinced of the plan's validity. On December 15, 1943, Gunn sent National Health's draft order in council proposing to amend Schedule B to DOJ. The proposal was twofold – it added the Committee's list of drugs, including oestrone, oestradiol benzoate, stilboestrol, and stilboestrol dipropionate, in a new Part V; and it revised Part II of the schedule by, among other changes, adding "Sex Hormones".[73] When transmitting the proposal to the Deputy Minister of DOJ, Gunn expressed his doubts that Cabinet had the jurisdiction to add the new Part V.[74]

The matter was assigned to Elmer Driedger, at that time a relatively junior counsel, but already with expertise in legislative drafting. Before preparing his advice, he met with Lancaster. In their meeting, Driedger suggested that the significance of the four Parts may have been removed by the statutory amendment adding s. 3(1)(i) in 1934, a suggestion finding no obvious

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[72] See Chapter 3, section 1. Lancaster and his staff continued to hold this understanding throughout 1943. See e.g. Davidson's letter in January 1944 noting that because PC 1944-96, adding Part V to Schedule B, had by that time been made, the Canadian Supplement could now be finalized in a formal regulation, in Davidson's Committee Materials, 1943-1944.

[73] In the draft order, and also the final order, Part II was amended to state:

> "Preparations of Pituitary, Adrenals, Sex Hormones and any other animal tissue preparations or any synthetics purporting to have physiological action similar to any of the foregoing.
>
> Parenteral products for the treatment of allergy; Antibacterial products of the growth of fungi or of bacteria, for example penicillin, their salts, derivatives and any preparation containing any of them."

[74] December 15, 1943 letter from Gunn to Varcoe, in EA Driedger's Schedule B File, 1943.

support in the text or legislative history of the 1934 amendments.[75] Together, they concluded that Part V could be justified as authorized by s. 3(1)(i) of the *Act*. Yet, lacking confidence in the legality of this conclusion, they decided to erase mention of s. 3(1)(i) from the face of the order amending Schedule B. Just as with the creation of the Committee, where the foundation of the order amending Schedule B was legally dubious, the solution was to render the order silent.[76]

Driedger then provided a written opinion that was equally difficult to square with the *Act*.[77] He framed the question as whether the Governor in Council had authority to add a new Part to Schedule B. In answering this affirmatively, he relied primarily on s. 3(1)(i). As he noted, this provision empowered the Governor in Council to add such "material" to Schedule B as the Minister deemed necessary in the public interest; he argued that, construed literally, s. 3(1)(i) authorized the Governor in Council to "add or remove *anything* from the schedule". However, to "add any material" had a different literal meaning than to "add anything, including new parts." Indeed, his construction of "any material" was inconsistent with National Health's own position a few years later (after Lancaster had retired). As explained in a 1949 journal article by its then legal advisor Robert Curran, "the Department interpreted the word 'material' to mean drugs or classifications of drugs".[78] That interpretation of "any material" to mean any *material substance* in the form of drugs is, literally, more defensible than "the parts comprising the schedule".

Driedger sought to bolster this questionable literal construction with a purposive one, opining that the purpose of the 1934 amendment adding s. 3(1)(i) to the *Act* was "to provide flexibility necessary to meet changing conditions resulting from advancements in science and alterations for trade conditions". Anticipating the question of why flexibility would somehow be frustrated by having to add the Canadian Supplement drugs to existing Parts of Schedule B, he wrote that the "Department does not wish to include them in the existing parts because then it would be necessary to revise completely the existing regulations." Without any further elaboration, this logic is flawed, as listing drugs in the existing parts of Schedule B did not trigger any regulatory action – listing was just a precondition for those drugs to be regulated later, if so desired. As he had discussed doing with Lancaster, Driedger also removed most preambular recitals from the draft order amending Schedule B, ensuring it was silent on its doubtful source of authority.

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[75] For discussion of this 1934 amendment, see Chapter 3, section 1, particularly the content associated with notes 63-64.

[76] December 1943 memo to file by Lancaster, in National Health's Parenteral Drug Regulations File, 1943-1944.

[77] December 15, 1943 opinion letter from Driedger to Varcoe, in EA Driedger's Schedule B File, 1943. For further context, see also National Health's Parenteral Drug Regulations File, 1943-1944.

[78] Curran 1949 at 403. Additionally, in his later book, Curran characterized s. 3(1)(i) as "merely authority to enable Schedule B to be kept up-to-date and to be amended in such as way as the public interest may demand", and he did not mention the provision in his discussion of the various "important sections" added to the *Act* in 1934; see Curran 1953 at 154, 178.

Through ongoing and routine interactions with departmental and DOJ solicitors on the ever-increasing volume of subordinate legislation being enacted under the *Food and Drugs Act,* National Health officials were coming to register the significance of this emerging technique of stripping enactments' preambular recitals of references to sources of authority.[79] For example, when later briefing Aime Valin, then in his role as the new Chief Dominion Analyst after Lancaster's retirement in 1945, Davidson carefully emphasized that the recitals in the order amending Schedule B had intentionally referred only to the *Act* generally and not to any specific sections of it. Silencing the recitals was, in this time, becoming a quotidian practice increasingly employed by National Health to enact delegated drug standards and thus to materialize drugs.

With no consultation within the wider Department on the contents or purpose of Part V, the (silenced) order amending Schedule B was made on January 11, 1944.[80] Before that date, sex hormones and estrogens had never been mentioned in Schedule B. After that date, with the addition of sex hormones to Part II, and of oestrone, oestradiol benzoate, stilboestrol, and stilboestrol dipropionate to Part V, the statutory scene changed from one of estrogen-deficiency to hormonal excess. The enactment of estrogenic multiplicity was not accidental; or, put more accurately, Lancaster and other departmental officials on the Committee were aware that estrogen was assuming multiple identities in Schedule B.[81]

National Health was now ready to incorporate into law the Canadian Supplement, with its pharmacopoeial monographs for each of the drugs listed in the new Part V. On April 11, 1944, the Canadian Supplement to the British Pharmacopoeia received legal imprimatur as Division III of the Food and Drug Regulations.[82] Once again, the order in council enacting the Supplement as part of the regulations was stripped of any content referencing its dubious source of statutory authority.[83] Henderson and Lancaster's plan had finally come to fruition. Nonetheless, as with the orders creating the Committee and Part V of Schedule B, departmental and DOJ solicitors

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[79] For recent socio-legal work examining the co-production of legal drafting, technicalities, and form, on the one hand, and time on the other, see Emily Grabham, "Time and technique: the legal lives of the 26-week qualifying period" (2016) 45:3-4 *Econ Soc* 379; see also Grabham 2016. For other leading scholarship on legal technicalities that bridges law, anthropology, and STS, see Annelise Riles, "New agenda for the cultural study of law: Taking on the technicalities" (2005) 53:3 *Buffalo LR* 973; and Annelise Riles, "Infinity within the brackets" (1998) 25:3 *Am Ethnol* 378.

[80] PC 1944-96 (10 January 1944), *Canada Gazette*, Vol LXXVIII, No 4, at p 354 (January 22, 1944). See also Chapter 2, note 16, and see National Health's Parenteral Drug Regulations File, 1943-1944. The publication of this order caused internal confusion within National Health. Superintendents of Laboratory from two regional offices each wrote to Lancaster and Valin in February 1944 seeking explanation as to why Part V had been added, what its significance was, and where to find any associated standards for the drugs listed; see National Health's Parenteral Drug Regulations File, 1943-1944.

[81] See e.g. Lancaster's comments to Davidson in June 1944, conveyed in a letter to Professor Henderson, regarding the future possibility of amalgamating the multiple standards that had emerged for sex hormones and other drugs as a consequence of National Health and the Committee's recent regulatory enactments; in Davidson's Committee Materials, 1944.

[82] PC 1944-2515 (11 April 1944), *Canada Gazette,* Vol LXXVIII, No 30, at p 2983 (July 22, 1944).

[83] Neither s 3(i) nor s 6(3) were mentioned, although some words from each found their way into the preamble; *ibid.*

considered that much of the Canadian Supplement was legally invalid, and to obscure this, they deployed the same technique of erasing uncomfortable information from preambular recitals.

Davidson approached National Health's solicitor in February 17, 1944, proposing to insert the Supplement and its monographs as a new Division III of the Food and Drug Regulations, for the purpose of creating legally binding standards for the drugs recently listed in Part V. Davidson explained to Gunn that the monographs first defined each drug substance, followed by a description of what each substance "must contain when assayed by a certain method". Still doubtful of the approach, Gunn suggested it might be better to amend the *Act*, but recognizing this was not desirable, he began working to finalize Davidson's proposed regulation.[84] It is unclear whether Davidson told Gunn, though, of the recent developments in Britain regarding estrogen; by this time, Davidson had received the British Pharmacopoeia Commission's draft monographs for its seventh addendum, which included draft monographs for oestrone and oestradiol benzoate. While taking pains to note its considerable agreement with the Canadian Supplement's monographs, the British Pharmacopoeia Commission stressed that Britain had "definitely abandoned" biological methods of defining and testing oestrone and oestradiol benzoate, and were treating them as "pure chemical substances". Likewise for DES, while noting Canada's use of a biological test, it advised that the "intention of the Commission is to continue treating this substance as a pure chemical compound and to rely on chemical tests."[85]

Perhaps unaware of this development, Gunn forwarded to DOJ his draft regulation for enacting the Canadian Supplement. His draft preambles stated, among other things, that these regulations defined official methods for biological testing of the drugs listed in Part V. In early March 1944, DOJ signed off on these proposed regulations.[86] Yet, likely spurred by reflection on the British Pharmacopoeia Commission's letter, National Health officials identified a validity concern soon thereafter. On March 15, 1944, the Assistant Chief Dominion Analyst, Aime Valin, alerted the Departmental Secretary that, while the *Act* empowered regulations mandating biological testing methods for drugs,[87] the "great majority" of the substances described in the Canadian Supplement monographs were "not susceptible to biological assay, but are tested by chemical methods only". Having absorbed the practice of erasing evidence of invalidity from the

[84] February 17, 1944 memo to file by Gunn, in (Possibly) Morrell's Committee file, 1942-1943.

[85] *Ibid*. Davidson replied to the British Pharmacopoeia Commission on February 17, 1944, the same date as his meeting with Gunn, so estrogen would have been on his mind. His letter, while addressing many substances, does not mention the countries' divergent approaches to defining oestrone, oestradiol benzoate or stilboestrol; see Davidson's Committee Materials, 1944.

[86] National Health's Parenteral Drug Regulations File, 1943-1944.

[87] *Food and Drugs Act,* s. 6(3)(b); see discussion in Chapter 3, section 1, particularly the content associated with notes 39-48.

face of delegated legislation, Valin concluded his letter by suggesting that the word "biological" be deleted from the regulation's preambular recitals.[88]

Despite that the *Act* expressly conferred power to prescribe only biological testing methods, DOJ agreed to this deletion.[89] Thus, spurred by National Health officials' reflection on divergent testing methods for estrogens, Canada knowingly enacted regulations that defined chemical testing methods for many Canadian Supplement drugs (if not for estrogens themselves), pursuant to a provision that empowered it only to define biological testing methods. In 1944, National Health's practice of erasing, from delegated legislation's preambles, reference to statutory provisions that provided only questionable legal authority was becoming entrenched.

Another regulatory practice relied on by National Health officials, surprising from today's vantage point, was their habit of engaging solicitors very late in the regulatory day. As with the decision to create the Committee, discussed in the last chapter, Gunn was consulted at the end of the process, rather than at a stage when officials were identifying and developing options for incorporating the Canadian Supplement into law. Only after these officials had settled on their desired option, and prepared a rough draft of the regulation, did they seek their solicitor's approval. Such practices risked solidifying path-dependence, fostering hesitance on the part of departmental solicitors to scuttle long-identified but legally invalid regulatory plans, and creating resistance among bureaucrats to legal advice that arrives late and is perceived as an impediment. This practice was viewed as enough of a barrier to coherent policy development and regulatory drafting that, by 1946, DOJ would create a new Legislative Section, with Driedger at its head, to discipline the preparation of all legislation. By the early 1950s, in an apparent effort to solidify this practice, Driedger was publicly emphasizing the need to involve departmental lawyers in policy decisions and for earlier involvement of legislative counsel.[90]

In February 1944, at the same time that National Health food and drug officials were working to enact the Canadian Supplement, they were also facing requests from other units within the Department to further revise Part II of Schedule B, which had just been amended in January. The Part II amendments were short-lived due to wider Departmental reaction to how parenteral products had been addressed.[91] As noted, senior Departmental laboratory officials had been

[88] March 15, 1943 letter from Valin to Barlow, in National Health's Parenteral Drug Regulations File, 1943-1944.

[89] March 28, 1943 letter from DOJ Deputy Minister Varcoe to Gunn, in National Health's Parenteral Drug Regulations File, 1943-1944. In later writing, Driedger characterized this issue of the *vires* of a regulation, in a situation where an act expressly confers power, as a simple question (in contrast to the more difficult issue of where a statute does not explicitly confer power to make a certain type of regulation); see Driedger 1960 at 22-27.

[90] Driedger 1953 at 38-41.

[91] Parenteral drugs are those administered by injection, either intravenously or intramuscularly.

taken aback and confused by the surprise amendments to Schedule B.[92] In particular, the Chief of the Laboratory of Hygiene, Dr. G. Donald W. Cameron, advocated for replacing the two paragraphs in Part II – the first on animal tissue preparations (now including "sex hormones"), the second on parenteral products serving as anti-allergens and antibacterials (in particular, penicillin) – with one paragraph capturing all parenterals, including sex hormones. [93] It is hard to discern what motivated Cameron's position, beyond perhaps frustration at not being consulted. It seemed counterproductive to his own staff's simultaneous efforts to finalize the draft Sex Hormone Regulations, which were meant to control not only parenterally administered products but the newer oral products made of DES or conjugated equine estrogens. Whatever the motivation, Cameron's reaction and Lancaster's counterreaction render visible yet further multiple versions of estrogen, as a substance to be taken orally or injected intramuscularly.

Aiming to correct Cameron's impression that Part II covered only parenteral products, on February 4, 1944, Lancaster dictated a memo to Davidson from a hospital bed at the Ottawa Civic.[94] Emphasizing that each of the two paragraphs of Part II covered drugs with many modes of administration, he explained that some kinds of sex hormones were not administered only by injection, and further that some penicillin preparations were anticipated for topical use. With that clarification, senior departmental officials then reached agreement that Part II should be revised such that the first paragraph would still list animal tissue preparations (including sex hormones) however administered, and the second should control all parenteral preparations.[95] Accordingly, Part II was amended again, in May 1944.[96] While not National Health's intention, it became arguable that both paragraphs of Part II covered injectable estrogenic drugs.

These efforts to revise Part II, in the spring of 1944, can be viewed as a simple matter of clarifying legislative text or of remedying insufficient internal consultation. Beyond this, however,

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[92] See *supra* note 80.

[93] National Health's Parenteral Drug Regulations File, 1943-1944.

[94] *Ibid.*

[95] *Ibid.* Additionally, Mr. Papineau-Couture, the Superintendent of Laboratory in Montreal, raised further issues with the clarity and scope of Part II in March 1944, identifying how the French version had been drafted with a narrower meaning than the English version. An *erratum* correcting the French version was published in the *Canada Gazette* on April 8, 1944.

[96] PC 1944-3308 (4 May 1944), *Canada Gazette,* Vol LXXVIII, No 21, at 2104 (May 20, 1944); see also Chapter 2, note 16. This amendment to Schedule B replaced Part II, as last amended through the January 11, 1944 order, with the following:

> "Preparations of Pituitary, Adrenals, Sex Hormones and any other animal tissue preparations or any synthetics purporting to have physiological action similar to any of the foregoing.
>
> Drugs of natural or synthetic origin, which are not hypodermic tablets, and which purport to be sterile and which are intended for parenteral administrations, including application to open wounds, alone or with any added solvent, diluent, preservative or other substance and including products for the treatment of allergy and anti-bacterial products of the growth of fungi or of bacteria (or which penicillin is an example), their salts, derivatives and any preparations containing any of them."

they illustrate conceptual confusion about "sex hormones", and furthermore, the ontological plasticity and adaptability of estrogen in its multiple modes. The Chief of the Laboratory of Hygiene viewed hormones as animal tissue preparations to be administered by injection. Yet, by this time, estrogens were being summoned synthetically. Further, the many modes of administering estrogen to human bodies – oral, parenteral, topical – were growing as diverse as their many modes of bureaucratic administration. These multiple drug forms were different estrogens. Even when products contained the same active ingredients, diverse modes of administration arose from and fostered divergent clinical, manufacturing, advertising and regulatory practices, and elicited varied effects in human and nonhuman bodies. [97]

Resistant to simple categorizations and materializations, estrogens continued to multiply with the enactment, in 1944, of the Sex Hormone Regulations. Since January 1943, these regulations had been National Health officials' desired means to define and control sex hormone preparations, although they had backed down and acceded to the view of Henderson and other Committee members that oestrone, oestradiol benzoate, stilboestrol, and stilboestrol dipropionate should be standardized through monographs in the Canadian Supplement. In contrast to the Supplement and Part V, though, the Sex Hormone Regulations faced the reverse reception from DOJ. As will be seen, not only did concern with the legal validity of these Regulations multiply estrogen's potencies, but these regulations also ushered in a new type of label that laid the groundwork for an early experiment with risk regulation in Canada.

The *vires* debates to this point, regarding Canadian drug standards proposed in 1944, were about the scope of authority to regulate. There had been no express and arguably no implied authority to add Part V to Schedule B, and similarly no authority to prescribe chemical rather than biological test methods in the Canadian Supplement. The Sex Hormone Regulations raised a new *vires* concern, regarding the validity of subdelegating standard setting. The peak of WWII proved, not surprisingly,[98] to be a critical moment in Canadian legal history for bolstering power to subdelegate to officials.[99] In January 1943, the Supreme Court of Canada decided the *Chemicals Reference.* The federal government had referred questions to the Court regarding the validity of regulations, made by the Governor in Council under the *War Measures Act,*

[97] In the context of oral contraception in Brazil, see Sanabria 2016 at 159, critiquing constructions of "similarity" in the Pill built only upon the active ingredient which fail to consider how diverse marketing and packaging practices produce different objects.

[98] See e.g. S.A. de Smith, "'Rule of Law', Book Review of Rule of Law: A Study by the Inns of Court of the Conservative and Unionist Society" (1955) 69:2 *Harv L Rev* 396, observing at 398 that, with the start of WWII, parties to the long-standing prewar debate about the merits and validity of delegation were increasingly ready to "concede wide regulatory powers to the state".

[99] It is not my goal here to trace changes in the *delegatus* rule over time, but rather to assess the likely influences on Elmer Driedger when he rendered his opinion, in 1944, that the potency provision of the Sex Hormone Regulations was *ultra vires*.

allowing civil servants to regulate the wartime control of chemicals, and the validity of an order thereunder, by the Controller of Chemicals, controlling production and consumption of glycerine. The Court held that, under the *War Measures Act,* the regulation granting civil servants power to legislate was valid.[100] Despite that the statute did not contain express authority to sub-delegate this power to administrators, reading across the opinions, it appears this authority was found to be implicit in the broad statutory delegation granted by Parliament to the Governor in Council.

On the heels of the decision, John Willis, at that time a professor at Dalhousie University's Faculty of Law, quickly wrote *Delegatus Non Potest Delegare*.[101] Published in March 1943, his short article effectively synthesized the "rule" against sub-delegation, which, in a "nutshell", provided that delegated powers cannot be further delegated.[102] In Willis' articulation, the sub-delegation rule was at best a presumption or maxim of statutory construction, which could be displaced by express statutory language or the wider context or purpose of the statute. He argued that lawyers and judges would need to balance the maxim against a recognition of the complexities and virtues of "modern government agencies", adopting constructions that "best accord with the facts of government" and that enabled expert civil servants to do their jobs.

For Willis, a legal realist and defender of an expanding administrative state,[103] the *Chemicals Reference* decision was a godsend. Willis "took the case as his point of departure and used it as a principal buttress for his conclusions", and in no small measure due to his article, the case has since been cast as a leading authority on sub-delegation.[104] However, and as persuasively shown by John Mark Keyes, armed with the unusually broad and explicit power of the *War Measures Act,* in fact it seems that "the majority of the court considered the maxim to be entirely irrelevant". Of the five concurring opinions, Chief Justice Duff "did not even mention it"; Justices Rinfret, Davis, and Kerwin "found the Governor in Council's powers to be so broad that there was no need to consider the maxim"; and only Justice Hudson gave any detailed consideration to the *delegatus* rule.[105] As Keyes concludes, "[t]he only generally applicable

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[100] *Reference as to the Validity of the Regulations in Relation to Chemicals Enacted by Order in Council and of an Order of the Controller of Chemicals Made Pursuant Thereto,* [1943] SCR 1. Only paragraph 4 of the regulation was held to be *ultra vires*.

[101] Willis 1943. Willis had also written an earlier article on delegation, published in the US ten years earlier and less frequently cited; see John Willis, "The Delegation of Legislative and Judicial Powers to Administrative Bodies" (1932-1933) 18 *Iowa LR* 150.

[102] For readers interested in the nutshell pun, see Willis 1938 or Chapter 2, note 38.

[103] See e.g. R Blake Brown, "The Canadian Legal Realists and Administrative Law Scholarship 1930-1941" (2000) 9 *Dal J Legal Stud* 36; and R C B Risk, "Lawyers, Courts and the Rise of the Regulatory State" (1984) 9 *Dal LJ* 31.

[104] John Mark Keyes, "From *Delegatus* to the Duty to Make Law" (1987) 33 *McGill LJ* 49 at 65.

[105] *Ibid* at 65-66.

principle that can be extracted from the decision is that the *delegatus* maxim is merely a rule of construction that can be excluded by express or implied authority to subdelegate."[106]

Published in the *Canadian Bar Review,* the article certainly would have come to Driedger's attention. Although no doubt greatly sympathetic, as government counsel, to Willis' political project, it is less clear that Driedger would have agreed entirely, in 1944, with Willis' analysis of the *Chemical Reference*. Writing in the same journal almost two decades later, and without citing Willis, Driedger drew a bolder conclusion that "there is no rule or presumption for or against sub-delegation".[107] He drew this conclusion even in the face of the Supreme Court later decision in *Brent,* which had invalidated regulations under the *Immigration Act* that unlawfully delegated to civil servants the Governor in Council's powers to limit admission to the country.[108] Relying on the *Chemicals Reference* as his sole counterweight to *Brent*,[109] he expressed the view that, rather than any presumption, "in each case it is a question of interpretation of the language of the particular statute."[110] Assuming that his views remained consistent over time, Driedger was not likely to rely on the *delegatus* rule in analyzing the validity of draft regulations.

At the end of March 1944, following uneventful consultations with industry, the Sex Hormone Regulations were ready for that analysis. As with previous enactments, the departmental solicitor believed that elements of the regulations were *ultra vires* – although there is no record of him so advising food and drug officials at National Health. He raised his concerns more surreptitiously. When sending the draft Sex Hormone Regulations to DOJ for review, Gunn apparently sought to neuter the Canadian Supplement monographs for estrone, oestradiol benzoate and DES, and subtly characterized the regulations' potency standards as *ultra vires*:

> I would ask you to consider whether it might not be desirable to have a definite statement in the recital to the effect that the standards of the drugs concerned are not otherwise dealt with by the Food and Drugs Act or the Meat and Canned Foods Act. May I direct your particular attention, too, to the last line of the Regulations under the caption "Potency". I wonder whether Parliament would pass legislation giving to the Chief, Laboratory of Hygiene, this power?[111]

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[106] *Ibid* at 66.

[107] Driedger 1960 at 23.

[108] *Attorney General of Canada v Brent,* [1956] SCR 318, 2 DLR (2d) 503.

[109] Driedger 1960 at 23, with reference to the opinion of Chief Justice Duff.

[110] *Ibid*.

[111] March 30, 1944 letter from Gunn to DOJ Deputy Minister Varcoe, in EA Driedger's Sex Hormone Regulations File, 1944. Driedger rejected this proposed recital, without giving reasons. Notably the *Act* already provided that Canadian standards in regulations took precedence over pharmacopoeial standards, making such a recital redundant; see the content associated with notes 39-42 in Chapter 3. This rule was complicated, though, by the fact that the pharmacopoeial standards in the Supplement were arguably themselves also Canadian drug standards in regulations; see the content associated with note 131 in Chapter 3.

The potency provision that Gunn took issue with, in section 3, provided that:

> The units of the sex hormones for the purpose of these regulations shall be International Units, wherever they exist, as estimated by the methods employed in the Laboratory of Hygiene. *In the case of products where International or Canadian Standards have not been established and stable standards cannot be furnished by the manufacturer, the methods of assay and of expressing potency shall be acceptable to the Chief, Laboratory of Hygiene*.[112]

Predictably, DOJ sent a question back to Gunn: were the Sex Hormone Regulations intended to permit the Chief to prescribe potency standards?[113] When that question was referred to the Assistant Chief Dominion Analyst, Valin tried to justify the clause as aiming to ensure that manufacturers' methods of "expressing potency or activity" of sex hormone products were acceptable. The clause "was inserted to prevent manufacturers using unreliable methods of assay and to prevent misleading and unwarranted statements as to potency for a class of products which are difficult to control on account of no stable or satisfactory reference standard being available." Valin explained that, as the control of hormone products was "very complicated" and as it was "not thought advisable for the present to put them under a license", it was felt necessary to give the Chief some discretionary power to scrutinize and if necessary to disagree with manufacturers' methods and claims about their products' potency.[114]

Unlike with earlier enactments, this time, Driedger's opinion was negative. In his view, the potency clause was invalid. Rather than the Governor in Council prescribing potency standards, as envisioned by the *Act,* the regulation subdelegated this power to a departmental official.[115] Faced with this wrinkle, National Health officials improvised. Valin proposed a solution for those products for which International or Canadian standards did not exist, and for which manufacturers could not furnish a stable standard. What if, he suggested, rather than requiring manufacturers to meet the Chief's standards for measuring the activity or potency of a sex hormone product, Canada instead required pharmaceutical firms to attach a label to the product? Such a label could furnish "full details of the unit of potency employed and of the

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[112] March 1944 version of the draft Sex Hormone Regulations, in EA Driedger's Sex Hormone Regulations File, 1944. The italicized text is that specific portion to which Gunn brought DOJ's attention.

[113] April 17, 1944 letter from DOJ Deputy Minister Varcoe to Gunn, and April 20, 1944 letter from Gunn to Valin, in National Health's Sex Hormone Regulations File, 1944-1945.

[114] April 24, 1944 memo from Valin to Gunn, in National Health's Sex Hormone Regulations File, 1944-1945. On April 26, 1944, Gunn forwarded this memo to the Deputy Minister of DOJ, stating that it appeared to answer the question that DOJ had asked; see EA Driedger's Sex Hormone Regulations File, 1944.

[115] May 4, 1944 legal opinion from Driedger to Varcoe, in EA Driedger's Sex Hormone Regulations File, 1944.

method of assay used" by the firm in manufacturing the drug product.[116] Driedger and Valin discussed the proposed solution on the phone. A few days later, Driedger gave a written opinion advising that the revised potency clause, which they had discussed on the phone as a "quickie amendment", was unobjectionable.[117] Or perhaps it was the "junkie amendment" – Valin's handwritten note of the phone call is hard to decipher:

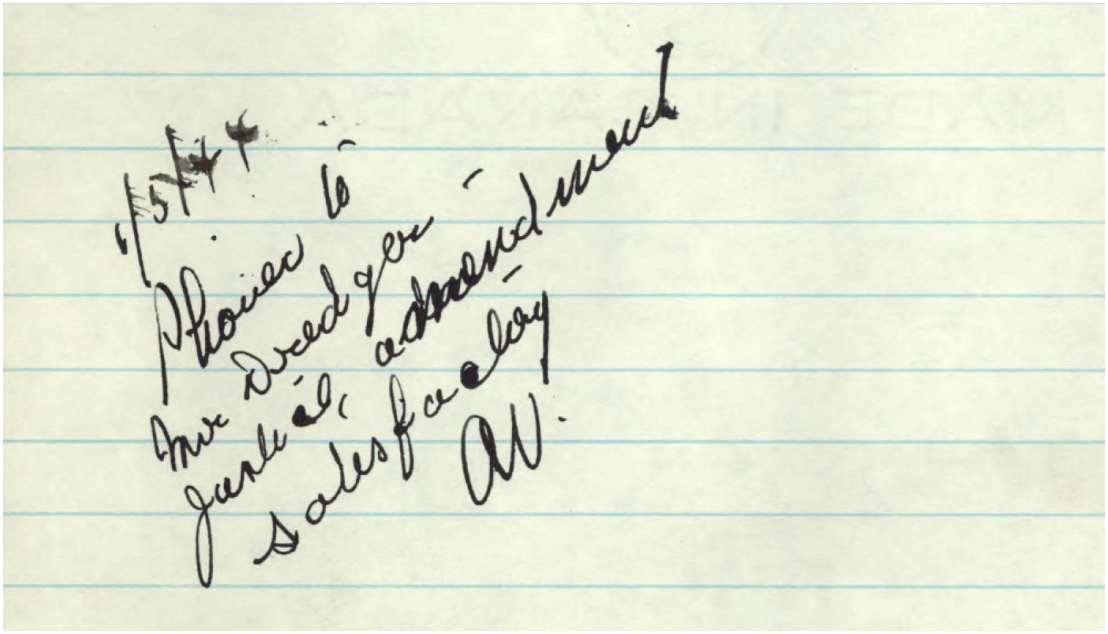

Figure 5: Portion of Aime Valin's notes of phone call with Elmer Driedger, May 1, 1944

Library and Archives Canada, "Canadian Committee on Pharmaceutical (Standards – Proposed Regulation – Sex Hormones", RG 29, Vol 250, File 339-4-3, reproduction copy no. e-01119340

Whether quick or junk, it was made.[118] On May 18, 1944, Cabinet enacted the Sex Hormone Regulations, complete with the clause requiring potency labelling in lieu of potency standards.[119]

Pharmaceutical manufacturers were not at all displeased by this novel turn to potency labelling. When consulted earlier that spring on the draft regulations, some firms had sought *additional* labelling requirements. As one example, British Drug Houses (Canada) Ltd., a manufacturer of potent DES products, had advocated that the regulations be revised to require

[116] *Ibid.* As shown by certain of the Canadian Supplement monographs, if National Health wished to prescribe potency units and official bioassay test methods within the regulations, it had the technical ability to do so.

[117] *Ibid.*

[118] PC 1944-3721 (18 May 1944), *Canada Gazette*, Vol LXXVIII, No 28, at p 2292 (June 3, 1944) ["Sex Hormone Regulations"]. The Sex Hormone Regulations were added to the Food and Drug Regulations as part of Division II. Subject to amendments, some of which are discussed in Chapter 5, the Sex Hormone Regulations remained in force until 1980; see SOR/80-544, s 9.

[119] Sex Hormone Regulations, s. 3.

that a product's potency be indicated, both on ampoule labels and on outer box labels.[120] Every manufacturer that commented on the draft regulations was content, in principle, with labelling requirements, proposing only minor adjustments.[121] Manufacturers wanted to be able to market their products as highly potent, regardless that the methods they used to ground such claims might be variable, unreliable or contrary to test methods underpinning International Units.

This turn to labelling in no way aimed to promote what, in modern parlance, might be called the consumer's "right to know". If anyone's right to know was at issue, it was the Department's. The information to be summoned by these potency labels discloses what the Department viewed as the problem: finding a means by which to assess pharmaceutical firms' claims about their drugs. With quantitative information about potency test methods and units, National Health could continue its long-established way of regulating drugs through misbranding or adulteration rules. Labels would therefore be Department's intelligence agents, the technology by which National Health officials could keep informed about what was materializing in industry's labs.

Born of a desire to avoid unlawfully delegating to government scientists, National Health instead, ironically, delegated to industry the power to set its own potency standards. By thus delegating the power to decide how to apprehend estrogenic activity, it was left to industry to decide what estrogen would be and what it would do. Furthermore, approaching delegation as more than an administrative law doctrine, labels also had a job to do. National Health delegated to industry the power to materialize potency and delegated to the new potency label the duty to report back on what industry was up to. Obviously, firms were required to print and affix this label. But the label would be an active participant in the Department's efforts to test these firms' products and claims, creating the possibility of mediation between industrial test methods and regulatory test methods. This form of "delegation" was also, of course, perfectly lawful.

What is most striking about Driedger's legal opinion on the Sex Hormone Regulations is not his reasoning or conclusion. Though his reasons were summary by present standards,[122] they appear unimpeachable, given the prevailing views on sub-delegation and his own more statutorily-driven interpretive approach. Rather, what is remarkable is the persistent silence, in Driedger's and National Health's files, on the consequences of his opinion for other biologics. In

[120] March 6, 1944 letter from British Drug Houses (Canada) Ltd., in National Health's Sex Hormone Regulations File, 1944-1945.

[121] Comments proposing minor amendments to the labelling requirements for sex hormone preparations were also submitted by Abbott Industries on March 18, 1944 and Charles E. Frosst on March 6, 1944. Davidson met with these companies' representatives, in person, in Montreal in mid-March 1944, and National Health incorporated their minor proposals into the final regulations; see National Health's Sex Hormone Regulations File, 1944-1945 and Davidson's Committee Materials, 1944.

[122] Driedger's opinion that s 3 was *ultra vires* was rendered in a one-page memo to the Deputy Minister of Justice. The substance of his reasons was distilled to a single sentence: "It seems to me that the prescribing must be done by the Governor in Council."); see May 4, 1944 legal opinion from Driedger to Varcoe, in EA Driedger's Sex Hormone Regulations File, 1944.

the preceding decade, under the same enabling provision, Canada standardized the potency of biological drugs, from digitalis to thyroid to epinephrine, using a clause very similar to that which Driedger concluded was invalid for sex hormones.[123] In the Biologicals Regulation, as it had been amended in 1934 and again in 1942,[124] Cabinet had repeatedly delegated its power to prescribe methods for testing drugs' potencies to the Chief of the Laboratory of Hygiene.

Perhaps Driedger was unaware that a similar clause was in place for many other drugs on Schedule B. But Lancaster, Valin, Davidson, and the Food and Drug Division knew. Having received an opinion indirectly confirming that National Health's approach to potency standards for many drugs was unlawful, they did nothing. They did not bring the issue to the attention of Driedger or the departmental solicitor. They did not bring it to the attention of the Committee. They did not fix the invalid aspects of the Biologicals Regulation. Sex hormones – mostly estrogenic products and administered almost exclusively to women – were put in a class of their own. These "drugs for women" were the only drugs for which National Health would claim that it could not require industry to meet departmentally determined methods for testing potency.

That estrogen was singled out for lesser regulatory treatment is confirmed when considering other regulations made within weeks of the Sex Hormone Regulations. In the spring of 1944, these other regulations either maintained government supervision over industry's methods of testing potency or continued to subdelegate power to prescribe potency tests to departmental scientists. In 1944, National Health recommended and Cabinet regulated new dose and potency standards for injectable liver extract.[125] Initially, the regulatory proposal was to limit the potency of liver extract sold in Canada to three strengths, and to make the usual sub-delegation to allow the Laboratory of Hygiene to set the test method.[126] The final regulation, in March 1944, continued to set three doses of liver extract injectable;[127] with respect to potency testing, it now required manufacturers to demonstrate acceptable potency as a condition of

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[123] Chapter 3, section 1, particularly the content associated with notes 59-70.

[124] Regulations for Fixing Standards of Quality and Potency, and Defining Official Methods of Biological Testing of Drugs Mentioned or Described in Parts I and II of Schedule B of the Food and Drugs Act, RS 1927; and Regulations for the Licensing, Manufacture and Sale of Drugs Listed in Parts II and III, Schedule B of the Food and Drugs Act, RS 1927, PC 1942-9056 (6 October 1942), *Canada Gazette,* Vol LXXVI, No 181, Extra, at pp 21-32 (October 16, 1942) [the "1942 Biologicals Regulation"].

[125] Liver extract injectable had already been regulated in the 1942 Biologicals Regulation, *ibid,* at p 25. Section 3 of the 1944 liver extract regulations did not speak expressly to potency, but rather made it a condition of license that manufacturers first satisfy the Deputy Minister of National Health that its manufacturing and test methods resulted in a drug producing a satisfactory clinical and hematopoietic response to pernicious anemia. This largely qualitative approach was likely difficult to enforce.

[126] For records of the Committee's discussions regarding revisions to the liver extract injectable regulations, see (Possibly) Morrell's Committee file, 1942-1943 and Lancaster's File, 1940-1943. Discussion here on liver extract is necessarily summary.

[127] PC 1944-2195 (27 March 1944), s 1, *Canada Gazette,* Vol LXXVIII, No 16, p 1553 (April 15, 1944), providing that "Liver Extract Injectable should contain 2 units or 10 units or 13 units per cubic centimeter".

license, to submit bioassay protocols every two years for approval, and to notify and obtain approval of the Deputy Minister of changed manufacturing methods that could affect potency.[128] In short, without prescribing test methods, National Health was still required to approve or reject the potency of liver extract products. Even more blatantly, in June 1944, National Health subdelegated to departmental scientists the power to set bioassay tests for penicillin. Critical to treating injured soldiers during WWII, penicillin attracted significant regulatory attention from National Health in 1943-1944, with draft regulations first considered by the Committee in June 1943,[129] and with penicillin added to Part II of Schedule B of the *Act* in January 1944.[130] To obtain advice on a regulatory approach to penicillin – and in particular to determine how to regulate dosage, reference standards, and potency testing – the Department called a special meeting of the Committee and other experts on June 10, 1944.[131] Despite the opinion received from Driedger a month earlier, the Committee, including National Health members, recommended that the methods for testing potency of penicillin be delegated to the Laboratory of Hygiene.[132] Made in September 1944, the penicillin regulations did precisely what DOJ and departmental solicitors had only just concluded was unlawful with respect to sex hormones.[133]

This chapter's thick description of Canadian regulators' standardization practices, in 1943-1944, displaces conventional understandings of drugs. Rather than stable substances with inherent properties that produce predictable effects, estrogen and its effects acted, and were enacted, in relation to other actors and practices. The drug standards resulting from these practices were themselves recipes for potent socio-material realities. Returning to the idea that biological standardization performs what a drug is by apprehending what a drug *does* – its activity, capacity, potency – the ontic potential of potency labels becomes evident. Estrogen was what estrogen did. And deciding what estrogen did was delegated to industry. Going back to an earlier equine metaphor, despite having no ability to close the regulatory barn door before the pharmaceutical "horse" bolted, Canada nonetheless handed over to industry its extant powers

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[128] *Ibid,* ss. 2-4.

[129] Davidson 1949a at 85-86.

[130] PC 1944-96 (10 January 1944), *Canada Gazette*, Vol LXXVIII, No 4, at p 354 (January 22, 1944).

[131] June 10, 1944 meeting minutes and documents, in Lancaster's File, 1940-1943 and in Davidson's Committee Materials, 1944.

[132] *Ibid.*

[133] PC 1944-7021 (8 September 1944), ss 12 and 15, in *Canada Gazette,* Vol LXXVIII, No 39, pp 3957-3958 (September 23, 1944). With the adoption of an International Unit for penicillin, the penicillin provisions in the Biologicals Regulation were revised in May 1945 to require that potency be expressed in the new Units (but continuing to subdelegate potency measurement methods to the Laboratory of Hygiene); see PC 1945-3201 (3 May 1945), ss 13 and 14, *Canada Gazette,* Vol LXXIX, No 20, p 2117 (May 19, 1945). With the end of the war and the release of penicillin for civilian use, the drug was addressed in a further discrete regulatory amendment in July 1945, which required orally-administered forms of penicillin to bear labels indicating dose and potency; see PC 1945-6230 (28 July 1945), s 7, in *Canada Gazette,* Vol LXXIX, No 31, pp 3415-3416 (August 4, 1945).

to decide what a horse could do. Estrogen was subject to different regulatory practices than any other drug in Canada in the 1940s. This differential treatment is troubling when one considers that, in contrast to those biological drugs that regulators worried would lose their potency or that were the subject of exaggerated potency claims by industry, estrogen was known to be highly potent and harmful at high doses.

Besides, it is not as if industry was given power to test the potency of estrogenic products for which National Health had nonetheless set mandatory doses.[134] As will now be analysed, the Sex Hormone Regulations were unusual in their definitions, vague on reference materials, and silent on dose. If the dose made the poison – as it was thought to for estrogen – the Regulations gave exclusive rights to pharmaceutical firms to make and measure their poison.

3. Substituting labels for standards: the Sex Hormone Regulations, May 1944

The provision that delegated power to materialize potency to industry, requiring labels in lieu of prescribing test methods, was not enacted alone. Section 3 had relatives, three to be precise, in the form of three other provisions. How did this provision relate to the rest of the Sex Hormone Regulations? How did the regulations, as a whole, enact estrogen and its effects? Empowered by the regulations, what could estrogen become – what was it activated to do – in bodies, clinics, laboratories, factories, markets, or homes, in the 1940s in Canada?

There are two directions from which such questions can be productively contemplated. First, I address some of the coordination efforts at work in the Sex Hormone Regulations, through the unusual definition of "sex hormones" and the vague requirement for reference standards, and how these provisions aimed to secure sex hormones as fixed, given, and natural. Second, I identify some critical absences, namely a lack of certain regulatory controls commonly used to protect Canadians from potent or unstable biologics in the 1940s. In light of these novel regulatory elements, I evaluate whether the Sex Hormone Regulations actually created any "drug standards" at all, which I approach by considering their "special labelling provision" and labelling's role in creating market access for products "standardized" through naming practices. The section concludes by addressing the "caution label" rule. Historically noteworthy as the first example under the *Food and Drugs Act* of labels being deployed to responsibilize consumers, the caution label functions as a cautionary fable, reminding us that mandatory labels on consumer products can originate as *substitutes* for or *alternatives* to safety standards.

[134] This is one way to characterize the 1944 liver extract injectable regulations (although those regulations went further in requiring National Health to approve or reject industry-selected potencies).

As will now be evident, the Sex Hormone Regulations were made under statutory provisions empowering the Governor in Council to set standards for quality,[135] and potency, of biological drugs. As an exercise in standardization, however, these Regulations were curious. In fact, compared to Canadian drug standards of the time, whether with respect to definitions, reference standards, dose, licensing, or labelling, the Sex Hormone Regulations were unique. Returning to Busch's typology, as already seen, the regulations did not create filter standards for potency, meaning estrogenic drugs were not required to meet any quality-driven test for estrogenic activity, as expressed using any specific potency unit. Nor, relatedly, did these regulations rely on typical logics underpinning what Busch calls *industrial standards,* which aim to ensure products as all "the same". Leaving aside potency, what other standards were enacted by the Sex Hormone Regulations? On their face, the regulations might be said to standardize estrogen through two means: a definition of sex hormones,[136] and the provision of reference standards.[137]

Definitions perform critical ontological and political work in regulatory regimes. They do not just reflect but also provoke and spur into action the objects being regulated, which in turn stimulates policy choices on how to control those objects.[138] Ontological description drives regulatory prescription and *vice versa.*[139] In the Sex Hormone Regulations, "sex hormone" was defined, and marshalled as an object for regulation, to "include all products synthetic or natural purporting to have oestrogenic, androgenic, gonadotrophic and progestational properties".

Under the *Food and Drugs Act,* biological drugs had been commonly defined with reference to their plant, animal, or bacterial source material; sometimes these definitions were augmented by indicating a requisite method of extraction from that source.[140] Furthermore, a few biological drugs included in their definitions a reference to the disease that the drug was used to treat; for example, insulin was defined as the active principle of the pancreas that affects the metabolism of carbohydrates in the animal body and is of value in the treatment of diabetes.[141] By contrast, sex hormones were defined *only* in reference to their purported properties – an estrogenic sex

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[135] In articles in the *Food Drug and Cosmetic Law Journal,* Curran argued that "standards of quality", for food and drugs in the *Food and Drugs Act,* captured all of what, in the US FDCA, was instead broken down into standards of "definition, identity and quality". See e.g. Robert E Curran, "Standards in Canada" (1951) 6 *Food Drug Cosm LJ* 204 at 210-211; and Robert E Curran, "Regulatory Control in Canada under the Food and Drugs Act" (1962) 17 *Food Drug Cosm LJ* 312 at 314-315, 322.

[136] Sex Hormone Regulations, s 1.

[137] *Ibid*, s 2.

[138] See discussion of Busch 2013 in Chapter 1, section 2.ii. Busch draws substantially, on this issue, on Bowker & Star 1999.

[139] See discussion of Jasanoff's co-production framework in Chapter 1, section 2.iii.

[140] See Chapter 3, section 1, particularly the content associated with notes 60-62 and 65-70.

[141] PC 1949-1536, SOR/49-145 (5 April 1949), s C.03.050, in *Canada Gazette,* Vol LXXXIII, No 10, p 950 (May 25, 1949). See also *infra* note 142.

hormone was something *purporting* to have estrogenic properties. This was a wholly novel approach to defining a drug under the *Food and Drugs Act*.[142] In the food and drug context, the regulatory genesis of the word "purporting" was the January 1944 amendment to Part II of Schedule B. To that list of animal tissue preparations, this amendment had added the clause "or any synthetics purporting to have physiological action similar to any of the foregoing".[143] Thus, the construction of sex hormones as products with purported properties is a direct legacy of DES. DES was the reason for the synthetics clause added to Part II of Schedule B, and, as of 1944, DES appeared to be the only synthetic hormone being marketed as a drug in Canada.[144]

To modern ears, the word purporting has a pejorative ring, evoking falsehood or pretense. To National Health officials in the 1940s, however, the word articulated the concept of "represented" or "claimed" properties.[145] An industry-made product would become a "sex hormone" if its manufacturer represented it to have estrogenic properties, and estrogenic properties were those capacities apprehended through a continued legacy of diverse bioassays for potency. Pugsley himself had described this as "a chaotic state of affairs".[146] However, with the choice of potency tests now confirmed, by law, to be delegated to manufacturers, this chaos would continue. Bringing the ontological politics of the Sex Hormone Regulations into clearer perspective, the definition of "sex hormone" reaffirmed that power over what an estrogen was, and what it could do, would be held by industry. National Health's concern was not "what should sex hormones be", but "how can we measure whatever industry claims is a sex hormone?"

The second way that the Sex Hormone Regulations appeared, superficially, to standardize estrogen was through reference standards.[147] For most drugs standardized by the Biologicals Regulation, an official standard was prescribed to be the reference material stored at the Laboratory of Hygiene and available upon request.[148] Although the Sex Hormone Regulations similarly indicated that reference materials would be kept by the Laboratory of Hygiene, they

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[142] See Chapter 3, section 1, particularly the content associated with notes 59-70. My research has not identified any other drug standard under the *Food and Drug Act*, in the 1930s or 1940s, that identified or defined a drug by its "purported" or represented effects. The only drug regulation that comes close to this approach is the March 1944 liver extract regulations, defining liver extract injectable as "a sterile liquid *purporting* to contain the soluble fraction of mamalian (sic) liver which increases the number of red blood corpuscles in the blood of persons suffering from pernicious anemia"; see *supra* note 127.

[143] The May 4, 1944 order re-amending Part II of Schedule B, to enumerate a list of parenteral products more comprehensively, adopted the "purport" concept as well, by listing parenteral products "which purport to be sterile"; see *supra* note 96.

[144] The synthetic estrogen ethinyl estradiol, later used widely in the contraceptive pill, had been synthesized in Germany in 1938 but does not appear to have been marketed in drug products in Canada in 1944.

[145] The Food and Drug Regulations were thoroughly revised in 1954, including to change the words "purporting to have" in s 1 of the Sex Hormone Regulations to "represented as having"; SOR/54-295, s C.02.001(b).

[146] Pugsley 1951 at 534.

[147] Sex Hormone Regulations, s 2.

[148] See Chapter 3, section 1, particularly the content associated with notes 60-62.

went on to provide, unusually, that either "International standards or Canadian Standards must be used wherever they exist". Further, the provision stipulated that if *neither* of these materials existed "the manufacturer shall be required to submit a suitable quantity of his product to be used as a standard for checking the uniformity of that product". This was vague, to say the least. Translated, the legal standard was one of two reference materials without saying which one; and where neither existed, the standard would be whatever a manufacturer chose to submit.

What was enacted by such "standards"? If anything, they provoked multiplicity, uncertainty, irregularity, even ungovernability. Seven years later, Pugsley would admit as much, acknowledging that under the Sex Hormone Regulations, "[t]he provision of reference standards for these preparations has been a difficult problem".[149] Though claiming that many problems had been solved by manufacturers supplying reference material for their products,[150] he nonetheless conceded that this problem continued for Premarin and other conjugated estrogenic drugs:

> The problem of adequately describing the unit of potency for products currently described as oestrogenic substances, and prepared as a concentrate of human or equine pregnancy urine, has not been solved to date. In the absence of significant amounts of material, considered by most authorities not to occur naturally in the urine, the stand has been adopted that the potency of these products is best described with reference to the International Standard Oestrone.[151]

Pugsley was by no means the only scientist to acknowledge this problem, as researchers struggled to propose defensible bioassay methods for standardizing orally-administered conjugated estrogens and revealed that very few manufacturers' products corresponded to their labelled potency.[152] Unbeknownst to Pugsley, this problem would remain a challenge long into the future; even today, there is no defined reference standard available for Premarin.[153]

The Sex Hormone Regulations are all too easy to identify as a failure of standardization. What if, however, one takes estrogen seriously as a bio-social actor? As an active participant in

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[149] Pugsley 1951 at 533. Valin had also acknowledged, prior to the making of the regulations, that sex hormone products, as a class, were "difficult to control" precisely because manufacturers had not made available stable or satisfactory reference standards; see April 24, 1944 memo from Valin to Gunn, in National Health's Sex Hormone Regulations File, 1944-1945.

[150] *Ibid* at 534.

[151] *Ibid* at 535.

[152] See e.g. Lawrence & Chapman 1952.

[153] Q. Ashton Actor, *Endometrial Cancer: New Insights for the Healthcare Professional,* 2013 ed. (Atlanta, GA: ScholarlyEditions, 2013) at 100: "The estrogenic content of PMU varies even with respect to the currently marketed product PREMARIN. The total estrogen content varies as well as the presence or absence of some of the estrogenic components depending upon the mare, and what stage of pregnancy the mare is in when the urine is collected. Thus, the simple extraction of 'estrogens' or 'conjugated estrogens' leads to a conjugated estrogen product that varies both in relative concentration (one steroid component relative to another steroid component) as well as in the presence of a number of the 'estrogenic species' (some species may be missing from one batch and present in another. This had lead to difficulties in the development of a generic equivalent of PREMARIN, mostly because of the lack of a defined reference standard and the complex nature of the product."

the always cultural, historical, and gendered performance of socio-material realities?[154] Springing from many sources, functional through many forms, estrogen was hard to pin down. Materialized through the measurements of bioassays, estrogen's effects within nonhuman and human bodies – and thus its very identities – were performed in encounters and in intra-actions. Refracted this way, through Barad or Haraway, estrogen does not precede or pre-exist its bodily or regulatory relations.[155] Might this cause one to see the Sex Hormone Regulations differently? Well, perhaps. After all, in defining a sex hormone as that which purports to have estrogenic properties, the question of estrogen's effects was left open, and this accords, in many ways, with a material-semiotic account of pharmaceuticals' "properties" as constituted through their social, legal, economic, informational, and bodily relations.[156] At the risk of presentism, it is now known that oestrone, oestradiol benzoate, DES, Premarin, and all the other estrogenic products, in their myriad forms – let alone all the (other) industrial chemicals that mimic estrogen – have a huge range of bodily effects, some of which lie latent for decades or are transgenerational.[157] To a lesser extent, though, estrogen's diverse effects were also understood in 1944, as shown in the historical accounts. Indeed, growing knowledge of diverse effects resulted directly from the same multiplicity of bioassay methods that, in the Sex Hormone Regulations, the Department chose not to stabilize. Further, the plethora of bioassays, while characterized some laboratory scientists who desired homogeneity as chaotic, had benefits for pharmaceutical innovation "since they became almost indispensable for assessing the diversity of functions – and therefore the diversity of indications – that potent physiological agents could display".[158]

In performing estrogen as open-ended, and with multiple and relational effects, the regulatory definition of "sex hormone" also declined to enact any clear nature-culture divide. Instead, it held "natural" and "synthetic" estrogens tightly together. Discourses on endocrine disruption that insistently separate natural hormones from synthetic chemicals have no resonance in these regulations; those desensitized to the ontological politics of DES or Premarin might even proclaim that they enact an estrogenic natureculture.[159] Alternatively, following Oudshoorn and Mol,[160] this estrogenic unity is best understood as an accomplishment.

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[154] See Chapter 1, section 1.i., particularly the content associated with notes 23-33.

[155] Barad 2003; and Haraway 2008.

[156] See Chapter 1, section 2.i., particularly the content associated with notes 138-144, and section 2.iii., particularly the content associated with notes 209-212.

[157] See e.g. Liboiron 2016 at 97-98.

[158] Gaudillière 2010 at 176.

[159] See Chapter 2, section 2.1., particularly the content associated with notes 156-165.

[160] See Chapter 1, section 1.i. and section 2.i.

The multiple bioassays and the chemical tests, the synthesis in labs and the collection of urine in horse stables, the injections by doctors and tablets from drug stores, these practices that enacted estrogens were numerous, varied, and often incompatible. To make diverse estrogens hang together, as "sex hormones" rather than as a swelling miscellany, National Health tried through this definition to present estrogen, natural and synthetic, as one singularity. Such coordination efforts performed sex hormones as stable, ahistorical, given by nature.

Whether reflecting naturecultures or naturalizing drugs for diseases that did not yet exist, the Sex Hormone Regulations did not only rely on novel standardization techniques and definitions. They also relied on two absences: silence on dose, and a refusal to license sex hormones. In Canada, dose specifications were a relatively common approach used to protect consumers from potent or unstable drugs. For pharmacologists and physicians in the 1940s, the safety of a potent drug was a function of its dose (and relatedly, of dosage administered over time). Discovering the relationship between dose and response was the magic key that would unlock the mystery of when a drug stopped being safe and instead became a hazard. Researchers strove mightily to determine and to document the safe therapeutic dose range for a drug; as seen, the Canadian Supplement monographs for oestrone, oestradiol benzoate, stilboestrol, and stilboestrol diproprionate all set dose ranges for intramuscular injection.[161] Likewise, for many other biologics regulated in the 1940s, whether in the Canadian Supplement or the Biologicals Regulation, dose was defined.[162] Dose was so central to safety that, in 1942, Canada enacted new regulations prescribing minimum and maximum dosage limits, in tablets, capsules, ampoules, and other forms of administration, for some 70 drugs.[163] However, sex hormones did not make the cut, then or in later amendments to the dosage regulations.[164]

Why did National Health not prescribe dose for sex hormone products, in the Sex Hormone Regulations? One might be tempted to conclude that Committee members assumed physicians would supervise dosage, tinkering with the amount of estrogen that they administered as their patients responded or had undesired "side effects". That might be a safe assumption by the mid-1950s, when sex hormones became prescription drugs, but in 1944, it was not. One lone Committee member had advocated that sex hormones be sold only on prescription, yet his

[161] The Canadian Supplement monograph for stilboestrol included dose ranges which also covered oral administration.

[162] For such an amendment to the Biologicals Regulation concurrent with the Sex Hormone Regulations, see *supra* note 127.

[163] PC 1942-9056 (6 October 1942), *Canada Gazette,* Vol LXXVI, No 181, Extra, at pp 21-32 (October 16, 1942).

[164] PC 1944-3520 (11 May 1944), *Canada Gazette,* Vol LXXVIII, No 21, at 2104 (May 20, 1944). See also March 20, 1944 memo from Driedger to Varcoe and March 20, 1944 letter from Varcoe to Gunn, in Library and Archives Canada, "Pension and National Health Amendments to Food and Drugs Regulations, 1944", RG 13, volume 2115, file no 1468.

recommendation had been ignored. While some Canadian physicians in the 1940s were administering estrogenic drugs, women could also buy them over the counter.

Recalling the Committee's debates during 1943, situated alongside industrial, political, and statutory developments, the answer seems clear. Ayerst – and perhaps also the CPMA – was opposed to standardizing dose, as this would limit its freedom to devise new products. Thinking again of Premarin, estrogenic drugs were recently being produced on assembly lines, arriving in Canada as tablets, capsules or other pre-made forms. Prescribing doses would therefore frustrate manufacturers' ability to produce new forms, no insignificant concern when Premarin's "flexibility of potency and dosage" was one of its major selling points.[165]

Without engaging here in any detailed semiotic analysis of Premarin advertisements,[166] in the years after the Sex Hormone Regulations were enacted, Ayerst targeted Canadian doctors with advertisements emphasizing Premarin's growing ranges of available doses and potencies.[167] In 1945, Ayerst was selling Premarin tablets (No. 866) "for the most severe symptoms", pitching a new "Half-Strength" Premarin tablet (No. 867) for "when symptoms are moderately severe", and promoting its ageing, placentally-derived product Emmenin as being "for mild symptoms". By 1950, Ayerst no longer needed to expressly convey, with text, that Premarin was a drug for menopause. Containing the infamous tagline that Premarin "imparts a feeling of well-being", an ad that year also conveyed the drug's ontologically precarious status as "highly potent" and "essentially safe". More to the point, this ad shows that dose had further diversified by 1950, moving beyond the full strength and half strength pills to include a double strength tablet (No. 865), quarter strength tablet (No. 868), new liquid dosage form (No 869), and, for the especially anxious woman – or her husband – the option of Premarin combined with a sedative. Messaging again to male physicians that Premarin would promote, in their female patients, "a feeling of well-being and a revival of interest in normal activities" – visually depicted as sewing, gardening, and painting – an ad in 1951 again emphasizes a range of potencies and dosage (now also bundled with methyltestosterone to boost wives' flagging libidos). In this period, the freedom to manufacture multiple doses and potencies was critical to the market differentiation strategy that Ayerst was pursuing to enroll physicians to medicalize menopause.

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[165] See Figure 8.

[166] For a semiotic analysis examining how Premarin ads, published in physicians' journals between 1986-2000, aimed to persuade Canadian physicians to prescribe the drug, see Patricia Peppin & Elaine Carty, "Semiotics, Stereotypes, and Women's Health: Signifying Inequality in Drug Advertising" (2001) 13 *Can J Women & Law* 326.

[167] See Figures 6, 7 and 8.

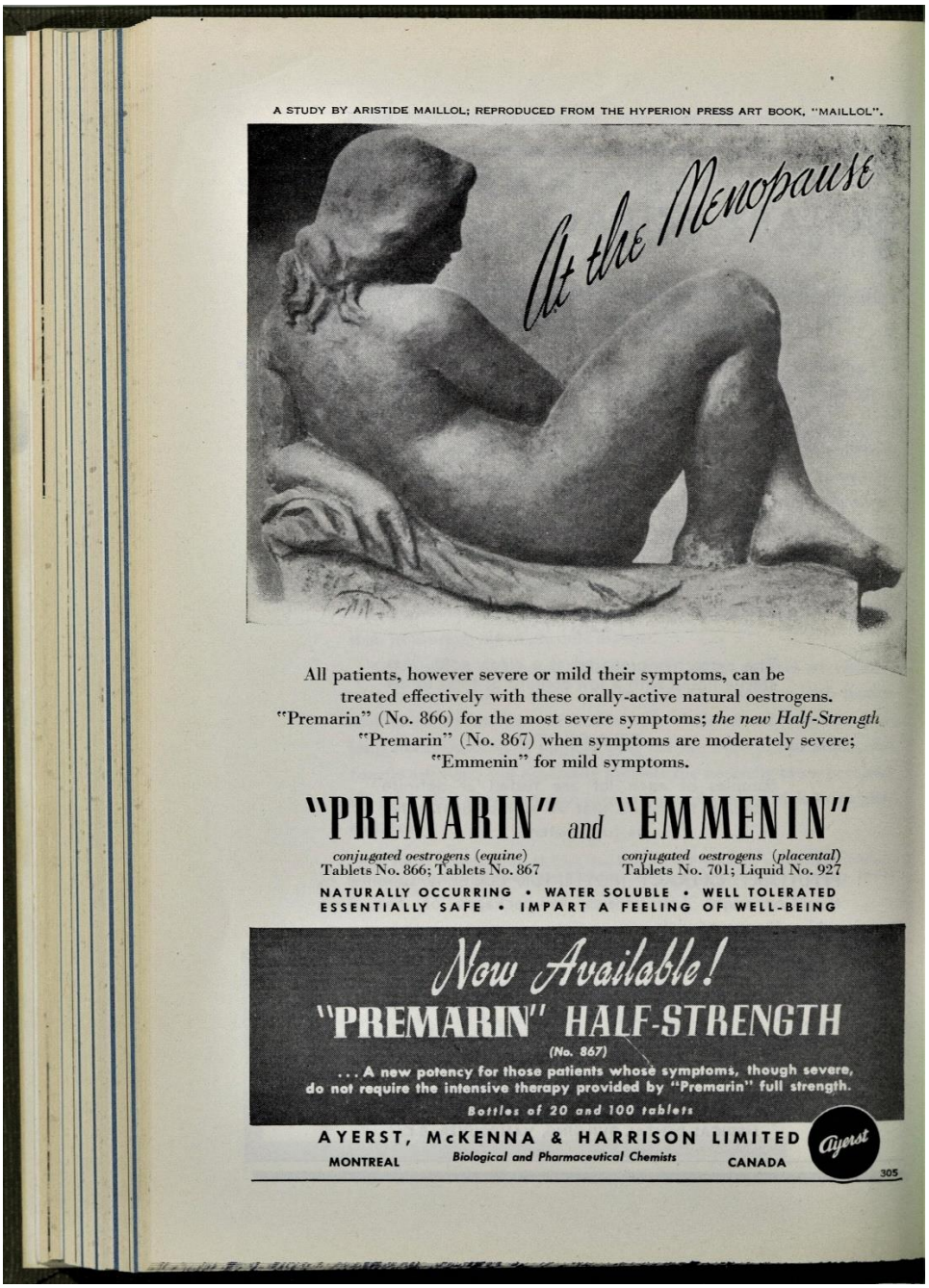

Figure 6: 1945 ad for Premarin and Emmenin, Ayerst, McKenna & Harrison Ltd.

Vancouver Medical Association. *The Vancouver Medical Association Bulletin: March 1945.* doi:http://dx.doi.org/10.14288/1.0214401 (Original work published March 1945).

UBC Open Collections, History of Nursing in Pacific Canada, online: <https://open.library.ubc.ca/collections/historyofnursinginpacificcanada>.

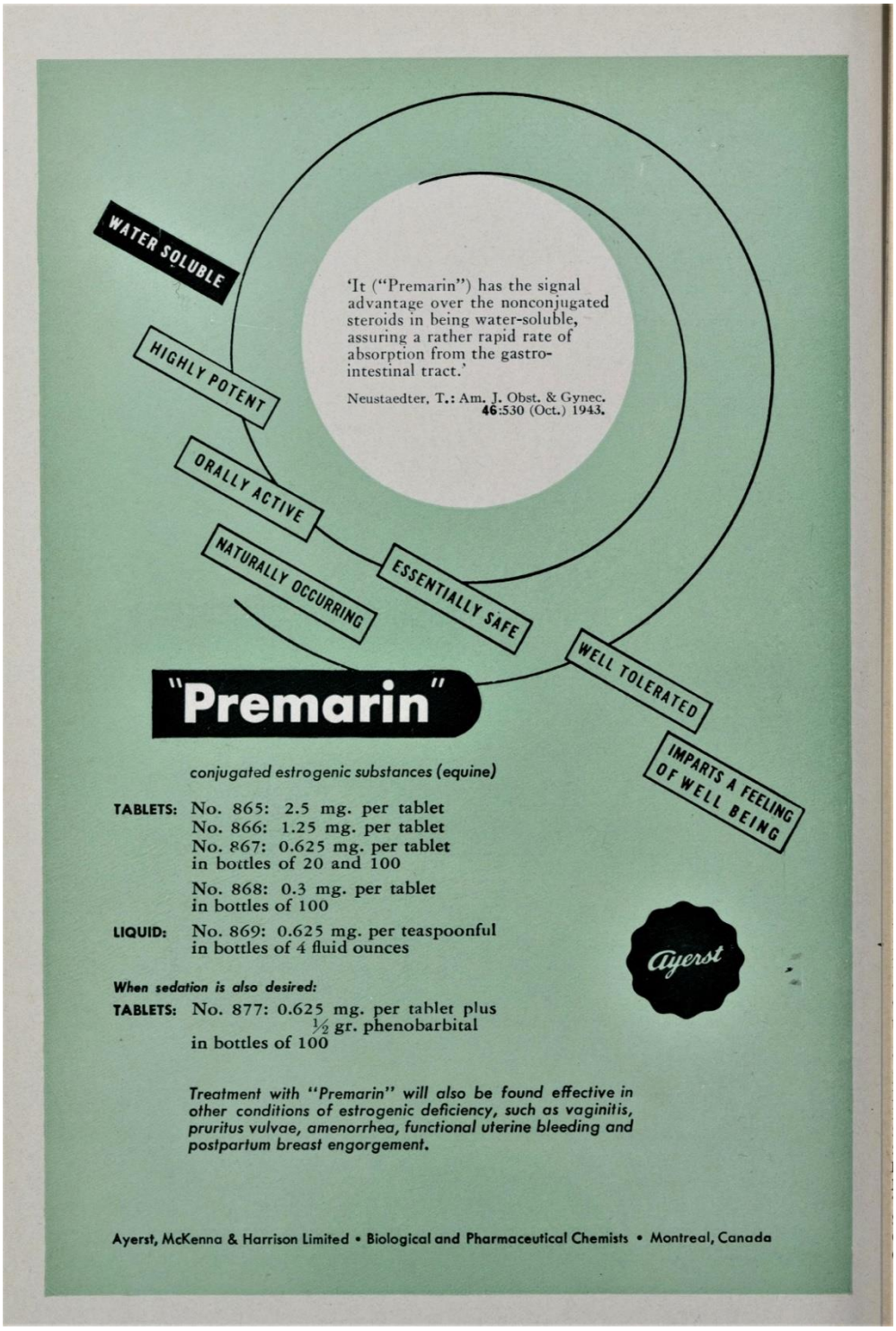

Figure 7: Ad for Premarin, Ayerst, McKenna & Harrison Ltd, 1950

Vancouver Medical Association. *The Vancouver Medical Association Bulletin: February, 1950.* doi:http://dx.doi.org/10.14288/1.0214411 (Original work published February 1950).

UBC Open Collections, History of Nursing in Pacific Canada, online at https://open.library.ubc.ca/collections/historyofnursinginpacificcanada

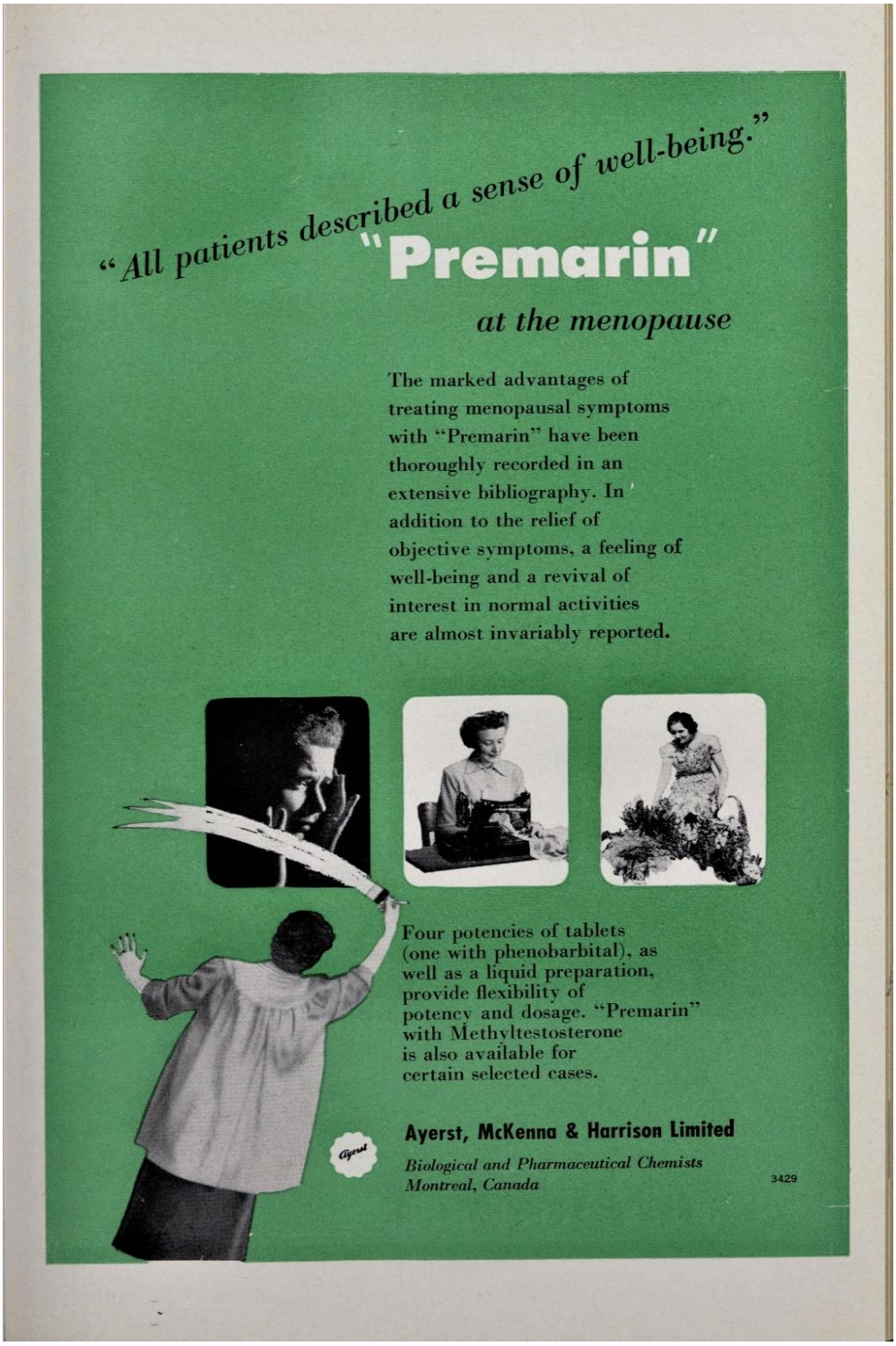

Figure 8: Ad for Premarin, Ayerst, McKenna & Harrison Ltd, 1951

Vancouver Medical Association. *The Vancouver Medical Association Bulletin: November 1951.* doi:http://dx.doi.org/10.14288/1.0214637 (Original work published November 1951).

UBC Open Collections, History of Nursing in Pacific Canada, online: <https://open.library.ubc.ca/collections/historyofnursinginpacificcanada>.

A cognate reason that the dose of estrogenic drugs was not regulated, though never made explicit in any of the Committee's deliberations, was that estrogen's diseases were still in the making. A therapeutic dose needs a disease. With Premarin and DES freshly unleashed and menopause not yet stabilized as a medical ailment, dosage remained uncertain. Finally, despite over a decade of research connecting estrogens to cancer, National Health continued to enact sex hormones as innocuous and ineffective. Safe and worthless drugs could be taken in any dose. At one level, this performance was personal. Pugsley, the departmental lead on the sex hormones file, was a former protégé of Ayerst's partner Dr. Collip and had worked in Collip's lab when Emmenin was at the peak of its success. At another level, scientists were beginning to perform Premarin as harmless; in 1943, the Journal of Clinical Endocrinology published a series of studies lauding Premarin, solidifying the idea that menopause was a disorder.[168]

Beyond scientists' predilections and practices, ineffectiveness and safety were also reproduced through a second key absence in the Sex Hormone Regulations. Though listed on Part II of Schedule B, sex hormone products were not made subject to licensing requirements. This meant that the regulations eschewed all controls on the manufacture and sale of estrogenic drugs: precluding inspection of plants, equipment, products, and records; preventing review of technical qualifications of staff; and pre-empting both batch testing and the approvals of batches for import or sale. Regardless of the emergence of DES, Premarin, and other new products, the regulations therefore maintained National Health's fifteen year-long practice of carving estrogenic products out of licensing. It should not be forgotten that the US did not license sex hormone products,[169] which undoubtedly created resistance to licensing within National Health. Nevertheless, to point only to American practices on sex hormones – when in other respects the Canadian regulatory regime on sex hormones diverged – would underdetermine the influences on National Health officials. This lingering licensing practice also flowed from a longstanding performance, by senior officials, of sex hormones as therapeutically ineffective and of licenses as endorsement. "Considering that many things have little or no value", Lancaster had told Davidson from his hospital bed in February 1944, it "would be a pity to require a licence for such things because a licence carries implicitly some form of approval by the Department."[170] Regulators were catalyzing sex hormones while refusing to sanction them, doing estrogens as simultaneously potent and weak, complicated and easy, effective and worthless, all the while

[168] See e.g. Laman Gray, "Clinical Study of a New Type of Estrogenic Preparation for Oral Use" (1943) 3:2 *J Clin Endocrinol* 92; and S Glass & Gordon Rosenblum, "Therapy of the Menopause, Superiority of Conjugated Estrogens—Equine over Diethylstilbestrol" (1943) 3:2 *J Clin Endocrinol* 95.

[169] See Chapter 3, section 1, particularly the content associated with notes 87 and 92.

[170] February 4, 1944 memo dictated by Lancaster to Davidson, National Health's Parenteral Drug Regulations File, 1943-1944.

bracketing and ignoring the differences between versions of estrogen. To return to an old metaphor: with no ability to close the barn door, and having failed to standardize horses to be less potent creatures, National Health could have repaired the pasture fence or made the barn more inviting. But thinking of all tamer beasts in the barn – the goats, sheep, chickens – and not wanting to overreact for those more domesticated creatures, National Health did nothing.

Hold these regulatory elements together: purported properties, vague reference standards, delegated potency tests, disavowal of licensing conditions, lack of dose specifications. In effect, the Sex Hormone Regulations fostered more rather than less variability, greater rather than fewer products, altogether an expanding range of doses, potencies, and bodily effects. Did the Sex Hormone Regulations create "drug standards" at all? Thinking again with Busch's typology, which has already caused rejection of the notion that these regulations either created "filter" standards or promoted a logic of industrial standards, did these regulations nonetheless create another type of standard? Recalling Busch's unranked "division" standards, exemplified by McIntosh and Granny Smith apples, did the regulations codify product differentiation, letting estrogenic products to be positioned as "different" from each other and thus assigned different market values and prices? At first blush, as the definition holds all "sex hormones" together as things of like kind, the regulations did not seem to create unranked categories. However, turning to the final section of the Sex Hormone Regulations, division standards suddenly emerge.

Section 4 governed labelling.[171] Contrary to the other provisions, this "special labelling provision" for sex hormones imposed more extensive requirements than did labelling rules for other biologics in Canada.[172] In addition to the typical requirements that labels identify the name and address of manufacturers, a product's proper name and potency, lot number, and expiration date,[173] the Sex Hormone Regulations created what in essence were division standards. Specifically, paragraph 4(c) required outer packages, and inner labels,[174] to state:

> (c) The descriptive or proper name of the product distinct from the trade name.
>
> > In the case of pure synthetic or natural crystalline products, the proper name shall be: -- Oestrone, oestradiol, oestriol, stilboestrol, androsterone, testosterone, progesterone, and esters and derivatives of these.

[171] Sex Hormone Regulations, s 4.

[172] For the general labelling rule for biological drugs at that time, see 1942 Biologicals Regulation, "General Requirements", s 1. Robert Curran described section 4 as a "special labelling provision" unique to sex hormones; see Curran 1953 at 185.

[173] *Ibid* and Sex Hormone Regulations, ss 4(a), (b), (d), (e) and (f). The only sex hormone requiring an expiration date on its label was "gonadotrophins in aqueous solution"; see s 4(f). Sex hormone labels were also required to include the "name of solvent or vehicle used in distributing products in liquid form and the name and amount of preservative in these products; see s 4(g).

[174] Sex Hormone Regulations, s 4(j).

> In the case of mixed or impure products, the proper names shall be: -- Conjugated oestrogenic substance (S), oestrogenic substance (S), androgenic substance (S), progestational substance (S) and esters and derivatives of these.
>
> In the case of gonadotrophins the proper name shall be gonadotrophin with a qualifying statement to indicate the source, e.g., chorionic gonadotrophin, gonadotrophin from pregnant mare's serum.

Section 4 thus prescribed proper names for both "pure synthetic or natural crystalline" estrogenic drugs and for "mixed or impure" estrogenic drugs. For mixed or impure products – DES in a sugar milk tablet, estrone with peanut oil in an ampoule for injection – the proper name would be "oestrogenic substance". At Cook's request, Premarin was given its very own proper name of "conjugated oestrogenic substance". Thus, while the coordination practices underlying section 1 joined all estrogens together as "sex hormones", the naming practices underlying section 4 enacted unitary and bounded estrogens.

Arguably, then, the Sex Hormone Regulations inverted the traditional relationship between standards, tests, and indicators, as mapped out by Busch.[175] In that traditional relationship, a label would indicate that a test for meeting a certain standard has been satisfied. Here however, the labels mandated by section 4 could not pronounce that any particular test for any particular standard was met. Rather, the primary effect of the requirement to assign proper names to sex hormone products was to crystallize these products as ontologically real, to call sex hormone products into being as distinct, all the while without knowing or indicating their beings or doings. Assigning proper names constituted an estrogen, legally and economically, as its own "thing", separate from other kinds of estrogens.

As Johnson beautifully analyzes in his legal-material medieval history of shipwrecks off the coast of Suffolk, naming shapes the real – the name assigned to a wreck "shaped the possibilities of its use, worth, distribution, and meaning".[176] In this legal-material history of estrogen in Canada in the 1940s, the conditions of possibility were likewise shaped by naming practices. These divisions allowed doctors, consumers, manufacturers, advertisers, retailers, pharmacists, and other market actors to enunciate what an estrogen "was" and to delineate differences with other estrogens. In this respect, the Sex Hormone Regulations would facilitate product differentiation, price discrimination, physicians' prescribing practices, pharmacists' dispensing and compounding practices, and pharmaceutical firms' marketing strategies. The divisions created by the requirement to label with proper names reflect the logic of merchant

[175] See Chapter 1, section 2ii.

[176] Johnson 2015 at 424-425.

standards, acting to gain estrogen access to markets through distinctions that solidified a product's unique identity while ensuring its comparability to other estrogenic products. Although other Committee members and National Health may have had quite different intentions than did Cook, requiring these proper names on product labels surely served to smooth market entry.

To be clear, using regulations to assign proper names to drugs was not a wholly novel practice at National Health.[177] Much more unique was the innovation in paragraph 4(h), which later attracted the characterization, by the Department's legal counsel Robert Curran as a "special" labelling provision for sex hormones that was appropriate "having regard to the dangers which may be inherent in their use".[178] Paragraph 4(h) required manufacturers to include the following statement on outside labels: "Caution Label–to be used only on the advice or on the prescription of a physician". For the first time in the history of Canadian drug regulation, a label was deployed to discipline consumers, almost all of whom would be women.

In devising this mandatory caution label, Pugsley, Morrell, and other National Health officials undeniably accepted that sex hormones posed a hazard. However, with the Committee rejecting Dr. Farquharson's suggestion that such products should only be sold on prescription, any pharmacist or retailer could lawfully sell an estrogenic drug to anyone. That this caution label would cause women to refrain from buying or using estrogenic products, without securing their physician's supervision, was magical thinking. As an American food and drug lawyer observed, in criticizing Canada's regulatory approach to sex hormones: "a label statement directing a person to see a physician about whether he should use a drug he has already bought is a futile gesture".[179] In this regard, the purpose of the caution label appeared to be less about protecting women and more about protecting National Health (especially as estrogen continued to remain exempt from prescription requirements). Thus, as a regulatory device, the caution label nakedly sought to make women consumers responsible for National Health's decision not to subject estrogenic drugs to classic drug standards, license conditions, or medical supervision.

When read in the context of the Sex Hormone Regulations as a whole, the caution label makes legible the fundamental trade-off at the heart of the regulations. As with the potency

[177] See e.g. Chapter 3 at note 146.

[178] Curran 1953 at 185.

[179] William W Goodrich, "International Uniformity – the Possible and the Impossible in Food, Drug and Cosmetic Laws" (1951) 6 *Food Drug Cosm LJ* 885 ["Goodrich 1951"] at 889. Under the US FDCA, approved drugs had to be labelled with both ingredients and warnings, and labels also had to provide adequate directions for use to the consumer. With concern that some directions for use were too complex to include in labelling, the Durham-Humphrey Amendment of 1951 exempted those drugs that could be safely used only under the supervision of a physician, requiring instead of a label the legend: "Caution: Federal law prohibits dispensing without a prescription." See Patricia I Carter, "Federal Regulation of Pharmaceuticals in the United States and Canada" (1999) 21 *Loy LA Int'l & Comp L Rev* 215 at 219. See also Davidson 1949a at 85-86.

labels that substituted for potency standards, the caution labels were not motivated by empowering consumers with information, nor by steering towards good market choices.[180] They were not intended to shape manufacturing practices, nor to convey or augment existing regulatory standards of safety. The special labelling rules for sex hormones were not adopted to *supplement* standards – rather, they were adopted as an alternative to standards. Rather than building safety into estrogen, the caution labels acted *in lieu* of regulatory standards of identity, potency, and dosage. Rather than assuming responsibility for ensuring that estrogenic drugs were crafted in doses and potencies that avoided toxicity, or delegating that duty to prescribing physicians, National Health delegated to the caution label the task of disciplining women consumers to avoid hazards. Scripted into products marked with this caution label was a mixed message to middle aged women, communicating that while the drug was safe enough to buy without a prescription, they should still follow their doctor's orders. Embedded is the further assumption that, given the social class and economic status of the women buying these drugs, the caution would reinforce their inclinations to be good girls and run along to their doctors. If less educated or imprudent women failed to exercise such common sense, any resulting harm could not be pinned on Canada. The caution labels could thus "standardize" subjectivities of women and prescribing physicians, and performatively enact the contradictory realities – "highly potent" yet "essentially safe" – materializing estrogenic drugs in clinics and markets.[181]

It was foreseeable that non-compliance with the Sex Hormone Regulations would go unenforced. Of its substantive provisions, arguably only the labelling section was enforceable. Presumably, violation of labelling requirements – representing one's product as more or less potent than it was according to the manufacturer's own test methods, misrepresenting the type of estrogen or the liquid formulant in the product – could be prosecuted, if not as a direct violation of section 4 of the Sex Hormone Regulations, then as the statutory offence of misbranding or adulteration.[182] On at least one occasion in the 1940s, National Health officials

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[180] Xaq Frohlich traces the history of US FDA nutritional labelling requirements, confirming that the "informational turn" in labelling governance, in which the FDA began to regulate food markets through consumer empowerment, emerged only in the 1970s. In the 1940s, however, health information on food labels was believed to "confuse" consumers. Instead, just as with drug regulation in Canada and the US, food labelling in the 1940s under the US FDCA focused on the "standards of identity" system, for which "the master metaphor was the recipe" (151). Xaq Frohlich, "The informational turn in food politics: The US FDA's nutrition label as information infrastructure" (2017) 47:2 *Soc Stud Sci* 145 ["Frolich 2017"] at 147, 151-154.

[181] See Figure 7.

[182] The question of whether violations of regulations under the *Food and Drugs Act* were directly enforceable was controversial and attracted commentary. In the 1927 statutory amendments, regulations were confirmed to have the same force and effect as the *Act*'s provisions; *Food and Drugs Act*, s 3(3), as added by SC 1927, c 56, s 9. Curran regularly argued that the Food and Drug Regulations were enforceable, making claims such as "[u]nder our Act, a violation of the regulations carries exactly the same penalty as a violation of the Act"; Curran 1953 at 316. Driedger did not so readily accept that s 3(3) of the *Act* had that legal significance. In his 1960 article, he noted that the *Food and Drugs Act* "did not expressly confer authority to prescribe penalties for breach of a regulation", and that the statute itself "prescribed a penalty only for breach of a provision of the Act."

warned a pharmaceutical company that it was in breach of the regulations' labelling rules.[183] By contrast, the reference standard rule was too vague on what the requisite standard was, in any given situation, to enforce. Besides, this rule caused such a "multiplicity of standards" that, by 1951, National Health officials had largely abandoned the law and instead entered "working arrangements" with manufacturers on the "adequacy of standards available for their product".[184] On the regulations' potency standards, with drug firms left to their own devices when measuring and expressing their products' potency, unless potency labels were missing, it is conceptually challenging to conceive of a violation of any potency "standard". These barriers to enforcement, combined with a National Health policy "to avoid court action if at all possible",[185] make it unsurprising that there were apparently no prosecutions during the 1940s or early 1950s.[186]

4. Confronting multiplicity and duplicity: the Committee meets, September 1944

In 1944, this assemblage of scientist-regulators would create Canadian standards for almost 200 drugs and biological products.[187] This was an accomplishment – though perhaps not in the sense intended by the Committee. One of its most thoughtful members spent time, over the summer of 1944, mulling over the consequences of Canada's new drug standards. After reflection, Esli Woods wrote to the Secretary of the Committee.[188] In an incisive appraisal, the Dean of Pharmacy diplomatically detailed the recent proliferation of "sources of official standards and methods", which he believed had unintentionally undermined the uniformity of drugs in Canada.[189] Troubled by the challenges that proliferating standards posed for training

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However, Driedger also noted an English decision, in *Willingdale v Norris*, [1909] 1 KB 57, that held that a statutory provision prescribing a penalty for a statutory breach extended also to a regulatory breach; see Driedger 1960 at 5-6.

[183] The matter concerned the failure of a US supplier, Adson-Intrasol Laboratories, to identify on its labels the lot number or the oil added to its oestrone preparation Estrovin, which was purchased by the Canadian company Hyman Surgical Supply Co. See the correspondence from December 7, 1944 to March 27, 1945, in National Health's Sex Hormone Regulations File, 1944-1945.

[184] Pugsley 1951 at 534-535.

[185] Curran 1953 at 193, adding that "[a]ccordingly, in the absence of a flagrant and defiant violation of the Act, every effort is made to bring about an adjustment of the situation without the necessity of prosecution."

[186] Food and Drug Newspaper Clippings, 1949-1953; Monthly Prosecutions and Seizures Reports, 1950-1953; Inspectors' Reports, 1950-1953; National Health's Sex Hormone Regulations File, 1944-1945; and Pugsley 1951.

[187] Curran 1946 at 501.

[188] August 25, 1944 letter from Woods to Davidson, in Library and Archives Canada, Department of Health fonds, RG 29, "Canadian Committee on Pharmacopoieal Standards", 1944/06-1945/05, volume 253, file no. 339-4-8 (Part 3) ["Possibly Morrell's Committee File, 1944-1945"].

[189] The proliferating sources of Canadian drug standards that Woods summarized, in addition to the British Pharmacopoeia which remained "official in Canada except insofar as its monographs are modified or replaced by Canadian regulations", were: 1) the Canadian Supplement dealing with the "miscellaneous" list of drugs in Part V of Schedule B of the *Act*; 2) a number of orders in council that were not necessarily connected to Schedule B but could also be authorized under s 3(a) of the *Act* (such as the vitamin regulations); 3) drug standards in Division II of the Food and Drug Regulations (such as the Sex Hormone Regulations); 4) the methods employed by the Laboratory of Hygiene "giving details of methods of biological assay which are

pharmacy students, Woods was also worried about the legal and moral implications for practicing pharmacists, as without fixed, stable, and readily available methods of determining conformity to standards, pharmacists could not meet their responsibilities to ensure the quality of their preparations. In his view, drug quality and professional responsibility would necessitate a greater "degree of stabilization of standards and methods". Woods was observing, in candid and careful fashion, what departmental officials were coming to acknowledge privately. That summer, Lancaster and Davidson had also discussed how the flurry of enactments had multiplied standards, including for sex hormones. Lancaster felt the best solution would be to amalgamate the Division II biological drug standards with the Division III Supplement monographs, through an eventual consolidation of the Food and Drug Regulations.[190]

When Committee members returned to Ottawa that September for the year's final meeting, assembling again in the Daly Building's comfortable library, Dean Woods explained with "some anxiety" how the "multiplicity of sources" of standards would materialize multiple versions of the same drug. This situation would presumably worsen after the war when, with the anticipated rescindment of orders under the *War Measures Act*, the addenda to the British Pharmacopoeia would once more apply in Canada. For example, there would be "two varieties of ephedrine" and "two kinds of thyroid". [191] Woods could have added "two varieties of oestrone" and "two types of oestradiol benzoate", let alone the other modes of estrogen that had been enacted.

Lancaster mounted a half-hearted defence, maintaining that the Committee's activities had not made the situation more confusing than it already was before, and stressing that, whatever standards might exist in foreign pharmacopeia, Canadian regulations took precedence. This was certainly correct, and yet, with respect to estrogen,[192] his answer dodged the issue. Canadian regulations themselves created two sets of standards. Estrogen was enumerated as sex hormones in Part II of Schedule B, with accompanying regulatory standards, and as four molecules in Part V, with accompanying regulatory monographs – but which trumped? For five

recognized as official"; and 5) the Canadian Formulary's Addendum, "the scope and status of which is not a present clearly defined". Woods provides the clearest summary of the enactments, their sources of authority and the relationship between them, of any found in the archival materials reviewed for this thesis, including memos by solicitors of National Health.

[190] June 19, 1944 letter from Davidson to Henderson, Davidson's Committee Materials, 1944. This consolidation eventually occurred, beginning in 1947 and concluding in 1949; see Chapter 5, section 1, particularly content associated with notes 17-19.

[191] September 18-19, 1944 meeting minutes and materials, in Possibly Morrell's Committee File, 1944-1945.

[192] Incidentally, this was also an issue for ephedrine and thyroid. As of 1944, each of these were addressed both in the Biologicals Regulation in Division II as well as in various Canadian Supplement monographs in Division III.

years, Lancaster had sidestepped that question, and no government solicitor had ever confronted it either.[193] By leaving it unresolved, estrogenic reality in Canada had multiplied.[194]

Dr. Cook did not attend the September meeting. Emboldened by the absence of Ayerst's scientist, Committee members voiced frustration with industry foot-dragging on test methods for sex hormones. Normally receptive to industry interests, Morrell was especially scathing. On behalf of their subcommittee on sex hormones, yet without Cook's input, Morrell tabled a status report. After recalling how the subcommittee had entrusted Cook with consulting US commercial laboratories regarding National Health's proposed bioassay methods for sex hormones, his report put on the record that, but for Parke Davis' constructive criticism of the method for gonadotrophins, manufacturers had failed to respond. Given that this effort had "extended for over a year and with very little response from manufacturers", he recommended its termination, as "[c]ontinuation of this procedure in respect to all new methods would, in our opinion, unduly delay our adoption of official methods." He proposed that National Health proceed to officially adopt its methods for oestrone and oestradiol benzoate, advising that the Laboratory of Hygiene was preparing what he referred to as a "book of official methods".[195] A portion of this book was already typewritten, and Morrell suggested that it would be complete by the end of 1944.[196]

Yet delay tactics were not exclusive to industry. The idea of a book of official methods had its genesis in the Committee's debate, at its very first meeting, regarding the centrality of test methods to the regulation of sex hormones. At that meeting, bureaucratic opposition to codifying methods in regulation, industry resistance, and academic willingness to concede the issue in exchange for teaching and research support had combined to pave the way for regulatory sanction of sex hormones without conventional standards. This compromise had been brokered through a promised book of methods, which would act as a companion to the regulations. But the book never materialized. In meetings and letters over the next seven years, Morrell and

[193] The only example of a National Health official starting to grapple with this question, before the meeting held on September 17-18, 1944, was in a draft memorandum by Davidson, which he apparently prepared in response to Dean Woods' August 25, 1944 letter. It asserts that Division II standards, such as the Sex Hormone Regulations, "are paramount in this country". See undated memo entitled "Pharmcopeoial Drug Control in Canada, in Possibly Morrell's Committee File, 1944-1945.

[194] Mol 2002.

[195] Appendix A to the September 18-19, 1944 meeting minutes, in Possibly Morrell's Committee File, 1944-1945.

[196] As of September 1944, official biological methods had been adopted, but not released outside the Laboratory of Hygiene, for the following substances: arsphenamine, neoarsphenamine, digitalis, pituitary extract (posterior lobe), androgenic hormones, oestrogenic hormones, thiamine, vitamin A, vitamin D, and some antisera and antitoxins. At this time, the Laboratory of Hygiene was studying potential bioassay methods for riboflavin, vitamin C, penicillin and pyridoxine, gonadotrophic hormones and progesterone. It also had settled on chemical test methods for vitamin C, vitamin A, pantothenic acid, pyridoxine, and thiamine. See September 18-19, 1944 meeting minutes and materials, in Possibly Morrell's Committee File, 1944-1945.

others would routinely promise a printed book of methods, at no distant date.[197] Although the Laboratory was developing and applying internal methods, National Health did not finalize or circulate any such book at any time before the early 1950s. By then, the Laboratory's resistance to publishing its methods no longer appeared motivated, as Morrell had professed at the Committee's first meeting, by administrative concerns about printing costs. Rather, consistent with Deputy Minister Wodehouse's intervention during the development of the Sex Hormone Regulations, in 1950, the Chief of the Laboratory of Hygiene candidly connected resistance to disclosing its methods to the Department's distaste for holding drug manufacturers to standards:

> "We are rather loath to outline procedures … since there is a marked tendency among manufacturers to look upon a method described … as the only method. This would be a backward step since there would be no incentive for manufacturers to develop their own techniques … We are most anxious to avoid becoming a party to any directives which could have the effect of stifling the initiative on the part of the manufacturers. That is why in the Biologics section of the Food and Drug Act, specific tests have been omitted."[198]

In this way, estrogen initiated new regulatory practices and, eventually, legislative change. Fuelled by estrogen, techniques of validating burrowed deeper into the bureaucratic culture of National Health. Not only did methods of standardization continue to be unlawfully subdelegated to departmental officials, but the Department's methods were not distributed to drug makers or made transparent. Eventually, the statutory provision requiring official test methods to be prescribed in regulations was simply dropped from the revised *Food and Drugs Act* in 1953.[199]

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This chapter has composed a Canadian history of the standardization of estrogen. In assembling the heterogenous activities, debates, and decisions of a group of scientist-regulators – including the physicians, pharmacists, industry researchers, and National Health

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[197] See e.g. June 19-20, 1945 meeting minutes and materials and May 31, 1946 meeting minutes, in Library and Archives Canada, Department of Health fonds, RG 29, "Canadian Committee on Pharmacopoeial Standards", 1945/06-1946/0, volume 253, file no. 339-4-8, (Part 5) ["Possibly Morrell's Committee File, 1945-1946"]; October 1, 1947 letter from Woods to Davidson and October 11, 1947 letter from Davidson to Woods, in Library and Archives Canada, Department of Health fonds, RG 29, "Canadian Committee on Pharmacopoeial Standards – Correspondence", 1946/11-1948/05, volume 252, file no. 339-4-7 (Part 7) ["Davidson's Committee Materials, 1946-1948"]; December 1947 meeting transcript, in Library and Archives Canada, Department of Health fonds, RG 29, "Canadian Committee on Pharmaceutical (sic) Standards", 1947/08-1948/10, volume 249, file no. 339-4-1 (Part 7) ["Unknown Committee Member's File, 1947-1948"]; July 6, 1949 letter from Mathews to Davidson and July 11, 1949 letter from Davidson to Mathews, in Library and Archives Canada, Department of Health fonds, RG 29, "Canadian Committee on Pharmaceutical (sic) Standards", 1948/10-1949/09, volume 249, file no. 339-4-1 (Part 8) ["Unknown Committee Member's File, 1948-1949"].

[198] May 4, 1950 memo from James Gibbard to Morrell, in Unknown Committee Member's File, 1948-1949.

[199] *Food and Drugs Act,* RS 1952-1953, c 38, s 24; see also Chapter 2, note 17.

officials on the recently formed Canadian Committee on Pharmacopoeial Standards, and extending this network to include the Laboratory of Hygiene and the Department of Justice – it has shown how, in the mid-1940s in Canada, estrogen was enacted with a variety of epistemic, institutional, and regulatory practices. Thinking with Mol's relational materialism,[200] I have illustrated that estrogen was done multiply in this regulatory network. Further, working with a co-production framework,[201] I have also begun to show how estrogen, with its variable potencies, unfixed doses, and unpredicted dose-response relations, in turn engendered new techniques in Canadian drug regulation. This second theme will be developed, in the context of estrogen's influence on cosmetics regulation, in Chapter 5. Thus, this composition builds two contrapuntal themes within one arrangement – as regulatory processes enact potent substances, and as potent substances catalyze legal change.

The concept of toxic enactment captures these two intertwined dynamics, approaching toxicity and law as enmeshed through practices. Toxic enactment rejects ontological understandings of substances – whether drugs, cosmetics, or other industrial chemicals – as fixed entities with inherent properties, varying only in how they might react within individual human bodies.[202] Instead, toxic enactment conceives of substances, and their potencies and effects, as performed in relation to regulatory actors, practices, and processes. This chapter has sought to further denaturalize the notion that estrogen existed in stable form outside of its socio-material relations with other substances, with lab instruments and animals in bioassays, with manufactured dosage forms, with advertising messages, and with human actors' attempts to define, enumerate, test, classify, and label estrogen as drugs – all of which were reflected in and produced by regulatory processes in the mid-1940s. Since then, estrogen has been thoroughly naturalized as a drug, indeed as one of the most prescribed drugs in the history of medicine. Yet this chapter has shown that estrogen is not an ahistorical or static substance, but a thing in the making, an object in the doing. Relatedly, it has challenged the conventional view that regulation reacts to innovation, responding to technological artefacts or to pre-existing material realities. That view often fosters critiques that law has failed to reflect established or emerging science, but without recognizing thicker entanglements of regulation and materiality. Just as laws can respond to techno-material realities, so can regulatory practices enact matter. Taking relational materialism seriously, law *substantiates* toxicity, in the epistemic sense of

[200] For a summary of Mol's empirical approach to theorizing ontology, see Chapter 1, section 2.i.

[201] For research done in what Jasanoff calls a co-production idiom, see Chapter 1, section 2.iii and Introduction at note 51.

[202] Beyond sex hormones, for work in ANT or material-semiotics on substances, drugs, or chemical exposures, see Chapter 1, section 2.i, particularly that content at notes 131-142 (Murphy 2006, Shapiro 2015), and 149-153 (Barry 2005); and Chapter 1, section 2.iii, particularly that content at notes 211-215 (Lezaun 2012) and 220-223 (Cloatre 2013).

providing a means by which toxicity is represented and proven in various regulatory fora and, concurrently, in the ontological sense of making toxicity real.

In the specific context of historically contingent enactments of estrogen, historians of sex hormones have persuasively described how measurement practices, in university laboratories and pharmaceutical firms, were central to calling estrogen into being.[203] More generally, STS scholars have long shown how, as a technique of definition, measurement makes matter and meaning.[204] This chapter builds upon this scholarship by uncovering the role of regulators and their enactments in materializing estrogen and its potency. The physicians and pharmacists on the Committee themselves apprehended that, in standardizing estrogenic drugs, "everything seemed to centre" on bioassays. However, reflecting and producing these professionals' declining influence on drug standards in mid-century Canada, the multiple regulations ultimately enacted in 1944 effectively endorsed diverse standardization, allowing industry to submit its own reference standards and to select its own test methods. These regulations effectively split bioassay methods into two types – those used by firms when manufacturing drugs, and those adopted in the Laboratory of Hygiene to control those products. If the purpose of standards was to ensure estrogenic substances in industry and government labs met a quality threshold and were the "same things", then by this measure, the regulations made in 1944 were a total failure. Instead, this chapter shows that, with the suite of regulations in 1944, estrogen was becoming multiple. Taken together, the Canadian Supplement and the Sex Hormone Regulations simultaneously performed estrogen as ready-made preparations and as pure substances, as biological and chemical substances, as synthetic and natural, and as drug substances that could be measured and materialized in different potencies, forms, and doses, without licensing oversight. These regulations also left open what estrogen did, and thus what it was, by refusing to define "purported" properties of estrogenic products or identify diseases for which they were indicated, creating space for industry, physicians, and women to experiment with its effects.

By another measure, however, the Sex Hormone Regulations succeeded in "standardizing" estrogen.[205] In the first of many moves to supplant traditional standards with labelling, these regulations devised proper names for various estrogenic drugs and required these names to be stated on product labels. In effect, this rule enacted distinctive classes of estrogen. Unwilling or unable to prescribe potency measurements or units, properties, sources, or diseases as their techniques for defining estrogen, regulators instead sought to define estrogen, and to make it

[203] For historical work on sex hormones by Oudshoorn and Gaudillière, and others, see Chapter 1, sections 1.i. and section 1.ii.

[204] For just one influential account, see Barad 2003.

[205] For Busch's relevant taxonomies of standards, see Chapter 1, section 2.ii.

standard, through naming. As Fausto-Stirling and others have shown, the naming of various sex hormones was hotly debated by scientists in the 1930s, and was a powerful technique for defining steroid hormones as sexed substances with particular functions. As suggested by Ayerst's advocacy for naming "conjugated substances" under this rule, naming was also a precondition for effective marketing and prescribing practices.[206] Conjugated substances thus became standard, even when the recalcitrant mix of estrogens comprising Premarin were strongly resistant to biological standardization. Using Busch's typologies, requiring estrogenic products to be labeled with distinctive names created the divisions that are commonly enacted in merchant standards, which aim at enhanced market access. Listing "different kinds" of estrogen aligned strongly with pharmaceutical firms' emerging marketing and advertising strategies, helping these drugs to circulate.

How had labels in lieu of standards been achieved? What tacit practices, tactics, and techniques had materialized estrogenic drugs to be potent and variable? One common practice was stalling.[207] Ayerst's scientist on the Committee repeatedly delayed efforts to standardize bioassay methods in the Sex Hormone Regulations and the Canadian Supplement, and the Department's Laboratory of Hygiene likewise dragged its feet, failing to release its own internal test methods for estrogen among other drugs. Other delay practices included National Health officials engaging legal counsel on proposed regulations at a late stage, after regulatory options had been developed, discussed in the Committee, sent out to industry, and drafted.[208] While stalling contributed to the enactment of regulations that left standards open, the more systemic and significant regulatory habit was a deepening culture of delegation within National Health. The multiplicity enacted in 1944 flowed from the Department distributing and diffusing its regulatory powers. For those tasks that National Health was unable or unwilling to perform itself, it effectively delegated to industry or consumers. For tasks that National Health officials wished to perform themselves (such as determine bioassay methods), while retaining the flexibility to change their minds or avoid publicity, they subdelegated responsibility down into the bureaucratic depths and kept commitments out of regulations.

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[206] See Fausto-Stirling 2000 at 187-193; see also Chapter 1, section 1.i, particularly the content associated with notes 20-22; and Introduction at note 43.

[207] For industry delay tactics in toxics regulation, see Jody A Roberts, "Unruly Technologies and Fractured Oversight: Toward a Model for Chemical Control for the Twenty-First Century", in Soraya Boudia & Nathalie Jas, eds *Powerless Science? Science and Politics in a Toxic World* (New York: Berghahn, 2014) at 288-296. Roberts argues that, in the history of industrial involvement in chemical regulation, industry tries to "stall attempts at the construction of new regulations for as long as possible", either by pushing for voluntary regulations or stressing the need for additional science. Here, CPMA members supported the Sex Hormone Regulations, but pushed for voluntary *test methods* and sought to delay finalization of methods within government.

[208] This practice would soon change. In 1946, DOJ established a Legislative Section, headed by Driedger. Driedger was soon emphasizing publicly that departmental and legislative counsel were typically involved early in the process; see Driedger 1953.

As the regulatory assemblage expanded to encompass government lawyers, so did the legal techniques evolve. Thinking with Shapiro,[209] this chapter has drawn out certain legal techniques that actively operated to install a potent and multiple estrogen into Canadian laws and bodies. In reviewing and revising the Department's draft regulations for form and validity, DOJ counsel routinely rendered these regulations as *intra vires* through what I have called techniques of validating. As also described in Chapter 3, one such technique used to work around concerns that enactments lacked validity was to "silence the recitals". Where it was doubtful that lawful authority existed to make an order in council, as with adding Part V to Schedule B and approving the Canadian Supplement where it primarily relied on chemical test methods, DOJ simply removed mention of any statutory provisions thought to (not) authorize the enactments. Originally a technique used where validity was uncertain, soon National Health and DOJ were stripping out or making vague any reference to authorizing provisions in regulations.

The Sex Hormone Regulations could not benefit from this technique. As a result of a legal opinion that only Cabinet had the jurisdiction to set standards for testing and expressing potency of sex hormones, National Health was uncharacteristically constrained in trying to enact an *ultra vires* regulation. In this case, the Department had to improvise. It did so by amending the Sex Hormone Regulations, before they were made, to require manufacturers to supply information on their potency test methods through labels. In its unpredicted potencies and unfixed doses, materialized as simultaneously safe and potent, estrogen would continue to provoke an evolving strategy of regulating drugs through labels. It spurred the Department to devise a novel "caution label" for estrogenic drugs, warning consumers who had bought these products not to use them except on a physician's advice. Rather than confine estrogen to sale on prescription, or set dose limits, National Health assigned responsibility for ensuring safety to women consumers.

As current day scientists know, whether "natural" or "synthetic", estrogens regularly resist the dose-response logics embraced by conventional pharmacology.[210] They know that effects can be as much a function of timing as dose, and that low doses may be more toxic than high doses. They know there is no safe threshold – no safe dose – for many estrogenic substances. However, in the 1940s, a simpler dose-response paradigm was almost universally accepted, including by the scientists appointed to the Committee or working at National Health. Viewing toxicity through monotonic dose-response curves, faced with potent substances that had been associated with cancer and reproductive problems in laboratory studies, these actors

[209] See Chapter 1, section 2.ii, particularly the content associated with notes 139-142.

[210] See Introduction particularly that content associated with notes 9-19.

nonetheless decided to allow the pharmaceutical industry to decide in what potencies and doses estrogen should be made and sold. In so doing, conventional dose-response logics were *written out* of estrogen regulation under the *Food and Drugs Act.* Potency was obscured through proliferating reference standards and test methods, and dose was erased entirely. As will be seen in Chapter 5, by rendering safe doses of estrogen largely imperceptible, the regulations would make it difficult to apprehend estrogen in cosmetics. Shortly after National Health evaded dose-response considerations for estrogenic drugs, it would re-introduce such considerations back into the regulation of “safe doses” of estrogenic cosmetics, once again by turning to labels.

Chapter Five

"An administrative ruling has been made on an upper limit of potency for one month's supply": regulating estrogen with labels, 1945-1953

> Estrogens will produce such changes in tissues and, in susceptible experimental animals at least, large doses of estrogens have increased the incidence of cancer. To quote one authority on this subject, Novak (1944) said, "it is the consensus that the clinical employment of estrogens in the customary therapeutic dosage presents no hazard, but prolonged used of these substances is contraindicated in persons suffering from cancer, or who have a familiar history of cancer. This is one potent argument against the use of proprietary cosmetics containing estrogenic substances." – EL Devlin, 1952.[1]

> …while the ordinary housewife is well able to determine when her food is grossly adulterated, subtleties and the refinements in sophistication in this modern world are likely to pass unobserved under her scrutinizing gaze and, therefore, an organization such as the Food and Drug Directorate is necessary to protect her and her loved ones from fraud, sickness and possible death. – A. Linton Davidson (1949a).

> Notwithstanding the opinion of a great constitutional lawyer of long ago that "Parliament can do anything except change a man into a woman or a woman into a man," it would have been preferable if cosmetics and devices were treated as individual subjects in the legislation, rather than to distort the ordinary meaning of a drug by including in it things which common sense rejects from it. – Robert Curran (1949)

In the previous chapter, the Canadian Committee on Pharmacopoeial Standards, National Health, and Department of Justice performed estrogen multiply. They did so through a series of enactments, themselves dependent upon techniques of validating, that declined to stabilize estrogen's potencies, doses, reference materials, forms, modes, or properties. Enacted as potent and multiple and unleashed into markets and bodies, by the end of the 1940s, estrogen was exerting its own influence on regulations under the *Food and Drugs Act*.

A new generation of National Health officials would seek to rein in estrogen. Unlike their predecessors, they were motivated less by securing independent Canadian pharmacopoeial standards, and more by avoiding irksome regulatory differences that interfered with trade with the US. In section 1, this chapter describes National Health's efforts to consolidate estrogen and its enactments. In 1949, the four estrogens were dropped from the Canadian Supplement, and the Sex Hormone Regulations were adjusted to subdelegate bioassay tests to the Laboratory of Hygiene, consistent with National Health's approach to many other biological drugs.

Estrogen continued to shapeshift, however, provoking new regulatory techniques in Canada. In 1949, the government finally brought into force those statutory amendments, passed in 1939,

[1] March 21, 1952 letter from Devlin to Venus Products Ltd., in Food and Drug Newspaper Clippings, 1949-1953.

allowing for cosmetics to be regulated as a sub-category of drugs. And it enacted the first cosmetics regulation in Canadian history – a regulation specifically governing cosmetics containing sex hormones. In another turn towards using consumer labels as a regulatory device, and in an early example of risk regulation in Canada, the Department directed women buying estrogenic cosmetics to ensure that they used these potent products "with care".

Soon, however, the Department concluded that being careful was not enough. Fearing that estrogenic skin creams could have hazardous or systemic effects, especially at high doses, National Health officials nonetheless had little means to prevent women from "overdosing" on these cosmetics. Indeed, as potency standards and dose ranges had been erased from estrogen regulations in 1943, the relationship between estrogenic dose and estrogenic effect had been rendered imperceptible. Section 2 describes how, in further amendments to the Sex Hormone Regulations in 1950, National Health required a new label unique to estrogenic skin creams. This time, women would be directed by a product label to "use only as directed", and the product package would be required to provide directions for use. Many of these products were high-end cosmetics imported from the US, arriving in Canada in jars containing a "30-day supply". For those products immune to the US FDA's regulatory supervision, however, National Health inspectors sought to negotiate the content of these "directions for use", by persuading manufacturers to direct women to use a certain amount of a certain potency of estrogenic skin cream every 30 days. Adopting a form of governance that they called "administrative ruling", their powers to standardize dose and potency delegated not by law but by labels, National Health officials quietly reintroduced dose-response logics back into estrogen regulation.

Absorbed into cosmetic products and regulatory practices, estrogen thus spawned new techniques of governance. Labels delegated power to National Health officials to govern administratively, and delegated responsibility to women to use products safely. Mediated by labels, estrogen and administrative practices were co-produced. This entanglement of estrogen, cosmetics, and labels was highly gendered. Section 2 includes some of the advertisements published by manufacturers of estrogenic breast and face creams that were investigated by National Health inspectors under the revised Sex Hormone Regulations in the early 1950s.

It is easy to read the techniques devised for estrogenic cosmetics as a sexist substitution of labels for standards. Still, estrogen had its own part to play. Having been performed in diverse ways in factories, clinics, laboratories, boardrooms, and now at women's vanity tables, its effects rendered unknown at different doses, and in myriad molecular and manufactured forms, estrogen was not a stable object with which regulators could smoothly interact. If not by Nature's design or regulators' intent, estrogen was prepared to act up.

1. Estrogenic consolidation and cosmetic innovation: 1945-1949

After decades of advocating for greater Canadian control over drug standards and for diminished British influence, in 1945, Harry Lancaster and Velyien Henderson exited the scene. Henderson died, and after years of poor health, Lancaster took early retirement. A new generation of scientists was responsible for food and drugs at National Health. Born and trained in the US, Dr. Clare Morrell was elevated after Lancaster's retirement to the position of Assistant Chief Dominion Analyst. When Aime Valin retired in 1946, Morrell became the Chief.[2]

Part and parcel of the explosion in regulated drug standards, the Department's bureaucratic machinery and infrastructure also expanded considerably in the second half of the 1940s.[3] In the fall of 1944, the government hived off pensions from the Department, creating a new Department of National Health and Welfare.[4] Shortly thereafter, the food and drug divisions went through a major reorganization and expansion. In 1946, National Health created a Food and Drug Directorate (often still referred to, in this period, as the Food and Drug Divisions), comprised of three divisions and five regional offices. Morrell was appointed Director of the entire directorate. He also headed the Food and Drugs Division, which was primarily responsible for administering the *Food and Drugs Act*. The remaining two divisions were the Proprietary or Patent Medicine Division and the Advertising and Labels Division. R.D. Whitmore was Chief of the latter, which assumed responsibilities for compliance and inspections; in 1947, this Advertising and Labels Division was rechristened Inspection Services.[5]

Morrell believed that, as in the US, Canada should regulate cosmetics that had the potential to be injurious to health. In the fall of 1945, he advocated for the creation of an advisory subcommittee on cosmetics, which would include dermatologists, to advise the Department on emerging cosmetics challenges. The Deputy Minister, Dr. Brock Chisholm, was unsupportive and the cosmetic subcommittee was never established.[6] Unfazed, National Health officials

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[2] Davidson 1949a at 93; Cameron 1959 at 323; Herder 2014 at S104; Henderson Obituary 1945; and "Retirement, J.G.A. Valin" (June 1946) 10:6 *Can J Comp Med* 180.

[3] Timmermans & Epstein 2010 reviews scholarship showing how standards have "proven enormously effective as dimensions of statebuilding", extending the regulatory state's administrative capacities and "consolidating bureaucratic rule"; at 82-83.

[4] *An Act to establish a Department of National Health and Welfare*, SC 1944-1945, c 22.; and *An Act to amend The Department of National Health and Welfare Act*, SC 1945, c 7. Pensions was now the responsibility of a new Department of Veterans Affairs.

[5] Davidson 1949a at 93; Davidson 1949b; Cameron 1959 at 323; About the Authors, 1954 at 500; and About the Authors, 1950 at 628. Whitmore joined the Department as a Dominion Analyst in 1920, analyzing drugs and reviewing claims by advertisers; see "Colleagues Honor R.D. Whitmore On His Retirement", *The Ottawa Journal* (10 March 1951), p 7 (Newpapers.com).

[6] September 21, 1945 memorandum from Morrell to Valin, April 9, 1946 letter from Chisholm to Valin, August 1, 1946 and September 18, 1946 letters from Morrell to Cameron, in Library and Archives Canada, Department of Health fond, RG 29, "Advisory Committees", volume 613, file no. 339-5-6.

began preparing to request that the statutory amendments regarding cosmetics, passed in 1939, be proclaimed into force. Officials advised the cosmetics industry of the Department's plans for regulating cosmetics; in response, the Toilet Goods Manufacturers' Association provided the Department with a lawyer's opinion that the statutory licensing provision was unconstitutional.[7] The Department of Justice ("DOJ") quickly confirmed this view. In Elmer Driedger's opinion, the cosmetics licensing provision was "of doubtful validity". The crux of Driedger's advice was that the provision could not be supported as criminal legislation "because nothing is prohibited". In effect, National Health was precluded from licensing a substance under the criminal law power unless licensing was integrated with a criminal prohibition, and relatedly, National Health was therefore precluded from licensing anything but injurious substances.[8]

However, as the Food and Drugs Division remained committed to regulating cosmetics, Driedger devoted significant efforts working with its officials in the spring of 1946 to draft a new bill. The draft bill added a new Part to the *Food and Drugs Act,* with a central provision that would prohibit the sale of "injurious cosmetics", and that furthermore would empower regulations respecting registration, packaging, and labelling of cosmetics; restricting the use of ingredients; and prescribing standards and fixing limits of variability.[9] In May 1946, on its way to Parliament, the bill hit a snag. The Minister of National Health and Welfare, Brooke Claxton, decided at the last minute that registering cosmetics might prove contentious and decided to drop all cosmetics provisions from the bill,[10] which otherwise passed.[11] Minister Claxton's resistance to regulating cosmetics went beyond the registration measures in the new bill as, on July 1, 1946, the definition of "drug" in the 1939 amendments was proclaimed into force "except the portion of it which applies to cosmetics".[12]

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[7] January 22, 1946 letter from Chisholm to Varcoe, in EA Driedger's Cosmetics Regulation File, 1946-1947.

[8] January 25, 1946 legal memorandum from Driedger to Varcoe, January 29, 1946 draft letter by Driedger, and February 1, 1946 final letter from Varcoe to Chisholm, all in EA Driedger's Cosmetics Regulation File, 1946-1947.

[9] January 25, 1946 legal memorandum from Driedger to Varcoe, and March 19, 1946 legal memorandum from Driedger to Varcoe, in EA Driedger's Cosmetics Regulation File, 1946-1947.

[10] May 27, 1946 letter from Curran to Varcoe, in EA Driedger's Cosmetics Regulation File, 1946-1947.

[11] The *Act* was amended in July 1946, but, as in 1939, without its intended cosmetics provisions. As in 1939, the central focus was on authorizing more expansive regulatory powers to control the sale of drugs by prescriptions, specifically for antibiotics like penicillin which were not "ordinarily injurious to health but if too frequently administered might lose their full effects". See Davidson 1949a at 92; and *An Act to Amend the Food and Drugs Act,* SC 1946, c 23.

[12] Proclamation, 1 July 1946, bringing into force part of section one of "An Act to amend the Food and Drugs Act", in *Canada Gazette*, Vol LXXX, No 29 at p 4837 (July 20, 1946).

At the end of 1946, Minister Claxton moved to National Defence.[13] With Claxton's departure came the possibility of renewed political priority for cosmetics. The new Minister, Paul Martin, would also have a new Deputy Minister. Having served as the Chief of the Laboratory of Hygiene since 1939, Dr. G. Donald W. Cameron was characterized as a "particularly happy appointment" as Deputy Minister of Health due to his familiarity with the Department and its priorities.[14] By 1947, the Food and Drugs Division was expanding its capacity to research and control cosmetics, having creating a Cosmetics Section within Laboratory Services and appointing an analyst as its cosmetics specialist.[15] Moreover, with Robert Curran, the new legal counsel to National Health, Driedger revised and polished the Department's draft cosmetics regulations in 1947, preparing for a time when the *Food and Drugs Act* would empower them.[16]

Cosmetics regulation was just one piece of a massive expansion of the Department's bureaucratic machinery and capacities. From WWII onwards, there had been an explosion of orders in council and regulations "which, through a mass of amendments, were fast becoming a labyrinth out of which even the administrative officials sometimes found it difficult to extricate themselves."[17] Beginning in 1947, the Food and Drug Divisions began the task of consolidating the Food and Drug Regulations, primarily aimed at streamlining but also introducing some substantive revisions.[18] The Food and Drug Regulations were repealed and replaced, in their entirety, on April 5, 1949.[19]

In revising the regulations, National Health officials endeavoured mightily to constrain and consolidate estrogen. Recognizing and troubled by the multiple drug standards wrought in 1944, they sought greater uniformity through amendments to three estrogenic enactments: the

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[13] Paul Martin Sr. was appointed as the new Minister of National Health and Welfare in 1946, serving in that portfolio for over ten years. At the same time, Dr. Brock Chisholm resigned as Deputy Minister of Health when he was appointed Secretary of the interim committee of the World Health Organization. See Davidson 1949a at 92; and Cameron 1959 at 323.

[14] Davidson 1949a at 92; and Cameron 1959 at 322-323. Cameron would serve as Deputy Minister of Health for two decades; see Canadian Museum of History, "Dr. G. Donald W. Cameron", online exhibition, "Making Medicare: The History of Health Care in Canada, 1914-2007", online: <https://www.historymuseum.ca/cmc/exhibitions/hist/medicare/medic-3k02e.shtml>.

[15] Davidson 1949a at 9; and March 1, 1946 letter from Curran to Driedger, in EA Driedger's Cosmetics Regulation File, 1946-1947.

[16] EA Driedger's Cosmetics Regulation File, 1946-1947.

[17] Curran 1949 at 391. Davidson 1949a at 105-106. Davidson's research showed that, from 1940-1945, there were 42 enactments, "many covering vast numbers of drugs" such the vitamin regulations and the Canadian Supplement. Among these regulations were many creating food standards, including for flour and bread, sausage, ice cream, grain and grain products.

[18] Davidson 1949a at 95; Curran 1949 at 391, 397 and 403-404; and December 11, 1948 letter from Davidson to Woods, in Unknown Committee Member's File, 1948-1949. The Food and Drug Regulations were consolidated in a new form and format. They were published in loose-leaf, to make amendments easier and cheaper. The format saw them divided into four parts: general administrative and interpretive provisions, foods, drugs, and vitamins. Appendix II listed certain drugs with dosage limits; Appendix III prescribed proper names for certain drugs; and Appendix IV listed certain drugs as prescription drugs.

[19] PC 1949-1536, SOR/49-145 (5 April 1949), *Canada Gazette,* Vol LXXXIII, No 10, at p 882 (May 25, 1949).

Canadian Supplement, Sex Hormone Regulations, and Schedule B to the *Food and Drugs Act.* The Department's primary strategy for bringing uniformity to the estrogens was to remove them from the Canadian Supplement.[20] Oestrone, oestradioal benzoate, stilboestrol, and stilboestrol dipropionate were all deleted from Part V of Schedule B,[21] and their monographs were removed from the 1949 Food and Drug Regulations. The old guard like Davidson clung to the idea that the Supplement had value, but other officials were coming to view the Supplement as spent; having served its purpose during and after the war, it was now ready to be retired.[22] The Supplement's obsolescence was hastened with a revised British Pharmacopoeia in 1948, which remedied the decline in pharmacopoeial standards occasioned by the "wartime addenda" and included most of the prewar monographs that National Health had incorporated, in 1944, into the Supplement. Thus, only a small subset of the monographs, about 40, were retained in the regulations.[23] Beyond this pragmatic reason for dropping monographs, however, was National Health's continuing and widening shift away from professional ways of regulating drugs and towards administrative modes of regulation.[24] Even the new name of the Canadian Supplement reflected this, now styled within the regulations as "Drugs of Part V of Schedule B to the Act". As Director of the Food and Drug Divisions, Morrell continued to entertain superficially the notion of a Canadian Pharmacopoeia, and he generally accepted that sometimes "peculiarly Canadian (drug) standards will have to be maintained", [25] but in a sharp departure from the wartime nationalism, he was strongly inclined to follow the Americans' lead on drug standards, particularly to better facilitate importation of drugs from Canada's largest supplier:

> It is always a subject for debate as to what standard shall be written into the Canadian Regulations. Shall that of the United States Pharmacopoeia be adopted, or of the British Pharmacopoeia, or some other existing standard, or shall a special Canadian standard be devised? Unless there are important reasons for doing so, the latter course is to be avoided. There is no point in having differences just to be different. It would be an ideal course to choose the International Standard and nomenclature, provided it was also used by a substantial number of countries trading with Canada. Many of the irksome differences in standards, which have no real significance from the medical point of view, but which if they

[20] The Canadian Supplement was now found in Division 6 of Part C of the Food and Drug Regulations; *ibid* at 973.

[21] PC 1949-1537, SOR/49-144 (5 April 1949), *Canada Gazette*, Part II, Vol LXXXIII, No 10, at p 879 (May 25, 1949) ["Schedule B Amendment, April 5, 1949"].

[22] See e.g. Davidson 1949b; Davidson 1949a; Curran 1949; Morrell 1950; Allmark 1954; Pugsley 1967.

[23] Allmark 1954 at 253; this trend continued and, by 1954, most of the Canadian Supplement monographs were discarded.

[24] On "ways of regulating drugs", see Chapter 1, section 1.ii., particularly content associated with notes 105-116.

[25] Morrell 1950 at 659.

exist mutually exclude the products of different countries, would disappear and the labeling of imports would not cause the trouble it now does.[26]

As the Department phased out the Supplement,[27] it also phased out the Canadian Committee on Pharmacopoeial Standards. Despite the heated debates on estrogen among Committee members in 1943, in 1949, National Health did not bother to seek the Committee's approval to drop the four estrogens from the Supplement, returning unilaterally to its original plan to regulate estrogenic drugs solely through the Sex Hormone Regulations. The exact timing of the Committee's demise is unclear, as rather than formal disbandment, it fizzled out. Yet it was certainly on its deathbed by 1950, and gone by 1952.[28] There were other deaths not metaphorical. On March 1, 1950, while at home writing a sermon, Linton Davidson had a stroke and died. With his passing, so passed the practice of correspondence, figurative and literal, between Department and Committee members on old and new ways of regulating drugs.[29]

In addition to dropping the four estrogens from the dwindling list of drugs in Part V and the Supplement, National Health also had amendments made to the Sex Hormone Regulations.[30] These amendments tinkered with the provisions that set standards (or more accurately, with the provisions that delegated standard setting to National Health officials or to manufacturers). Under the vague provision enacted in 1944 for reference standards, many manufacturers had submitted reference materials for their products. With the proliferation of commercially available sex hormone products in the 1940s, this meant that the samples submitted also proliferated, becoming an unwieldy "multiplicity of standards" in the Laboratory.[31] In 1949, National Health ended manufacturers' duties to submit standards and instead delegated to the Food and Drug Laboratories the power to decide which materials it would keep as standards.[32] With respect to

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[26] *Ibid* at 660; see also 656-656.

[27] According to Professor Ferguson, the Committee member who replaced Henderson after his death, by 1951, the Canadian Supplement had been discontinued; see JKW Ferguson & GHW Lucas (revising authors), *Henderson's Materia Medica* (Toronto: University of Toronto Press, 1951), at the Preface. Pugsley later wrote that it was discontinued in 1949; Pugsley 1967.

[28] *Ibid.* Pugsley later wrote that the Committee was renamed the Canadian Drug Advisory Committee in 1953; Pugsley 1967.

[29] Davidson Obituary 1950. Davidson had been a lay member of the Anglican clergy, in charge of services at the parish of St. Peter's Carlington, and Assistant Lay Secretary of the Synod of the Diocese of Ottawa. A month before his death, his wife had died after a long ailment; see January 1950 correspondence, in Library and Archives Canada, Department of Health fonds, RG29, "Canadian Committee on Pharmaceutical (sic) Standards", 1949/09-1950/12, Volume 249, file no. 339-4-1, (Part 9) ["Unknown Committee Member's File, 1949-1950"].

[30] In this chapter, except when indicated otherwise, the "Sex Hormone Regulations" refer to Division 2 of Part C of the Food and Drug Regulations; PC 1949-1536, SOR/49-145 (5 April 1949), in *Canada Gazette,* Vol LXXXIII, No 10, at p 945 (May 25, 1949) ["Sex Hormone Regulations"].

[31] Pugsley 1951 at 534-535.

[32] Sex Hormone Regulations, ss C.02.003 and C.02.004. The Laboratory of Hygiene and Food and Drug Laboratories were different entities. The former continued after the 1947 re-organization, but some responsibilities for testing and controlling food and drugs, like sex hormones, were transferred to the Food and Drug Laboratories; see Cameron 1959 at 320-324.

potency, there were minor revisions that, contrary to Driedger's legal opinion in 1944, expressly subdelegated power to the Food and Drug Laboratories to set test methods for measuring the potency of any products expressed in terms of the International Standard or the Canadian Reference Standard. The potency labels remained, though, with tweaks to the rule for clarity.[33]

The most substantive amendment to the Sex Hormone Regulations was the addition of cosmetics. On May 1, 1949, Canada finally brought into force the 1939 amendments to the *Act,* making the legislative decision to define cosmetic and to make "any cosmetic" a subcategory of drug (the unconstitutional licensing provision was never brought into force).[34] As a result, in 1949, cosmetics became subject to the general provisions of the Food and Drug Regulations related to drugs. Further, cosmetics could now be specifically regulated. The first – and the only – cosmetics that Canada regulated, in 1949, were cosmetics containing sex hormones.[35]

By 1949, estrogen had been infused into skin creams for a decade. Consistent with the fact that it was primarily white middle and upper-class women who sought out hormone replacement therapy,[36] estrogenic cosmetics were similarly classed. By 1939, they had arrived for sale in Eaton's and other Canadian department stores as luxury skin creams,[37] though breast enlargement creams also arrived by the slightly seedier route of mail order.[38] With estrogenic activity conjured from oestrone, oestradiol, oestriol, equilin, equilenin, and even from DES, these products contained hormones whipped into emulsion creams or mixed into oils.[39] Imported from the US, where, unlike drugs, cosmetics did not require pre-market approval under the US FDCA, they were not supported by scientific studies showing their safety.

There was, in particular, a paucity of physiological evidence of whether, and to what extent, estrogens in skin creams were absorbed into the blood stream and into bodies, although some

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[33] *Ibid,* s C.02.005. One small difference between s C.02.005 and section 3 of the 1944 Sex Hormone Regulations is that, rather than give potency information on a label, it was now to be given "with every package". Scholars have explored how packaging practices and materials enact different drugs, including for estrogen (see e.g. Cloatre 2013; and Sanabria 2016). I have no physical product packages from that time, nor images thereof, and examining packaging is beyond the scope of my thesis.

[34] *An Act to Amend the Food and Drugs Act,* SC 1939, c 9 (most cosmetic provisions), proclaimed into force 5 April 1949, SOR/49-143, *Canada Gazette,* Part II, Vol LXXXIII, No 10, at p 878 (May 25, 1949).

[35] Sex Hormone Regulations, s C.02.000; and Curran 1949 at 411.

[36] Watkins 2007 at 8, adding that "as more women obtained health insurance, either privately or through government-funded programs in the 1960s and 1970s, and as HRT became more popular in the 1980s and 1990s, more women of lower socioeconomic status joined the ranks of hormone users", and "[w]omen of color took HRT in much lower proportions".

[37] See Chapter 3, section 1, at note 103. In the US, hormonal cosmetic products became available for sale at roughly the same time in the late 1930s; see Hugo Mock, "Legal Limits of Cosmetic Labeling and Advertising" (1951) 6 *Food Drug Cosm LJ* 865 ["Mock 1951"] at 870-871; and James Bennett, Cosmetics and Skin: Hormone Creams, Oils and Serums" (2018), online: http://www.cosmeticsandskin.com/bcb/hormone-creams.php ["Bennett 2018"]. However, it was not until the early 1940s that these hormonal cosmetics were identified as containing estrogen or estrogenic substances *per se*.

[38] See e.g. Figure 2.

[39] Bennett 2018; and Watkins 2007 at 85-86.

researchers had tested the systemic effects of such creams. For example, in a 1938 study, researchers examined creams that contained either androgens or estrogens.[40] Using what was characterized as a low dose, they established that sex hormones were easily absorbed through the skin of various animals, and that face cream "sold commercially and recommended for the removal of wrinkles from normal women has decided internal effects when applied daily on the skin of experimental animals".[41] They concluded that the ready absorption of topical estrogen, and the demonstrable effects on lab animals, presented a possible hazard to female reproductive functions and urged more study.[42] However, over the next decade, the studies were sparse, and the cosmetic industry's newfound enthusiasm for estrogen was abundant. As Elizabeth Watkins shows, in assembling advertisements from the 1930s and 40s, the industry promoted the message that youth and beauty were synonymous, and its "ads imparted a clear message: use of estrogen-containing creams would make a woman's skin look younger".[43]

Neither the FDA nor the American Medical Association ("AMA") harboured any positive feelings towards estrogenic skin creams. To the contrary, from the late 1930s to the early 1950s, there was "a strong bias by the US medical profession against the over-counter sales" of estrogenic cosmetics.[44] Concerned about their carcinogenic potential, the AMA had initially campaigned against these creams. After the AMA published a 1939 editorial that was highly critical of Estrocreme, a product represented for use in breast enhancement,[45] its manufacturer, Hirestra, sued the AMA in defamation. Supportive of the AMA's position, the FDA supplied expert evidence. However, in its decision, the Federal Court rejected this evidence, holding that the animal studies relied upon by the FDA to claim that estrogens were carcinogenic were insufficient to prove a likelihood of cancer in women. Langston finds that, as a result of the court decision, the FDA backed down from efforts to regulate estrogenic breast creams, its resolve deflated.[46] Taking a longer view, however, the FDA regained its enthusiasm by the late 1940s, when it began targeting all sorts of estrogenic creams with prosecutions for misbranding.[47]

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[40] Carl R Moore, Jule K Lamar & Naomi Beck, "Cutaneous Absorption of Sex Hormones", (1938) 111:1 *JAMA* 11.

[41] The researchers used one-fifth of the recommended "daily dose" for women; *ibid* at 13. These effects included stimulating mammary growth in normal male guinea pigs, inducing vaginal cornification in spayed female rats, maintaining or increasing growth of the uterus in spayed rats, and reducing the weight of testes (by 80 percent) and the weight of seminal vesciles (by 90 percent) in young male rats; *ibid* at 12-14.

[42] *Ibid* at 14.

[43] Watkins 2007 at 84-85; see also Rothman & Rothman at 95-97.

[44] Mock 1951 at 870.

[45] "Endocreme: A Cosmetic with a Menace", Editorial, (April 9, 1938) 110:15 *JAMA* 1194.

[46] Langston at 47. I have not been able locate any reported copy of the court's decision in *Hirestra* in electronic databases.

[47] Bennett 2018.

Though it is not apparent whether Elmer Driedger knew of estrogenic creams, he had no difficulty, conceptually or legally, with apprehending cosmetics as a subcategory of drugs. Robert Curran, in contrast, often overtly disparaged this legislative decision. Curran was National Health's chief legal advisor, having joined the Department at the end of the war, and so his public disdain for Canada's legislative approach can be jarring. Right after the statutory amendments were brought into effect in 1949, he wrote a journal article for a mainly American audience, mocking the Canadian legislation in sexist terms (as set out in the quote at start of this chapter),[48] advancing in less than subtle rhetoric a gendered distinction between drugs and cosmetics. Acknowledging that medicinal ingredients were found in cosmetics, he nevertheless opined that cosmetics were "not expected to contain a high degree or medication nor are extensive therapeutic claims likely to be made for them". For Curran, the boundary was clear: "[t]he borderline between cosmetics and drugs, of course, rests upon the claims which are made".[49] Moreover, he felt that cosmetic companies' claims must be given broad latitude, and puffery should not be discouraged.[50] After all, the public was not deceived by exaggerated or false claims, as nobody really thought that cosmetics would do "what Nature has failed to do".[51]

No substance challenged such rigid distinctions more strongly than estrogen.[52] As will be seen, some estrogenic "cosmetics" were more potent than "drugs", and manufacturers often implied therapeutic values for their estrogenic cosmetics. In the late 1940s and early 1950s, advertisements for Premarin, a "drug", and Helena Rubinstein's hormone cream, a "cosmetic", made many of the same claims: youthful beauty, reproductive femininity, natural vitality, and happier husbands. Yet Curran never mentioned estrogen, or the new regulation governing estrogenic cosmetics, in his criticisms of the cosmetics scheme under the *Food and Drugs Act.*

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[48] *Ibid;* see also Robert E. Curran, "Revision of Canadian Food and Drugs Act", (1952) 7 *Food Drug Cosm LJ* 711 ["Curran 1952"] at 715.

[49] Curran 1952 at 718. In this paper, originally delivered at a September 1952 meeting of the American Bar Association's Division of Food, Drug and Cosmetic Law, Curran explained that the upcoming revised *Food and Drugs Act* would no longer include a misbranding offence for cosmetics, for the reason that puffery was to be expected for cosmetics.

[50] Curran 1946 at 503; see also Curran 1952. The AMA published a study, in 1954, concluding otherwise: "it is recognized and accepted that a certain amount of puffery is necessary in the field of promotional cosmetic advertising. However, some manufacturers of creams containing estrogens have made claims, either directly or by innuendo, that overstep these limits"; see Howard T Behrman, "Hormone Creams and the Facial Skin" (May 8, 1954) 155:2 *JAMA* 119 ["Behrman 1954"] at 122.

[51] Curran 1952 at 718.

[52] In contrast, Hugo Mock, counsel to the Toilet Goods Association, accepted the overlap between cosmetics and drugs, with estrogen a frequent example. In a 1951 article, he wrote of estrogen as a "physiological cosmetic"; Mock 1951 at 870-871. In a 1946 article, he wrote: "I submit that the definition of cosmetics and drugs in both these Acts is purely one of convenience rather than one of scientific terminology and that the distinction between drugs and cosmetics is largely an artificial one which will tend more and more to be broken down. … Necessarily, hormone preparations sold at cosmetic counters are both drugs and cosmetics." See Hugo Mock, "Cosmetic Law … History and Observation" (1946) 1 *Food Drug Cosm LQ* 61 at 63.

Perhaps his silence on estrogen was because it challenged his insistence on "common sense" distinctions between drugs and cosmetics. The evolving scheme on sex hormones also appeared, at least superficially, to challenge this distinction. Beyond recognizing that cosmetics could be just as potent as drugs, in 1949, the term "sex hormones" disappeared from the *Act.* Concurrent with the regulatory amendments and the cosmetics proclamation, Schedule B was amended, with the term "sex hormones" deleted from Part II of the schedule, and the phrase "hormones, and preparations of hormones" added to Part I.[53] Were hormones being de-sexed? The change was part of an intentional, broader policy decision that the only hormonal drugs still requiring licensing were insulin and liver extract.[54] Yet these sexless hormones did not last. Whomever had held the pen, in redrafting Schedule B, had forgotten its integration with the standards in the Sex Hormone Regulations. As of April 5, 1949, those regulations provided that "[t]he drugs referred to in this Division are included in the term sex hormone as mentioned or described in Part I of Schedule B to the Act".[55] Without the term sex hormone, this cross-reference was meaningless. Soon realizing its error, National Health returned the term to Schedule B three months later.[56] Momentarily gender-neutral, estrogen was rapidly re-sexed.

Tempting to shrug off as a drafting error, triggered by a well-intended but legally mistaken effort to remove the "sex" from sex hormones, in fact this incident was less benign. Recall that, under the scheme for biologics, drugs on Part 1 could be standardized but not controlled through licensing. Why did National Health officials feel it necessary, in the first place, to move (sex) hormones from Part II to Part I? Why did they wish to make (sex) hormones not just unlicensed, as they had already been for two decades, but also "un-licensable"? One reason is that, in 1947, the US formally excluded all hormones from licensing through regulatory amendments, codifying a longstanding informal policy of the Public Health Service.[57] National Health's decision to shift all "hormones" from Part II to Part I of Schedule B reflects how the Food and Drug Divisions were increasingly inclined, by the late 1940s, to shadow US developments. Although this is a convincing explanation on the face of the Schedule B, Canada

[53] Schedule B Amendment, April 5, 1949.

[54] Pugsley 1951 at 536-539. That insulin and liver extract were licensed was confusing (and arguably unlawful), considering that the April 1949 amendments to Schedule B relocated all hormone products to Part I rather than Part II. In his article, Pugsley takes obvious pains to justify this, claiming that, regardless of the plain language of Parts I and II, the reference to hormones in Part 1 really meant sex hormones (whether parenterally or orally administered), and Part II was really for parenteral drugs including non-sex hormones like liver-extract, insulin, and anterior pituitary preparations; see Pugsley 1951 at 532-533. Further, National Health also decided to treat drugs prepared from anterior pituitary hormones as if they were "parenteral" products on Part II and not "hormones" on Part I, to preserve the possibility of licensure; see Pugsley 1951 at 533 and 539-540.

[55] Sex Hormone Regulations, s C.02.001.

[56] PC 1949-3483, SOR/49-281 (13 July 1949), *Canada Gazette,* Part II, Vol LXXXIII, No 15, at p 1533 (August 10, 1949).

[57] Coleman 2016 at 578.

did not, in fact, fully emulate the US regulatory decision. In practice, National Health officials decided to keep a few hormonal drugs, like liver extract and insulin, under licensure, and to reserve the possibility of licensure for pituitary hormones. Put another way, and by Pugsley's own admission, the only hormones made un-licensable, in practice, were sex hormones.[58]

The second reason that estrogen was made un-licensable was driven by prevailing gender norms – which found expression in the journal articles by Curran discussed above – that viewed cosmetics as little more than natural products for deceptive women. On the same day that hormones were moved to Part 1, Canada obtained legislative authority to regulate cosmetics generally,[59] and amended the Sex Hormone Regulations to regulate estrogenic cosmetics specifically.[60] Cosmetics, however, were legally difficult to license. At least, that was the message that National Health officials had taken from Driedger's legal opinion in 1946, which had caused them concern that licensing rules in the Biologicals Regulation might also be invalid (though Driedger had brushed off that concern in his opinion). With sex hormones now legally recognized, as of April 1949, as superficial stuff of ladies' make-up, cosmetics dragged estrogen down into an "un-licensable" class. Far from being de-sexed, estrogen was being reproduced as ever more gendered, as natural feminine substances that did not require licensing.

That estrogen was provoking gendered distinctions within Canadian law is supported by the techniques through which the Sex Hormone Regulations newly regulated hormonal cosmetics, in the absence of either licensing or registration. While these regulations continued to prescribe (or rather to delegate the prescription of) unconventional "standards" for sex hormone products, beyond this, in its newly endorsed form of cosmetic products, estrogen would again be ruled through labelling. Once again, the label devised was novel to Canadian food and drugs law, and once again, these labelling innovations were only used for products sold to women. Section C.02.0009 now prohibited the sale of cosmetic products containing a sex hormone unless the label carried the statement: "This preparation contains a potent sex hormone. Use with care".[61]

No Canadian consumer had previously been directed by a label to use a product "with care".[62] In the 1940s, most food and drugs in Canada bore labels that served to state what the

[58] See *supra* note 54.

[59] See *supra* note 34.

[60] See *supra* note 35.

[61] Sex Hormone Regulations, s C.02.009(a)(v).

[62] The phrase "use with care" had its origins in a proposal by the Dominion Council of Health, a federal-provincial advisory body. In 1939, the *Act* was amended to empower Cabinet to define conditions of sale of drugs likely to be injurious to health. This was in response to the Council urging greater control of over-the-counter sales of potent drugs. However, a regulation imposing prescription controls was not immediately made. According to Davidson, the "first thought in dealing with this subject was to require a caution to appear on the label to the effect that the contents should be used with care". However, when National Health consulted the Canadian Pharmaceutical Manufacturers Association on this proposal, it had "approved the principle but

product was purported to be. These labels impliedly represented that the product met regulated standards of quality or identity, and exposed manufacturers to misbranding prosecutions if their products did not "measure up" to these regulated recipes, comparable to the US regulatory approach.[63] At this time, labels did not typically bear health information, including because regulators believed that "such information would 'confuse' the ordinary food consumer."[64]

Thus, as with estrogenic drugs five years earlier, in 1949, National Health performed a novel regulatory move, enlisting labels to direct women to attend carefully to their own safety when using estrogenic cosmetics. For these products, only used by women, the rules were suddenly different. Safety would no longer be ensured by a "recipe", built into the drug or food product by a standard found in a pharmacopoeia or a conventional regulatory standard. Women consumers would instead be made responsible for ensuring their own safety through careful product use.

It would be easy to conclude that this differential regulatory treatment, in which consumer warnings were substituted for safety standards, reflected gendered norms about cosmetics. Yet estrogen was now a wily substance, not readily amenable to regulatory controls. As materialized by physicians, manufacturers, and government regulators in 1944, and by ongoing inattention in National Health's laboratories in the intervening years to its physiological activity,[65] estrogen was both powerful and indeterminate. When National Health had avoided traditional standards for estrogenic drugs – such as those afforded by dose limits, prescription controls, or ingredient restrictions – it had scripted into estrogen an inherent unpredictability. Enacted as both potent and safe, estrogen naturally provoked the injunction to "use with care". Rules had engendered estrogenic crystals, and now estrogen was crystallizing gendered rules.

2. Resurrecting dose through "administrative ruling", 1950-1953

One year after introducing "use with care" labels to regulate estrogenic cosmetics, Canada again amended the revised Sex Hormone Regulations.[66] Repeating the pattern, the amendments adopted another new form of product label, which continued the trend of delegating responsibility for safety to women consumers. National Health's latest labelling innovation was specific to estrogenic cosmetics, provoked by the ambiguities that had been

asked for such modifications as might easily have nullified its effect"; Davidson 1949a at 84. In 1941, a different regulatory approach was taken. Nevertheless, Davidson and Morrell would have been aware of the earlier "use with care" proposal.

[63] Frolich 2017 at 147, 151-154.

[64] *Ibid* at 147; and Curran 1953 at 29.

[65] See *infra* note 72.

[66] PC 1950-2084, SOR/50-170 (25 April 1950), *Canada Gazette,* Part II, Vol LXXXIV, No 10, at p 626 (May 24, 1950). Section 15 of this amending regulation revised the existing s C.02.009 and added a new s C.02.010.

materialized in estrogenic drugs. Having erased dose and potencies from standards for sex hormones in 1944, by rejecting the notion that these qualities and capacities should be legally prescribed, departmental officials now subtly reintroduced dose-response considerations into the regulation of estrogen. They did so through a combination of imposing new labelling rules and by purporting to make "administrative rulings", an unorthodox mode of regulating food and drugs in Canada. In the process, estrogen and labels became ever more entangled.

The amendment split the existing cosmetic rule in two. A new provision now exclusively governed estrogenic cosmetics,[67] while the existing rule was limited to cosmetics "containing any sex hormone *other* than a sex hormone purporting to have oestrogenic properties".[68] Why National Health retained this latter provision is unclear, as at the time, there were no cosmetics being sold with purported androgenic, gonadotrophic, or progestational properties– no testosterone tonics, no gonadotrophic lip gloss.[69] Only estrogen, that spring of youthful and reproductive femininity, had infiltrated cosmetics. Nevertheless, should any other hormonal cosmetics ever materialize, their manufacturers would continue to be obliged to advise consumers to "use with care".[70]

The new provision, limited only to estrogenic products, prohibited sale of any "preparation manufactured for use as a cosmetic containing a sex hormone purporting to have oestrogenic properties unless demonstrated to be free from systemic effect from sex hormones", and unless new labelling requirements were satisfied.[71] In promoting this amendment, National Health officials were alive to physicians' continuing concerns about the carcinogenic hazards of estrogen in cosmetic products. As cosmetics were now a legal subcategory of drug, National Health could have limited these preparations to sale only under prescription, though physicians presumably would not have been receptive to being asked to prescribe creams intended to reduce wrinkles. Alternatively, National Health could have standardized cosmetics. For potency, in theory, Canada could have prohibited the sale of cosmetics containing estrogenic substances that exceeded a certain potency expressed in international units, using test methods determined by the Laboratory of Hygiene and measured against reference materials, as for drugs.

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[67] 1949 Sex Hormone Regulations, as amended in 1950, C.02.010 (emphasis added).

[68] *Ibid*, C.02.009.

[69] As James Bennett documents, some major cosmetics firms, including Helena Rubinstein and Revlon, added progesterone or pregnenolone (or esters thereof) to estrogenic face creams in the late 1950s; see Bennett 2018.

[70] 1949 Sex Hormone Regulations, as amended in 1950, C.02.009(a)(v). Estrogenic cosmetic labels would also need to include a statement of the sex hormone's potency in terms that met the revised approach of 1949 to defining potency; s C.02.009(a)(iv).

[71] These labelling requirements are discussed in detail below; see that content associated with *infra* notes 77-81.

Standardizing dose, however, was more elusive. Pharmacopoeial monographs could fix estrogen dose ranges to guide drug dispensers and prescribers, and regulated drug standards could dictate the dose of certain dosage forms, whether in ampoules, suppositories, tablets, or capsules. As seen in the previous chapter, though, in designing its Sex Hormone Regulations in the mid-1940s, National Health had written dose out of estrogen regulations. Eschewing such standards made it difficult to conceive of a "safe" or "hazardous" dose of estrogen. Instead, the regulatory regime left it to firms to standardize products' doses and to physicians to supervise dosage over time (assuming women who purchased estrogenic drugs over the counter in the 1940s asked for physicians' advice). Consequently, in the latter half of the decade, the Laboratory of Hygiene had little incentive to monitor pharmaceutical companies' evolving dose ranges, or to research their physiological impacts. Nor is there evidence that it did so.[72] What amount of estrogen in an oral, injectable, or topical preparation was safe? What dose made the poison? National Health did not know. Its scientists, and those on the Committee, had focused squarely on knowing potency through measuring, but had ignored the other half of Paracelsus' formulation. Imperceptible within regulatory control activities, dose was left to clinicians and their patients, delegated to the unpredictable relations between drugs, bodies, and time.

Once statutorily empowered to regulate skin cream, National Health had to face up to dose. Content to defer to the expertise of large pharmaceutical firms with in-house laboratories, alchemical experiments by cosmetics outfits elicited more skepticism. Steeped in a regulatory culture resistant to imposing limits on borderline products out of fear that this would amount to endorsement, National Health officials were in a bind. With dose erased from drug standards, how could they determine what dose – what *amount* – of a cosmetic was safe?

This question was complicated by the fact that skin cream, infused with hormones or not, rarely came packaged in daily "doses". Even had National Health scientists monitored the effects of estrogenic preparations, in cold laboratories with mass-produced rodents and in comfortable homes of middle-aged women, face cream and bodies met each other in ways less precise. In that creamy form, in registers both material and conceptual, estrogen was slippery.[73] Performed simultaneously as safe and potent in mass-produced pills and medically-supervised injections, in daily, mundane beauty regimens, estrogen was less knowable and more fluid.[74] How much cream a woman applied before going to bed in the evening, or when starting her day

[72] The Laboratory did do this research for agricultural uses of estrogen, however; see content associated with *infra* notes 75-76.

[73] For a post-ANT (material-semiotic, relational materialism) study that attends among other things to the "texture" of ordering practices, see John Law & Marianne Elisabeth Lien, "Slippery: Field notes in empirical ontology" (2012) 43:3 *Soc Stud Sci* 363.

[74] Marianne De Laet & Annemarie Mol, "The Zimbabwe bush pump: Mechanics of a fluid technology" (2000) 30:2 *Soc Stud Sci* 225. In the context of pharmaceuticals, see e.g. Cloatre 2013 and Sanabria 2016.

in the morning, was not determined quantitatively or mechanically, but through manual, sensory, affective practices. How much cream does it take to make your skin *feel* softer, smoother, firmer, less wrinkled? A dry winter's wind, a poor night's sleep, a husband's bad mood – one's relations with estrogen changed. When these practices changed, so did estrogen. In its cohabitation with wealthy women and their skin, estrogen enacted an ambiguous toxicity.

Dr. Leonard Pugsley was responsible for advising on this question. Like Morrell, Pugsley had also been promoted after the war. In the 1947 re-organization, he became the Chief of Laboratory Services, overseeing ten sections within the central laboratory in Ottawa and serving as the technical adviser to five regional laboratories by guiding research and testing for food, drugs, and cosmetics. He also continued to research and analyze hormonal products.[75] In this capacity, his research was quietly influential, leading National Health and eventually the US FDA to end the agricultural practice of using DES in chicken feed.[76] With cosmetics though, Pugsley would prove much more willing to take his cues from US companies and regulators.

In 1951, Pugsley wrote a journal article about the Canadian regulation of endocrine products, in which he simultaneously highlighted and obscured Canada's practices.[77] Aimed primarily at an audience of American regulators and industry, he sought to explain and defend the recent amendment for estrogenic cosmetics. He claimed that, while National Health had considered it advisable to "limit the amount" of estrogen in cosmetic products, it had nonetheless decided against setting any upper limit on potency in the regulations "because such would tend to indicate approval and freedom from any undesirable side effects" at lower potencies.[78] Instead of regulated limits, Canada had chosen to limit the amount of estrogen that women would use through a new labelling requirement added to the regulations. This double-barreled labelling rule, in section C.02.010, required estrogenic cosmetic labels to include the statement: "Use only as directed",[79] and then required manufacturers to indicate "directions for use".[80]

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[75] About the Authors, 1951 at 483-484; Davidson 1949a at 92-94; and SJ Cook, "Canadian Chemistry" (1947) 25:32 *Chem Eng News Archive* 2326. The sections of Laboratory Services were Food Chemistry, Pharmaceutical Chemistry, Cosmetic Chemistry, Biophysics, Pharmacology and Toxicology, Vitamins and Nutrition, Animal Pathology, Physiology and Hormones, Biometrics, and Organic Chemistry and Narcotics. The Ottawa laboratory was "devoted almost entirely to work of an investigational character, such as the development of improved methods of analysis and biological tests"; Davidson 1949b.

[76] Langston 2010 at 67-68 and 178 (notes 15 and 16).

[77] Pugsley 1951. Half of Pugsley's article addressed the regulation of sex hormones, in drugs and cosmetics, including "sex gland tissue". The other half addressed new regulations on liver extract injectable, insulin, and anterior pituitary preparations.

[78] *Ibid* at 536.

[79] 1949 Sex Hormone Regulations, as amended in 1950, s C.02.010(a)(v). This requirement applied to inner and outer labels.

[80] *Ibid,* s C.02.010(b)(ii). Additionally, unmentioned by Pugsley and seemingly innocuous, but necessary to the practices later adopted by National Health officials to put an upper limit on potency, the amended regulations also required a statement of the product's weight or "net contents"; *ibid,* s C.02.010(b)(iii).

Thus, as with the caution label for estrogenic drugs and the self-care label for cosmetics, again National Health expressly chose a label as an alternative to a safety standard. In 1949, women had been told to "use with care", but care of the self was no longer enough – women would now need to comply with explicit directions to keep themselves safe from cancer. Yet what exactly those directions should be was not articulated in the Sex Hormone Regulations, and, in his article, Pugsley maintains a strategic silence on how this new labelling rule would limit estrogenic exposures. Were directions being left to manufacturers, or were National Health officials "directing the directions"? Most glaringly, his article is silent on what amount had been identified by the Department as its "upper limit of potency.[81] Thus, the reintroduction of dose-response logics to estrogen regulation in Canada was left implicit and made discretionary.

Digging deeper, it seems that potency limits were set through two distinct practices: first, by a practice of US cosmetics firms under the influence of the US FDA (and by the FDA under the influence of Helena Rubinstein); and second, through administrative practices of National Health officials negotiating label directions with those firms that had not received the FDA's message.

Though the legal source of the FDA's authority to stipulate the potency of estrogenic skin creams is murky,[82] the material source of the "rule" is not. The rule was enmeshed in the products and marketing practices of Helena Rubinstein, the upscale cosmetics firm that led the industry in luxury hormonal products. In the 1940s, the company had packaged its "Estrogenic Hormone Cream" in jars that it advertised as containing one month's supply.[83] By indicating that the jar held a "30-night supply" and that women should "use it for one month" to obtain results, such ads implied how much cream should be used.[84] Part of a wider strategy to paint its product as scientific and therapeutic,[85] this marketing tactic made cream seem like medicine and the amount like dosage. Such ads aimed to persuade women to view the 30-night supply as the *minimum* amount needed for a wrinkle-free complexion, and thus to buy a jar every month.

[81] Pugsley repeatedly references a "upper limit"; Pugsley 1951 at 536. I found no evidence of any quantitative upper limit.

[82] This thesis does not attempt to trace comprehensively the US FDA's efforts, in the 1940s and early 1950s, to control hormonal skin creams. A summary of those efforts is given simply to situate National Health's approach to implementing the "directions for use" labelling requirement in the 1950 amendment.

[83] Pugsley echoed this advertising language and endorses the expertise of the cosmetics industry in setting this standard: "These preparations are recommended by cosmetic manufacturers in terms of one month's supply"; see Pugsley 1951 at 536.

[84] See Figures 8 and 9, *infra.*

[85] Bennett 2018; and Watkins 2007 at 85-87.

Figure 9: Ad for Helena Rubinstein's Estrogenic Hormone Cream, 1945.[86]

"A scientific preparation that will help you achieve beauty for your skin by retarding the effects of aging. *30-Night Supply.*"

[86] Advertisements, *Toronto Daily Star (1900-1971)* (6 April 1945), 21, ProQuest Historical Newspapers: *Toronto Star.*

Figure 10: Ad for Helena Rubinstein's Estrogenic Hormone Cream, 1947.[87]

"Estrogenic Hormone Cream – Contains natural hormones which your skin absorbs? Result? You look younger! Use it for one month. See the change. 4.50." This direction that the product be used for a 30-day period was *only* made for estrogenic cream, and for no other of these products.

[87] Advertisements, *Toronto Daily Star (1900-1971)* (17 October 1947), 11, ProQuest Historical Newspapers: *Toronto Star*.

By the late 1940s, Helena Rubinstein's marketing moves were taken up, tentatively, as an informal policy position by the US FDA. In effect, the FDA adopted the position that existing manufacturing and marketing practices of Helena Rubinstein (and other reputable firms) reflected a permissible potency and dose for estrogenic skin creams. In 1951, counsel to the US Toilet Goods Association disclosed the FDA's "latest pronouncement on the subject":

> As to the local effectiveness of estrogens in the doses commonly used, we believe that the literature as of today shows, after allowance is made for enthusiasm in some of the publications, slight morphological and physiological alterations in older skins not produced by the same ointment base without the estrogen. Whether or not these effects can be extended for more than two or three months has not yet been determined. *In replying to inquiries in regard to harmful local systemic effects we have pointed out that the cosmetics on the market in this country contain from 10,000 to 20,000 units of estrogenic substances per ounce. The directions in most cases specify that a small quantity be applied to the face.* These articles have been widely distributed for about ten years and there have been no reports in medical literature which suggest harmful effects resulting from their application.[88]

Similarly, Bennett finds that the FDA "appears to have settled on 10,000 International Units (IU) of oestrogens per ounce as an acceptable amount for hormone creams, as long as the amount used was no greater than 2 ounces per month." This limit was intended "to ensure that a user would have a maximum exposure of 670 IU of oestrogens per day."[89] It seems that the "limit" was an administrative interpretation by the FDA of whether an estrogen cream was a drug or cosmetic (and whether it was misbranded as either).[90] The ambiguity of this interpretation makes more sense in context of ongoing debates in which pharmaceutical firms and their lawyers increasingly challenged the FDA's authority to issue regulations and, relatedly, often opposed the FDA's efforts to regulate with administrative rulings or interpretations, insisting such efforts were "simply advisory in character" and lacked the force of law.[91] At one point, the

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[88] *Ibid* at 870-871 (emphasis added). Mock does not provide any citation or source for the quoted US FDA position statement.

[89] Bennett also finds that "[t]he amount of oestrogens present in American OTC hormone creams differed widely but most fell below the 10,000 IU per ounce limit that the FDA used as a safe measure" and that "[w]hen products exceeded the 10,000 IU per ounce the FDA usually confiscated them." He lists these creams and their potencies: "Nu-Youth Hormone Day or Night Cream (1,500 IU oestrogens); Second Youth Estrogenic Hormone Cream (7,500 IU oestrogens); Bette Knowlton Special Formula Cream (50,000 IU oestrogens); Revlon White Sable Hormone Liquid Cleansing Creme (6,000 IU oestrogens); Allure Fountain of Youth Wrinkleproof Cream (7,500 IU oestrogens); Dorothy Gray Cellogen Cream (10,000 IU oestrogens)." See Bennett 2018.

[90] This informal rule persists to the present day in the US, where: "[p]roducts containing estrogen, estrone, estradiol, progesterone, placental extract or vitamins may be considered drugs, misbranded drugs, or misbranded cosmetics … the estrogen content of an OTC product, be it a drug or a drug as well as cosmetic, may not exceed 10,000 IU per ounce. Users must be directed to limit the amount of product applied daily so that no more than 20,000 IU of estrogen or equivalent be used per month." MLM Law, "FDA Cosmetics Handbook" (2018), online: https://www.mlmlaw.com/library/guides/fda/Coshdbok.htm.

[91] Charles Wesley Dunn, "The New Prescription Drug Law Enacted by the Durham Bill (H.R. 3298) As A Part of the Federal Food, Drug, and Cosmetic Act" (1951) 6 *Food Drug Cosm LJ* 951 at 955.

FDA tried to crystallize its "rule of thumb" on estrogenic cream into a firmer rule. In 1950, when the House Commerce Committee was considering amendments to make it easier to restrict the sale of prescription drugs, the FDA asked Congress to write into the act an "exemplary list of prescription drugs" to guide interpretation of a new definition of prescription drugs.[92] On that list was "Estrogenic Substances - except skin creams containing not more than 10,000 International Units of estrone, or the equivalent of other estrogens, per ounce of cream".[93] Industry opposed this list and the Durham-Humphrey bill passed in 1951 without it.[94] Regardless, right after the bill passed, the FDA officially limited estrogenic drugs to sale on prescription.[95]

As in the US, Canadian practices of setting upper potency limits on estrogenic cosmetics did not depend on any express authority to limit potency or dose. By emulating the Americans' policy, Canada appeared to be a "shadow regulator",[96] and yet its legal forms and processes were modified. Rather than a murkily authorized limit of 10,000 IU of estrone potency per ounce, Canadian regulators chose a qualitative standard to distinguish cosmetics from drugs, with the test requiring estrogenic cosmetics to be "demonstrated to be free from systemic effect".[97] This test did *not* necessarily depend on dose-response reasoning or evidence. Moreover, on paper, this appears to be a highly precautionary standard requiring positive proof of safety. How could this test be congruent with the American policy, derived from cosmetics manufacturers, of limiting the potency of estrogenic cosmetics to a certain strength in a certain amount of cream?

The answer lay in labelling. Under section C.02.010, to be permissibly marketed as a cosmetic, not only did a preparation need be free of systemic effect, but as noted, it must include the statement "Use only as directed" and provide "directions for use".[98] These labels were the technique by which dose-response considerations, erased from the Sex Hormone Regulations in 1943, were smuggled back into Canadian estrogen regulation. By requiring cosmetic estrogen to bear product labels that directed use, in practice, National Health inspectors could attempt to force companies to direct the *amount* of cream that women should

[92] *Ibid* at 966. The definition of prescription drug was seen by the pharmaceutical industry as the "major controversy" in the bill.

[93] *Ibid* at 969 (emphasis added). This articulation of what, presumably, was already the FDA's working rule gets the closest to expressing estrogenic potency units in a way that reflected the science of the day. As noted in Chapter 4, while this had been widely misunderstood amongst regulators and manufacturers alike, there was not in fact *one* International Unit in which estrogenic activity was expressed, but two; see Chapter 4, section 1.i, particularly that content associated with notes 10-11.

[94] *Ibid* at 951.

[95] Goodrich 1951 at 888-889.

[96] The concept of "shadow regulator" is mentioned in Lexchin 2016 at 133.

[97] 1949 Sex Hormone Regulations, as amended in 1950, s C.02.010.

[98] 1949 Sex Hormone Regulations, as amended in 1950, s C.02.010(a)(v) and s C.02.010(b)(ii). Additionally, the amended regulations also required a statement of the product's weight or "net contents", at s C.02.010(b)(iii).

use. If a certain amount of cream contained a certain amount of estrogenic activity, National Health could deem it to have no systemic effect. If a firm was not willing to issue directions to use those amounts of cream – in another idiom, doses – its product would be deemed a drug.

Pugsley painted this labelling approach as deriving from a "ruling on potency", writing that "[a]n administrative ruling has been made on an upper limit of potency for one month's supply."[99] The dose of a potent estrogenic substance would determine if it was a cosmetic or a drug, in accordance with some ruling by some unidentified official. Having eradicated dose from standards for estrogenic seven years earlier, National Health officials were awarding themselves the discretion to determine dose through "rulings". Clearly, the techniques for standardizing dose had shifted far away from traditional dose specifications, bioassay methods, and reference standards. Dose was now a matter of standardizing women's behaviour and, to that end, enrolling manufacturers to include specific directions on their product labels.

There is no evidence, to be clear, that any "ruling" in an adjudicative sense had in fact been made. Pugsley's article was translating the Canadian approach to his American audience. US food and drug lawyers, bureaucrats, and industry representatives were accustomed, if not always favourable, to the FDA's administrative rulings, which were authorized by legislation. The *Food and Drugs Act* and its regulations did not, in contrast, permit National Health officials to make administrative rulings. The officials administering the *Act* and its regulations were permitted to interpret their language, subject to the possibility of judicial review, but had not been delegated power to issue rulings. Pugsley's assertion to the contrary was unusual. Yet it provides another example of the Department's ongoing practice of delegating power to make biologics standards to civil servants and industry, rather than codify standards in regulation.

Nevertheless, this story stays with the term "administrative rulings". In many respects, it perfectly captures a mode of regulation emerging for biological drugs at National Health in the 1950s. The term strongly evokes American regulatory practices, which National Health was increasingly emulating and reproducing, albeit with variations, including in its new approach to estrogenic cosmetics.[100] The term also holds in mind the move away from regulated standards, prescribed in subordinate legislation, and towards more individualized standards, exercised through administrative discretion. In contrast to an administrative "rule", administrative ruling

[99] In the same article, in the context of pituitary extracts, Pugsley claimed the Food and Drug Regulations "allow the Division to exercise administrative rulings to ensure that crude preparations do not appear on the market"; Pugsley 1951 at 539-540.

[100] In September 1951, William Goodrich, counsel with US Federal Security Agency, responded to Pugsley, noting discrepancies in Canadian and US law on sex hormones in a paper delivered at a conference and published later in the same journal. While he was critical of Canada's failure to put sex hormones under prescription and of the futility of labels directing patients to get a physician's advice on drugs after purchase, Goodrich did *not* note any differences between Canadian and American approaches to estrogenic cosmetics, presumably because, on that front, Canada was emulating its southern neighbour. See Goodrich 1951.

reflects the processual dynamic in this mode of governance. Administrative rules tend to be written down, codified, intended to apply generally; rulings, by contrast, evoke orally rendered judgement unique to individual cases. Rather than one fixed interpretation, rulings were more fluid and flexible. As shown by Pugsley's article, the "upper limit" in his ruling remained unspoken and unlocatable, except perhaps in private communications. Moreover, the term helps to reveal the ambiguity of the source of authority for the ruling. "Administrative rulings" were made by unidentified rulers, their authority delegated by an unidentified source of power.

For the purpose of this history of estrogen regulation, "administrative ruling" also provides a convenient label not found in the historiography of Canadian public law. The interwar "battle over the legitimacy of delegated legislation" is well-known, the protagonists and antagonists including Hewart and Dicey, the American legal realists, and Canadian scholars like John Willis, and I do not rehearse it here. Yet by WWII, this battle was won (or lost, depending on one's perspective). Delegating authority through subordinate legislation, much of which subdelegated power to administrative officials, was the new constitutional and political reality in Canada, just as it was in Britain and the US. However, and put here in very general terms, the regulatory state – or perhaps better, the administrative state – was moving into a deeper and more thoroughgoing form of delegation by the 1950s, developing a range of practices by which administrators governed through discretion. As Michael Taggart put it, by the late 1940s, "subdelegated legislation was difficult to distinguish from less formal guidance or advice, often contained in circulars or the like".[101] In addressing the conceptual and nomenclatural confusion over this emerging form of administrative governance, which "in other forms is with us today", he settles on the concept of "quasi-legislation".[102] Reminding us that R.E. Megarry had adopted this label in 1944,[103] and had "included under this rubric administrative interpretations of statutes, glosses on statutes, and officially sanctioned arrangements between private parties that waived the law or affected operation of the law between citizen and citizen", Taggart characterizes the defining feature of quasi-legislation as a lack of "binding legal effect". One can understand National Health's approach as quasi-legislation, although in repurposing "administrative ruling", I hope to capture the fluidity, informality, and discretionary nature of this way of regulating.

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[101] Michael Taggart, "From 'Parliamentary Powers' to Privatization: The Chequered History of Delegated Legislation in the Twentieth Century" (2005) 55:3 *Univ Tor Law J* 575 at 603.

[102] *Ibid* at 603-605. Taggart also notes that, as of 2005, "the sobriquet 'administrative quasi-legislation' has fallen a little out of fashion; in fashion are 'soft law' (adopted from international and EU law), 'bureaucratic law' (from the United States), and the anodyne 'tertiary rules.' In many respects, concern about quasi-legislation has displaced that about delegated legislation proper. Indeed, it is possible to see history repeating itself, with quasi-legislation or soft law provoking the same sort of vitriolic reaction from latter-day Hewarts"; *ibid* at 604.

[103] RE Megarry, "Administrative Quasi-legislation" (1944) 60 Law Q Rev 125.

Dose-setting through administrative ruling was especially common for estrogenic creams marketed for breast enhancement. In the early 1950s, National Health inspectors contemplated "directions for use" for firms selling breast creams. Officials adopted varying performances of the dose-response relationship. For example, in 1950, spurred by a series of ads for five breast creams, Inspection Services asked the department's cosmetics lead whether estrogenic breast creams had systemic effects.[104] J.T. Thompson reported back with a particular enactment of the dose-response relationship. He started with the desired physiological response, growth of mammary tissue, then worked backward to judge what amount would achieve it. In his view, the requisite dose would be so high as to cause systemic effects. Admittedly, this view allowed Thomson, responsible only for cosmetics, to take a hands-off approach to breast cream:

> "I don't think bust development creams should be classed as cosmetics or USED except under medical supervision. To be effective, the dosage must be heavy, and I should think some degree of systemic effect would be unavoidable. Enough at least to put the preparations out of the cosmetic class. Having thus politely washed my hands of them, I get out from under!"[105]

Pugsley, however, sent his own separate report to Inspection Services, taking issue with Thomson's view that breast creams had systemic effects (and thus could not be cosmetics). Pugsley enacted the dose-response relationship differently. He acknowledged that these estrogenic creams would cause growth in mammary tissue, but rather than move on to ask what dose was needed to achieve that physiological response, he argued that growth in mammary tissue was inherently cosmetic: "I would say this is an effect on local tissue and not necessarily systemic action". Ironically, Pugsley's articulation suggested that breast creams did not actually meet the legal test for an estrogenic cosmetic, which provided that a product was a drug "unless demonstrated to be free from systemic effect". Moreover, to ask if a product was "necessarily" harmful reflected a lower threshold than to require it be "proven free" from harm. Pugsley's enactment of this weaker standard was entangled with his commitment to the idea that labelling provided an adequate regulatory response. Even though the five creams were advertised at 30,000 I.U. of estrogenic potency – three times stronger than what the US FDA commonly tolerated for cosmetics – Pugsley felt that a label with directions would suffice. He advised Inspection Services to ensure that the manufacturers agreed to "the 30 day limit", yet gave no

[104] November 7, 1950 memorandum from Curran to Whitmore enclosing five breast cream advertisements, in Food and Drug Newspaper Clippings, 1949-1953.

[105] November 1950 handwritten note from Thomson to Whitmore, in Food and Drug Newspaper Clippings, 1949-1953.

advice on what that amount should be.[106] His advice would have confused the inspectors, as the five creams had already been advertised for sale in a 30-day supply. In this case, the "30 day rule" would have required inspectors to ask the US firms to shrink down the size of the jars they sold in Canada. Neutered by this regulatory approach, inspectors predictably took no action.

National Health's most protracted investigation of estrogenic creams was pursued from its Vancouver office in 1952.[107] Inspector E.L Devlin was dutifully trying to bring Venus Products into compliance with the Sex Hormone Regulations. Venus sold a breast cream called Formula V-7, advertised with a pseudoscientific booklet. Devlin crafted a long, careful letter setting out regulatory requirements and the "potential dangers" of estrogens taken at high doses or for prolonged periods. His letter performed a subtly different variant of dose-response. Like Pugsley, he began by focusing on the intended response. Unlike Pugsley, he found that, given effects of estrogen on breast tissue, one should assume that applying Formula V-7 to breasts would affect "the body hormone balance", such that the product must be "regarded as having systemic effects". Thus, he deemed Formula V-7 to be drug (though at 6000 I.U., it was one-fifth the potency of the five creams deemed to be cosmetics in 1950). As a drug, Formula V-7 would need to comply with the drug labelling rule in Section C.02.007 which, according to Devlin, "requires that the proper name, Oestrogenic Substance, be used and the potency be declared in International Units per ounce, indicating what amount is to be used over a 30 day period."[108]

Without question, Devlin's interpretation was legally incorrect, although it further exemplifies how the distinction between cosmetics and drugs was enacted in informal, fluid administrative ruling of officials. Unlike section C.02.010 governing cosmetics, the drug labelling rule in section C.02.007 did not, in fact, require any labels to provide "directions for use" or to stipulate what amount should be used. By allowing its officials to indirectly influence use and dose, cosmetic labelling rules afforded National Health more power to limit estrogenic dosing than it had for drugs. In any event, Venus Products complied with Devlin's direction,[109] promising to label its jars with the weight, the fact that the product contained 6000 I.U. of Oestrogenic Substance per ounce, and a direction to not use more than 1 and 2/3 ounces each month".[110] Whether women hoping for fuller chests would follow that direction was another matter. Arguably, National Health's turn to regulating through label directions may have made the creams more dangerous.

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[106] November 7, 1950 memo from Curran to Whitmore (note by Pugsley), in Food and Drug Newspaper Clippings, 1949-1953.

[107] While Vancouver was the lead, advertisements for Formula V-7 were identified by inspectors in Winnipeg and monitored by Ottawa; see April 17, April 25, April 28, and May 6, 1952 letters, in Food and Drug Newspaper Clippings, 1949-1953.

[108] March 21, 1952 letter from Devlin to Venus Products Ltd., in Food and Drug Newspaper Clippings, 1949-1953.

[109] Sex Hormone Regulations, SOR 49-547, s C.02.007. Devlin also requested other labelling changes pursuant to s C.002.007.

[110] March 26, 1952 letter from Venus Products Ltd. to Devlin, in Food and Drug Newspaper Clippings, 1949-1953.

In this case, Devlin asked Venus to remove an insert from its advertising booklet for Formula V7. The insert outrageously asserted that while "Formula V7 is not intended for the discovery of existing cysts but if its use is instrumental in doing so, then it may be considered an additional though unintentional benefit", and Venus tried to argue that the insert was an "amplification" of the directions for use on the label. In its startling association of Formula V-7 and breast cancer, the insert may very well have caused women to have second thoughts about using the product. Because it was a "somewhat misleading" direction, though, Devlin insisted that it be removed.[111]

Leveraging power through labels, the Inspection Service was enacting dose controls that National Health senior officials and Committee members had rejected in 1943. Taking a vague labelling rule for cosmetics that had become infused in practice with dose-response considerations, shifting those considerations back into the regulation of drugs, asking not just "how to measure" but also "how much", inspectors resurrected dose and reinserted it into the regulatory regime. Without doubt, reining in a little local company dabbling in quackery was not the same as interfering in innovations of major pharmaceutical firms. Power was material. Yet estrogen too was powerful, insistent that regulators re-embrace logics previously disavowed.

Devlin wrapped up his compliance efforts with Venus Products in May 1952. Less than a month later, a Select Committee of the US House of Representatives, known as the Delaney Committee, released its final report on chemicals in cosmetics. The report followed two years of high-profile congressional hearings, chaired by Congressman James Delaney, to investigate the use of chemicals in foods and cosmetics.[112] Medical experts of various specialties, including endocrinologists, allergists, and dermatologists, had testified at the hearings, and many had been questioned regarding the potential hazards of estrogenic skin creams.[113] Some witnesses equivocated,[114] while others were crystal clear that these products could be hazardous.[115]

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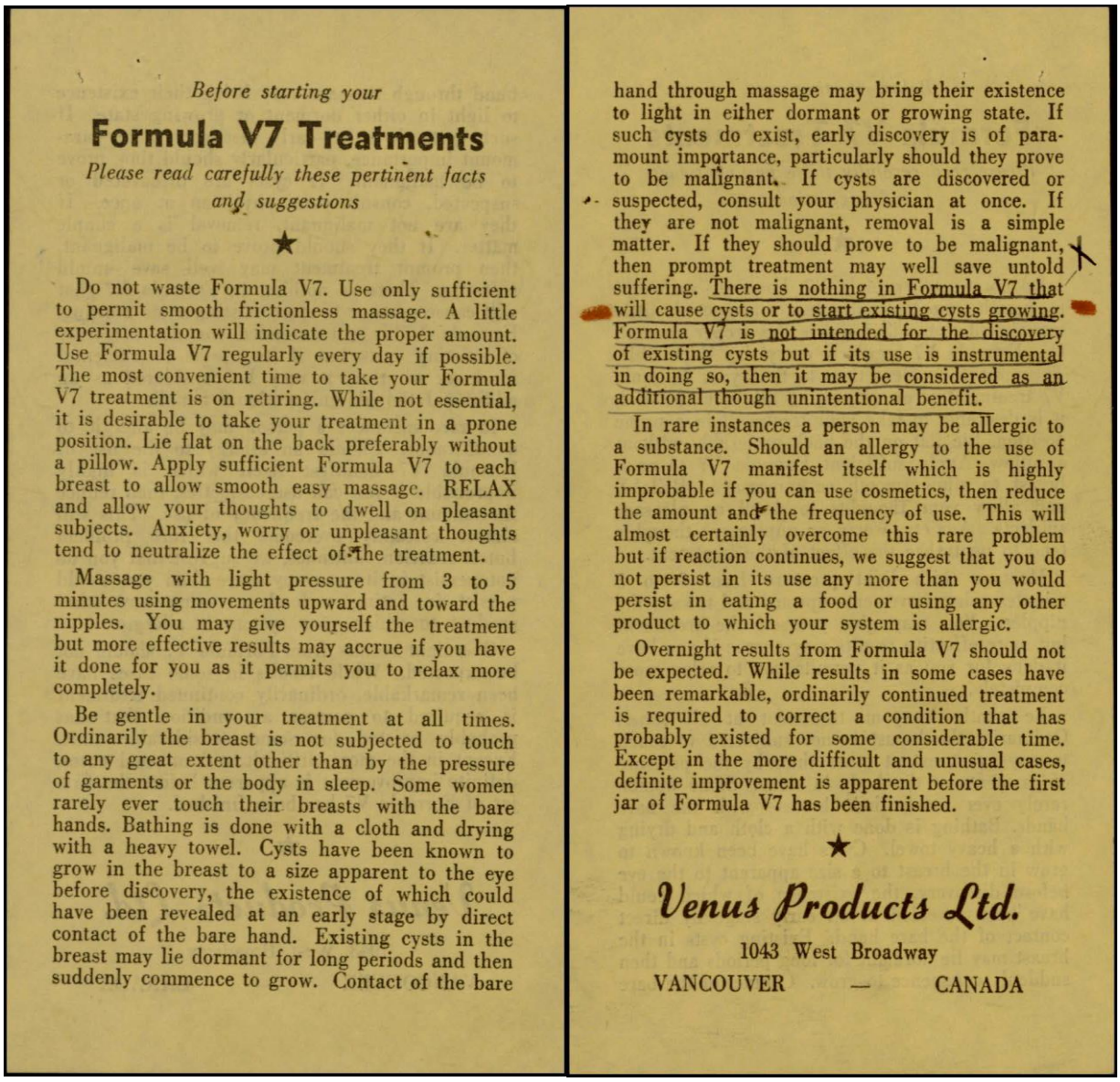
[111] March 26, 1952 letter from Venus Products to Devlin, March 28, 1952 letter from Devlin to Venus Products, and May 16, 1952 letter from Devlin to senior National Health officials, all in Food and Drug Newspaper Clippings, 1949-1953.

[112] H.R. REP. No. 2182, 82d Cong., 2d Sess. (1952), as published in (1952) 7 *Food Drug Cosm LJ* 563 at 564 ["Delaney Committee's Report on Cosmetics, 1952"].

[113] House of Representatives, *Chemicals in Food Products: Hearings Before the House Select Committee to Investigate the Use of Chemicals in Food and Cosmetics,* Hearing Transcripts, 82d Cong., 1st Sess. (October-November 1951) ["Delaney Committee Hearing Transcripts, 1951"].

[114] *Ibid,* Testimony of Dr. Ervin Erstein, Assistant Clinical Professor of Dermatology, Stanford University, 20 November 1951 at 739-740; and *ibid,* Testimony of Dr. Thomas H. Sternberg, Professor of Dermatology, University of California at Los Angeles, 23 November 1951 at 919-920, testifying that estrogenic creams were unsafe and that he had seen "cases of poisoning by estrogen overdosage", but that he was not prepared to conclude that such creams were carcinogenic.

[115] Dr. Carl Hartman, Ortho Research Foundation; see *ibid* at 751 and 755, and About the Authors, 1951 at 486. See also Dr. H.V. Allington, Dermatologist, 20 November 1951 at 750-751, testifying that "the hormone preparations are in every sense of the word potent and potential dynamite" and there "should be a great deal more known before hormones are released for general distribution indiscriminately"; Dr. Samuel Ayres, Dermatologist, 23 November 1951 at 925-927, testifying that "continued use of



Before starting your

Formula V7 Treatments

Please read carefully these pertinent facts and suggestions

★

Do not waste Formula V7. Use only sufficient to permit smooth frictionless massage. A little experimentation will indicate the proper amount. Use Formula V7 regularly every day if possible. The most convenient time to take your Formula V7 treatment is on retiring. While not essential, it is desirable to take your treatment in a prone position. Lie flat on the back preferably without a pillow. Apply sufficient Formula V7 to each breast to allow smooth easy massage. RELAX and allow your thoughts to dwell on pleasant subjects. Anxiety, worry or unpleasant thoughts tend to neutralize the effect of the treatment.

Massage with light pressure from 3 to 5 minutes using movements upward and toward the nipples. You may give yourself the treatment but more effective results may accrue if you have it done for you as it permits you to relax more completely.

Be gentle in your treatment at all times. Ordinarily the breast is not subjected to touch to any great extent other than by the pressure of garments or the body in sleep. Some women rarely ever touch their breasts with the bare hands. Bathing is done with a cloth and drying with a heavy towel. Cysts have been known to grow in the breast to a size apparent to the eye before discovery, the existence of which could have been revealed at an early stage by direct contact of the bare hand. Existing cysts in the breast may lie dormant for long periods and then suddenly commence to grow. Contact of the bare hand through massage may bring their existence to light in either dormant or growing state. If such cysts do exist, early discovery is of paramount importance, particularly should they prove to be malignant. If cysts are discovered or suspected, consult your physician at once. If they are not malignant, removal is a simple matter. If they should prove to be malignant, then prompt treatment may well save untold suffering. There is nothing in Formula V7 that will cause cysts or to start existing cysts growing. Formula V7 is not intended for the discovery of existing cysts but if its use is instrumental in doing so, then it may be considered as an additional though unintentional benefit.

In rare instances a person may be allergic to a substance. Should an allergy to the use of Formula V7 manifest itself which is highly improbable if you can use cosmetics, then reduce the amount and the frequency of use. This will almost certainly overcome this rare problem but if reaction continues, we suggest that you do not persist in its use any more than you would persist in eating a food or using any other product to which your system is allergic.

Overnight results from Formula V7 should not be expected. While results in some cases have been remarkable, ordinarily continued treatment is required to correct a condition that has probably existed for some considerable time. Except in the more difficult and unusual cases, definite improvement is apparent before the first jar of Formula V7 has been finished.

★

Venus Products Ltd.

1043 West Broadway

VANCOUVER — CANADA

Figure 11: Booklet insert for Formula V-7 Treatment, Venus Products Ltd, 1952.

Library and Archives Canada, RG29, Vol 259, File 347-1-6 (part 4), reproduction copy number I-115336

Venus Products objected to National Health's request that it remove this insert from its advertising booklet, claiming it was part of its directions for use. Venus was candid about its reasons for these "directions" to women users: "Our only hope was that in the event of cancer being discovered coincidental with the use of Formula V7 that the victim would think and do a little investigating before going off half cocked and blaming us unjustly. One claim with the publicity that would be sure to attend regardless of how unjust that claim was or whether our product was proven harmless in the highest court the results to us would be so adverse that it could well put us out of business".[116]

sex hormones in certain amounts are capable of producing malignant change", the creams might stimulate existing malignancy, and there was not enough evidence to conclude the creams could be used safely except under a physicians' supervision.

[116] March 26, 1952 letter from Venus Products to Devlin, in Food and Drug Newspaper Clippings, 1949-1953.

Almost all stated, or at least implied if they recommended physician supervision, that the hazard would be a question of dosage.[117] As the products were sold as both night creams and day creams, the Committee's report observed that women could be "covered by these substances 24 hours of every day".[118] The Committee also expressed concern that, as it was known that estrogens were absorbed dermally, these cosmetics may cause "undesirable physiological changes".[119] However, as the expert witnesses had disagreed on the likelihood of systemic effects, the Committee recommended only that there should be more research.[120]

Only a few such studies were ever done. One found that, even at small doses, estrogenic cream could produce systemic effects – namely, endometrial hyperplasia – if applied over a long period.[121] Another found that the creams did not induce any visible or clinically observable changes to the appearance of facial skin.[122] Overall, the small body of research indicated that not only were estrogenic skin creams ineffective, but they were harmful.[123] Regardless, some researchers were willing to argue the industry position that, even if used for years, there was no evidence they caused "cancerous changes in the skin", and there was "a consensus of opinion amongst experienced observers that cosmetic hormone creams with a maximum potency of 10,000 IU per ounce (31 g.) of vehicle, if used in the manner by the informed manufacturer, are free from systemic effects."[124] Estrogen was being performed as harmful and worthless by medical practitioners, and as safe and controllable by cosmetic manufacturers and researchers.

Faced with a substance that could not be pinned down, National Health officials retreated to regulating claims rather than regulating potency. By 1953, the centrality of labelling to the safety of estrogen had become routinized. When local Toronto inspectors raised questions about an advertisement for Lady Esther Hormone Cream, which boasted of the cream's high potency and ability to "renew the beautifying effects of your own waning hormone supply", Whitmore

[117] Testimony of Dr. Ervin Erstein, assistant clinical professor of dermatology, Stanford University, 20 November 1951 at 740, and Dr. Thomas H. Sternberg, Professor of Dermatology, University of California at Los Angeles, 23 November 1951 at 919, *ibid.*

[118] Delaney Committee's Report on Cosmetics, 1952 at 613.

[119] *Ibid* at 613-614.

[120] *Ibid* at 614.

[121] Minnie B Goldberg & Franklin I Harris, "Use of Estrogen Creams" (1952) 150 *JAMA* 790-791 1952.

[122] Behrman 1954 at 122; and Watkins 2007 at 86.

[123] In the early 1960s, the AMA and the FDA would issue statements opposing estrogenic cosmetics, but these declarations "had little effect on the marketing of estrogen skin creams"; Watkins 2007 at 86.

[124] SM Peck & EG Klarmann, "Hormone Cosmetics" (1949) 173:1034 *Practitioner* 159 at 165, as cited in Bennett 2018.

Figure 12: "Stay Lovely … Stay Loved … with *Lady Esther* Natural Estrogenic Hormone Cream", 1953

Library and Archives Canada, RG 29, Vol 258, File 347-6-6 (Part 2), reproduction copy number e-011195706

How women over 35 can look younger!

"YOUR HUSBAND LOOKS AT YOU WITH NEW INTEREST"

A Frank Statement about Estrogenic Hormones by Helena Rubinstein

"Estrogenic Hormones are the most effective agents yet discovered for helping women to look *younger*"

I believe, with all my heart, that Estrogenic Hormones can make you look younger. While leading scientists have carried out exhaustive experiments with Estrogenic Hormone Cream, *I have been using my own skin as a testing ground.*

More than 20 years ago I started applying Hormone cream to my own skin. Since then I have observed the effects on thousands of other women. All this time, too, I have kept abreast of hormone studies in universities, and in my own laboratories.

Dramatic Proof

We, now have dramatic proof that Estrogenic Hormones can often bring about a decided improvement in the appearance of dry, oldish skin.

One of the many important tests which have contributed to this proof took place recently at a leading university in New England.

1. The hands of twenty-five women between the ages of 35 and 55 were placed under scientific observation for six months.
2. Two different creams were applied to their hands daily. One cream contained Estrogenic Hormones. The other did not. The creams *looked identical.* Even the doctors making the study *did not know* which hands received the Estrogenic Hormone Cream!
3. At the end of 6 months, the doctors formed their conclusion: "The skin of the left hands (with one or two exceptions) looked *fuller, less wrinkled, more youthful.*"
4. It was then learned by the experimenting doctors, that Estrogenic Hormone Cream was the one which had been used on these younger-looking left hands!

Yes, we now have *proof* that these Estrogenic Hormone preparations can safely give women younger-looking skin.

Important to Women Over 35

If you are over 35, then you must realize that your skin *is steadily losing its youth-giving substances.*

Estrogenic Hormones are *natural* substances. And they really work in a very simple way. When gently massaged into your skin, they make your *under-skin* fill out. This in turn stretches the *outer-skin.* When this happens, tiny lines become less visible. Your skin, as the doctors reported, looks *"fuller, less wrinkled, more youthful."*

Works in Two Ways

My Estrogenic Hormone Cream works in two ways to help your skin look more youthful. It works from *within* . . . as your skin absorbs the natural estrogenic hormones. And it works from *without* . . . as its rich emollients smooth away dryness, help you recapture that *young look.*

But these admirable results *don't happen over night.* Even though women tell me they note an improvement after *only one week* . . . I always advise them to try out my Estrogenic Hormone Cream and Oil for at least 3 months.

But even at the end of 30 days, I am sure you will note a real change — *a younger-looking skin.*

A Thrilling Experience

If you are over 35 it is a thrilling experience when you begin to look younger. Compliments come your way. "What have you been doing to yourself?" ask your friends. You yourself are gloriously aware that you look prettier, brighter. You have a new assurance. A new poise. Your husband looks at you with new interest. Life suddenly seems *more exciting.*

HR-352

Helena Rubinstein's Special Offer

ESTROGENIC HORMONE CREAM
ESTROGENIC HORMONE OIL

8.25 VALUE
BOTH FOR 5.00
THIS BEAUTY OFFER GOOD FOR A LIMITED TIME

Figure 13: "Your husband looks at you with new interest", 1952

***Toronto Daily Star* (1900-1971). Feb 6, 1952: 27. ProQuest Historical Newspapers: Toronto Star.**

confidently advised that the claims were "within the realm of permitted cosmetic puffery".[125] Labelled at 10,000 I.U. and marketed as a 30 days' supply, Lady Esther's Hormone Cream exemplified compliance with the unwritten rules and bureaucratic discretion characterizing this mode of "administrative ruling". Advertisements by Lady Esther, Helena Rubinstein, and other hormone cream manufacturers exploited North American women's fear of aging and "preyed on women's economic and emotional dependence on men", raising the scenario "of a husband fleeing his wife's wrinkled skin and finding comfort in the arms of a smoother-skinned woman".[126] However, National Health inspectors had no power, and perhaps no inclination, to find any "objectionable greasiness" in the many ads warning middle-aged women that, if they did not use these potent estrogenic skin creams, they would lose their husbands.[127]

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Ten years before Lady Esther's advertisement came to the attention of National Health inspectors, the Deputy Minister of Health, Robert Wodehouse, had intervened to ensure that the Canadian Committee on Pharmacopoeial Standards would endorse the Sex Hormone Regulations without recommending dose or potency limits. In the intervening decade, with the practices of Canadian regulators, estrogens had become biologics that eluded measurement and domesticated cream permissibly claimed as the "Greatest Agent Known for Counteracting Signs of Age",[128] potent substances that some physicians believed should only be sold on prescription and "natural" cosmetics that would let middle-aged wives "Stay Loved",[129] substances of questionable therapeutic value that should not be endorsed through licensing and medicine effective for "menopausal symptoms" and other "estrogenic deficiency".[130]

Potent but safe, hazardous but ineffective, natural but an artifice, systemic but cosmetic, estrogen was a provocation to regulators. By the early 1950s, regulators continued to view "low doses" as the key to ensuring that estrogen was safe. However, whether for drugs or cosmetics, Canadian regulators never studied, defined, or regulated any thresholds for safe doses. Dose

[125] October 26, 1953 memorandum and November 2, 1953 memorandum, in Food and Drug Newspaper Clippings, 1949-1953. In the early 1950s, there were no seizures or prosecutions involving any sex hormone preparation, whether drug or cosmetic; see Monthly Prosecutions and Seizures Reports, 1950-1953.

[126] Watkins 2007 at 87.

[127] See e.g. Figures 12 and 13. In the bottom right corner, the ad for Lady Esther Hormone Cream indicated that the product had "no objectionable greasiness!"

[128] Figure 12.

[129] *Ibid.*

[130] 1950 and 1951 Premarin ads, in Figures 7 and 8 respectively.

had been repeatedly delegated – to pharmaceutical manufacturers, clinicians, cosmetics firms, and women consumers.

National Health did attempt to consolidate and unify estrogen in 1949, by removing four estrogenic molecules from the Canadian Supplement and by extending to sex hormones its practice of (unlawfully) subdelegating bioassay methods to government scientists. Rather than regulate dose, however, National Health began regulating "potency limits" through administrative practices – first for cosmetics, then for breast creams deemed to be drugs. Still, National Health officials did not enact dose-response relations in a uniform way. Its inspectors, tasked with scrutinizing advertisements to identify and pursue non-compliance, always on the alert for fraudulent or misleading claims in pursuit of the *Act*'s public health and consumer protection purposes, were inherently suspicious of overblown claims made for estrogen creams and inclined to assume adverse effects, working from this assumption of hazard to ensure safe doses. The Chief of National Health's Laboratory Services, by contrast, as an endocrinologist, had an openness to hormones and scientific skepticism of unproven claims that these creams caused systemic effects. Pugsley worked from an assumption of safety that viewed labels less as a means to reduce dosage, and more as a performance of administrative oversight. Both practices, however, ultimately sought to accomplish "potency limits" through regulatory techniques and material technologies of labelling. For regulating ambiguously potent substances marketed exclusively to women, labels were becoming instrumental.

In this entanglement of law, gender, and toxicity, estrogen was not the only phenomenon becoming naturalized. The concept of menopausal women was also being normalized. Estrogen was a substance whose bodily effects were being rendered, in regulatory practices, as unpredictable, deceptive, malleable, and individual. In turn, National Health began regulating dose and potency through labelling directions that displaced responsibility for safety away from the Department, targeting directions at women assumed to have those same characteristics.

Born from a "junkie" or "quickie" improvisation aimed to sidestep perceived legal constraints, with estrogen, consumer caution labels were also becoming naturalized as a regulatory technique. As seen in the previous and current chapters, estrogens were the first substances for which labels were used in lieu of standards in Canada, first for drugs and then for cosmetics. Labels allowed regulators to require potent ingredients to be identified in consumer products, to caution women to use cosmetics "with care", to discipline women to regulate their own exposure by following directions, and, in all of these functions, to displace responsibility for ensuring a standard substance with predictable properties away from the state. Caution labels for drugs and cosmetics made it explicit, for the first time, that women would need to assume

responsibility for their own safety. National Health's potent mixture of labels, delegation, and administrative governance to apprehend and respond to the hazards of estrogen is, therefore, an early example of risk regulation in Canadian law.

Mandatory labelling of gendered consumer products would soon travel to other contexts. While the 1949 Sex Hormone Regulations had contained the first cosmetics regulation in Canadian history, standalone cosmetic regulations followed three years later.[131] With a focus on dangerous ingredients, these regulations governed cosmetics with "appropriate cautions as well as with advertising or label claims" – techniques first introduced with estrogen.[132] In cosmetics regulation and beyond, estrogen would leave its mark on Canadian law.[133]

[131] Part E of the Food and Drug Regulations, SOR/52-271, in *Canada Gazette,* Part II, Vol LXXXVI, No 14, at p 585 (July 23, 1952) ["1952 Cosmetic Regulations"]. See also Curran 1953 at 181. Sex hormones in cosmetic products were still regulated, in 1952, by the Sex Hormone Regulations, although this changed in 1954 when the relevant provisions were transferred into Part E.

[132] Curran 1953 at 181. See also 1952 Cosmetic Regulations, s E.01.001(c) (label requirements included "adequate directions for safe use" and any required "warning, caution or special direction"). These regulations also required some labelling cautions specific to certain cosmetic products, such as hair dyes that contained para-phenylene-diamine or other coal tar dye base.

[133] The 1952 Cosmetic Regulations also had other influences, shadowing in many respects the US FDCA approach to cosmetics.

PART III

Musings on potency, on power, on possibility: a conclusion

This thesis has shared an account of law-in-estrogen and estrogen-in-law, in Canada in the 1940s and early 1950s, examining how these realities were enacted with regulatory practices. In this time and place, regulating estrogen was coterminous with materializing estrogen as a potent substance. Put differently, I have argued in this thesis that toxicity and law – or, further collapsing the distinction between the onto-epistemological and the political that this formulation solidifies, that potency and power – were co-produced.[1] In exploring the historicity of estrogen as a legal phenomenon, and the historicity of labelling as an estrogenic phenomenon, I have illustrated how mid-century regulatory practices performed the dose and made the poison. By the early 1950s, a potent estrogen was thoroughly installed into Canadian laws and soon to encounter millions of Canadian bodies, and Canadian regulators had conducted their first experiments with using labels, rather than standards, to intervene in dose-response relations.

In these concluding reflections, I return to the present, to ask whether this historical entanglement of potency and power might resound in current regulatory performances. Does this story of estrogen and regulation matter today, and if so, for whom? I also briefly consider the concept of toxic enactment that has arisen from and driven this historical narrative.

The Introduction provides a sense of where this history travels.[2] By the mid-1950s, estrogen was already being performed differently in Canada; prescriptions were required for the sale of estrogenic drugs and, in a move that would radically change socio-material realities, estrogen emerged in the form of the contraceptive pill. Yet the multiple potencies and doses, scripted into estrogen in the 1940s, continued. Premarin became hugely popular in the 1960s, fuelled by its promotors' injunctions to be "Feminine Forever".[3] By the 1970s – after decades in which DES, Premarin, and the Pill circulated in doses and dosages, in forms and formulations, no longer conceivable – stories began emerging of suffering and illness, disease and death. As estrogen turned from "hero to villain",[4] the main regulatory response was patient package inserts – in essence, a new, lengthier, more informative label.[5] As in the 1940s and 1950s, if for different

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[1] Antonio Negri, *The Savage Anomaly: The Power of Spinoza's Metaphysics and Politics,* trans. Michael Hardt (Minneapolis: University of Minnesota Press, 2003). Originally published as *L'anomalia selvaggia. Saggio su potere e potenza in Baruch Spinoza,* Negri identified as "potere" and "potenza" what in English translations of Spinoza had both been reduced to "power".

[2] See Introduction, particularly that content associated with notes 11-18.

[3] Robert Wilson, *Feminine Forever* (New York: Evans, 1966).

[4] Watkins 2007 at 93.

[5] Another response, in Canada, was to ban the sale of cosmetics containing estrogen; *Cosmetic Regulations*, CRC, c 869, s 15(b).

reasons, compared to other drugs, estrogen was unique in attracting these inserts. Beyond these labelling techniques, the material residue of this legal history persists in many bodies.

Perhaps this story of law-in-estrogen and estrogen-in-law can generate historically informed debates about how endocrine disrupting chemicals should be regulated today.[6] Toxicity and labels, after all, seem ever more imbricated.[7] Go to the drugstore, stand in an aisle, scan the shelves for a moisturizer without parabens, a sunscreen without oxybenzone, a non-toxic nail polish. Do you see other people – probably women,[8] maybe with small children in strollers – reading the labels? Ponder that, on average, American women use 12 personal care products, containing 168 cosmetic ingredients, every day,[9] and that teenaged girls use nearly 17 products containing an estimated 174 ingredients daily.[10] Recall how, in 1952, the Delaney Committee worried that women might be covered by creams containing estrogen 24 hours of every day".[11]

Then think of Environment and Climate Change Canada and Health Canada's joint response, in June 2018, to the lengthy report released a year earlier by the House of Commons' Standing Committee on Environment and Sustainable Development.[12] After hearing evidence and receiving briefs,[13] the Standing Committee had made numerous recommendations for amending CEPA to provide greater protection from endocrine disrupting chemicals.[14] The two departments

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[6] Many scholars have connected histories of hormonal drugs, especially DES, to current debates about endocrine disrupting chemicals, see e.g. Roberts 2007 and Langston 2010.

[7] It should be noted that when it comes to hormonal changes materialized through topical skin products, not everybody has been given the option of attending to their own exposures. Transgender women and genderqueer people wanting softer skin, less body hair, or breast enhancement may find themselves limited by the option of buying over-the-counter drug and cosmetic products and following label directions. If they wish to use estrogen to shape their embodiments, their care is medicalized, supervised by a physician who may be willing to prescribe estrogen off-label. While boundaries between estrogenic drugs and cosmetics were blurred in the 1930s-1950s, for trans or genderqueer people seeking more feminine embodiments in 2018, those boundaries are rigidly enforced. Indeed, in this enactment, labelled drug indications are necessarily disregarded.

[8] For the gendered nature of "precautionary consumption" of toxics, a phenomenon that typically relies upon product labels, see Dayna Nadine Scott, Jennie Haw & Robyn Lee, "'Wannabe Toxic-Free?' From precautionary consumption to corporeal citizenship" (2017) 26:2 *Environ Politics* 322; Norah MacKendrick, "More work for mother: chemical body burdens as a maternal responsibility" (2014) 28:5 *Gend Soc* 705; and Norah MacKendrick & Lindsay Stevens, "'Taking Back a Little Bit of Control': managing the contaminated body through consumption" (2016) 31:2 *Sociol Forum* 310.

[9] Environmental Working Group, "Exposures add up – survey results" (2004), online: http://www.ewg.org/skindeep/2004/06/15/exposures-add-up-survey-results/#.W1fbT2inE2w. Men were found to use, on average, six products daily, containing 85 unique chemical ingredients.

[10] Environmental Working Group, "Teen Girls' Body Burden of Hormone-Altering Cosmetics Chemicals: Detailed Findings" (September 2008), online: https://www.ewg.org/research/teen-girls-body-burden-hormone-altering-cosmetics-chemicals/detailed-findings#.W1ffCminE2w.

[11] See Chapter 5, section 2, particularly that content associated with notes 112-119.

[12] Environment and Climate Change Canada, "Follow-Up Report to the House of Commons Standing Committee on Environment and Sustainable Development on the Canadian Environmental Protection Act, 1999" (June 2018), online: https://www.canada.ca/content/dam/eccc/documents/pdf/cepa/FollowUpCepaReport-eng.pdf ["Canada's Follow-Up Report on CEPA 1999, June 2018"].

[13] I disclose that I contributed to the three briefs authored by Dayna Nadine Scott.

[14] See Introduction at note 1.

agreed with the recommendations, even choosing to highlight endocrine disruptors as "chemicals of high concern" in the Minister of Environment's press release accompanying their response.[15] However, with not enough time (or priority) to introduce legislative amendments in this parliamentary session, the departments indicated that, for the time being, they would continue to employ "available risk management tools" – including product labels. Product labels may "further improve Canadians' access to information they need to make informed decisions about the products they use", and, moving beyond label technologies, the "use of technologies such as cell phone apps could help consumers make point-of-purchase decisions".[16] Thus, as in the 1940s and early 1950s with estrogen, as an alternative to stronger legal tests for what substances can be and do, Canadian regulators are considering using labels and other information-providing technologies to delegate to (women) consumers the responsibility to make decisions about whether to buy and how to use chemicals of high concern. Though using labels in lieu of standards was an estrogenic innovation 75 years ago in Canada, today it has become thoroughly naturalized as a regulatory response for products containing ingredients of concern.

In summarily noting the continued entanglement of hormone-disrupting chemicals and labels, it is important not to lose sight of how these relations materialize. Whether working explicitly with enactment, or within other frameworks that account for what people think, say and do, dose-response relationships are done in different ways by different people, institutions, interactions, disciplines, times, and places. As conceptualized in this thesis, toxicity is enacted by and enacts regulatory practices – and practices change. Contrary to unnuanced claims being made by some STS scholars working on toxicity, it is not the case, at least in Canada, that "[n]early all existing environmental regulations and laws around toxicants are based on threshold limits – normally measured in relation to effects on human bodies".[17] When examining environmental laws governing toxic substances like endocrine disruptors, an approach recognizing that

[15] Government of Canada, "Government of Canada is Working to Improve Canada's Law on Pollution Prevention and Toxic Chemicals, the Canadian Environmental Protection Act, 1999" (29 June 2018), press release, online: https://www.canada.ca/en/environment-climate-change/news/2018/06/government-of-canada-is-working-to-improve-canadas-law-on-pollution-prevention-and-toxic-chemicals-the-canadian-environmental-protection-act-1999.html

[16] Canada's Follow-Up Report on CEPA 1999, June 2018, at 34-35.

[17] Max Liboiron, Manuel Tironi & Nerea Calvillo, "Toxic politics: Acting in a permanently polluted world" (2018) 48:3 *Soc Stud Sci* 331 at 335. The sole citation for this claim is an article limited to examining the nuclear industry (Shannon Cram, "Living in dose: Nuclear work and the politics of permissible exposure" (2016) 23:3(80) *Public Culture* 519). The three co-authors then appear to qualify their claim, temporally if not jurisdictionally, writing that "almost all environmental laws developed *since the 1970s*" are based on these thresholds; at 335. I note these ahistorical and universalized claims not to single out these authors – other STS scholars also make unfounded claims about law – but to emphasize that interdisciplinary work on toxicity, and its interactions with law, benefits from careful study of legal and regulatory processes and practices. For example, though this can also be empirically debated, Dayna Nadine Scott allows space for varied regulatory practices by making the more insightful, nuanced claim that "all of our current regulatory regimes are based *on the notion* of a threshold"; Scott 2015 at 387 (emphasis added).

governance and law are contingent, mutable achievements would instead examine ways that regulatory practices intervene in and produce variable dose-response relations or thresholds.

While this point can only be sketched summarily here in this conclusion – more definitive claims would require careful, empirical research and analysis – there appear to be parallels between how Canada regulated estrogen in the 1940s and current federal regulation of endocrine disrupting chemicals. The *Canadian Environmental Protection Act, 1999* ("CEPA") is the primary legislation governing the assessment and regulation of toxic substances,[18] and central to CEPA's toxics scheme is a legislated test for determining if a substance is "toxic".[19] That toxicity test fundamentally relies on dose-response logics (although not necessarily conventional ones), by providing that a substance is only harmful to the environment or to human life or health if it is entering or may enter the environment in a quantity, concentration, or under conditions that make it harmful. In other words, to determine if a substance is toxic, Canadian assessors must consider *how much* or *what amount* of a substance is sufficient to make it harmful – that is, what dose makes the poison. Yet the legislation is silent on the question of "how much is safe", disavowing any quantitative thresholds and leaving this question to varied administrative practices.[20] Evidence of exposure quantities and concentrations is scant or speculative, particularly for exposures through consumer products (which, unlike some industrial point sources, are not monitored under the act). With the question of "how much" Canadians are exposed to an endocrine disrupting chemical made very difficult to answer, administrators are left to their own discretionary practices to determine how to perform an exposure-response assessment. This resonates with the historical case in this thesis. For National Health's endocrinologist, relatively high potency estrogenic creams did not have systemic effects because the amount of exposure could be hypothetically limited through labels; for National Health enforcement officials, a relatively low potency estrogenic cream was deemed to have systemic effects because it was intended to grow mammary tissue. Current Canadian practices for regulating endocrine disrupting chemicals appear steeped in the same potent mixture of imperceptible exposures, uncertain thresholds, and dose-response logics: in determining if a substance is toxic, assessors faced with the *absence* of any pre-determined safe thresholds enact multiple, varying, discretionary administrative practices to apprehend how much of a substance is harmful, how much is released, or how much Canadians are exposed.

[18] *Canadian Environmental Protection Act, 1999*, SC 1999, c 33. Part 5 of CEPA governs the control of toxic substances.

[19] *Ibid,* s 64.

[20] For clarity, I do not take a view here on whether quantitative thresholds are normatively preferable, but merely explain s 64.

Just as National Health officials in the 1940s and 1950s turned to labelling to grapple with exposures to unstandardized potent substances, today, well-intentioned advocates and academics posit that, in the absence of regulatory prohibitions on endocrine disrupting chemicals, labelling can serve as a stop-gap or a band-aid.[21] This recalls the position that Dr. Henderson and his academic colleagues on the Canadian Committee on Pharmacopoeial Standards enacted, in January 1943, when they abandoned a call for regulated potency standards in exchange for National Health's promise to circulate information about bioassay methods, including to researchers.[22] Yet enacting endocrine disrupting chemicals as entities for which consumers and researchers need "more information" may buttress the Canadian government's plans to postpone legislative reform by promoting labels, and other technological fixes, to help (women) consumers navigate their own safety in the marketplace.

This thesis has experimented with a concept that I have called toxic enactment. It conceives regulatory practices as actively involved in enacting toxicity, and toxic substances as actively involved in enacting legal orders. In musing about whether toxic enactment helps to make better sense of the world – whether that world is in the past, the past folded into the present, or in possible futures – I do not wish to exaggerate its potential. One concern with using the concept, at least in the field of legal history, is that it potentially reifies the problematic idea that 'theory" is the *only* legitimate means of producing scholarly knowledge. Compelling, well-researched accounts of the legal past can have value regardless of whether they engage directly with theoretical constructs. Perhaps this study did not need to tinker with Mol's concept of enactment, toxic or otherwise, to describe how estrogen emerged with evolving modes and techniques of drug and cosmetic regulation in Canada in the mid-20th century.

Conversely, enactment has given me a unique entry point into understanding this topic and constructing this narrative. The historiography of sex hormones, particularly in the work of Nelly Oudshoorn, Anne Fausto-Sterling, Celia Roberts, and Jean-Paul Gaudillière, often builds, if to different extents, on network theories, examining how interactions between the material and discursive practices of scientists, industry, clinicians, and other social actors materialized estrogenic drugs. Other regulatory histories of sex hormones, such as that by Nancy Langston,

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[21] Environmental Defence Canada, "Full Disclosure: the case for stronger household product labelling – Full Research Report" (Environmental Defence, 2017), online: https://environmentaldefence.ca/report/full-disclosure/; and Endocrine Disruptors Action Group, "Toxic by design: Eliminating harmful flame retardant chemicals from our bodies, homes, and communities" (Endocrine Disruptors Action Group, 2006), online: https://endocrinedisruptorsaction.org/2016/10/11/toxic-by-design/.

[22] Endocrine Disruptors Action Group, *ibid,* at 17: "Although labelling is a limited solution to a flawed regulatory system, it may help us track and advocate against the ongoing substitution of one harmful chemical for another. What labelling can do is provide researchers, consumers and organizations with data … labels can be a tactical way to monitor the activities of manufacturers and gather data…".

provide crucial insights without explicit reference to theory, using source material evidencing the deliberations and activities of federal food and drug regulators. By extending a focus on networked practices to regulators and regulation, while still attempting to hold onto how estrogen materialized through material practices like diverse bioassay methods, varying forms and modes of application, and different labelling practices, toxic enactment has helped me to bridge potent methodological elements from these multiple historiographical traditions with my largely regulatory source materials. Following Gaudillière, this bridge has allowed me to narrate a more integrated history of estrogen and regulation, unlocking fresh ways of approaching each.

Furthermore, if one takes seriously, as I do, Mol's argument that it is possible to approach ontological questions empirically in social science and humanities research, and that relational materialism is more of a methodological commitment than a theoretical explanation, then I believe it is no great leap to conclude that (toxic) enactment can be a productive framework for empirical legal research, including in legal history. While the term enactment may have been popularized by an ethnographer, archival documents are just evidence of past human activities, and there is no principled reason that legal historians cannot adopt praxiological methodologies.

If anything, the larger challenge is thinking law and materiality together. As Tom Johnson notes, despite the suspect politics of severing law from the world, law is still "commonly seen as a discourse, something that is distinct from, yet gives meaning to, things in the 'real world'." However, for at least some topics, close readings of certain types of historical evidence can reveal law's material formations and matter's legal forms. Holding together matter and law – or, even more tightly, potency and power – subverts insistent representations of toxicity as "wayward particles behaving badly",[23] allowing us to approach toxicity as "a way to focus on how forms of life and their constituent relations, from the scale of cells to cultures, are enabled, constrained, and extinguished within broader power systems".[24] In this way, toxic enactment might potentiate efforts to apprehend and intervene in the chemical reactions of law and toxicity.

For scholars of public law or the regulatory state, enactment may no longer feel like a theoretical concept. The metaphor has been literalized in law, much like "constitution". Many lawyers and legal scholars think of enactments as concrete nouns – statutes and regulations, physically printed in books or from websites, rules that you hold in your hand. Long buried is the sense of enactment as an abstract noun — an activity that is made to happen and that makes other acts happen. As Mol puts it, to speak of objects being enacted in practices "suggests that

[23] Max Liboiron, Manuel Tironi & Nerea Calvillo, "Toxic politics: Acting in a permanently polluted world" (2018) 48:3 *Soc Stud Sci* 331 at 333.

[24] *Ibid* at 336.

activities take place – but leaves the actors vague. It also suggests that in the act, and only then and there, something *is* – being enacted".[25] In law, enactments as statutes and regulations can seem like codified, calcified, captured objects, rather than dynamic things, performed in practices, which themselves activate new actions, practices, and realities. By re-apprehending laws and regulations as enactments compounded in relational practices, rather than as separate and static elements, perhaps we can begin to see the possibility of formulating other worlds.

[25] Mol 2002 at 32-33.

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