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CONNECTING PRE-MARKETING CLINICAL RESEARCH AND MEDICAL PRACTICE

Opinion-based Study of Core Issues and Possible Changes in Drug Regulation

Nicolien F. Wieringa
Jules L. Peschar
Petra Denig
Pieter A. de Graeff
University of Groningen

Rein Vos
Maastricht University

Abstract

Objectives: To identify core issues that contribute to the gap between pre-marketing clinical research and practice as seen from the perspective of medical practice, as well as possible changes and potential barriers for closing this gap.
Methods: Interviews with 47 physicians and pharmacists who were liaised to drug regulation through their role in the pre- and post-marketing shaping of new cardiovascular drugs. Data were analyzed using methods of grounded theory and analytical evaluations.
Results: Six core issues were identified that referred to the standards in drug regulation, the organization of the regulatory system, and conflicting interests. Pre-marketing trials should focus more on populations and research questions relevant to medical practice. In particular, variability in drug responses between subgroups of patients and demonstration of effectiveness should become major principles in drug regulation. An interactive post-marketing process in which public interests are represented was considered necessary to further guide research and development according to the needs in daily practice. Strategies for change could be applied within the present system of drug regulation, or affect its basic principles. Regulatory authorities were primarily identified to initiate changes, but many other parties should be involved. Barriers for change were identified regarding differences in interests between parties, organizational matters, and with respect to broader healthcare policies.
Conclusions: Based on the respondents' opinions, there is a need to focus regulatory standards more on the needs in medical practice. Therefore, regulatory authorities should further develop their influence in the pre- and post-marketing drug development process, together with other parties involved, in order to bridge the gap between clinical research and medical practice.

Keywords: Drug approval, Drug policy, Cardiovascular drugs, Qualitative evaluation, Professional practice

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Assessment of the efficacy and safety of new drugs in randomized controlled trials forms the basis of drug registration. New drugs are tested in short-term trials with limited numbers of selected patients (25). Elderly patients, female patients and patients with comorbidity are often excluded from pre-marketing trials, for example, in the case of cardiovascular drugs (48;50). The selection of homogeneous trial populations is often justified by the need to enhance the internal validity of clinical trials, but as a result limitations in the generalizability and applicability of results from clinical trials to daily medical practice emerge (32). The question of to which groups of patients the results of clinical trials can be applied reflects a key topic in evidence-based practice.

To obtain marketing approval, the efficacy and safety of new drugs are tested according to legal requirements and scientific standards (13). These regulations and requirements have a major impact on the research and development of new drugs. Therefore, regulatory authorities take a role in the broader reorientation of medicine towards patients' needs and interests (44). Since 1995, the inauguration of the European Medicines Evaluation Agency (EMEA) ensures a homogeneous regulatory policy throughout the European Union (19). According to this harmonization, pharmaceutical companies can apply only once for marketing authorization. Harmonization was reached on requirements for approval, for example, about the nature of specific (pre-)clinical studies. Additionally, many guidelines were produced containing recommendations, for example, regarding trial methodology, such as the inclusion of elderly patients. The new regulatory system also provides harmonization in drug information. Since 1995, this includes publication of European Public Assessment Reports (EPARs) on the Internet for all drugs approved by the centralized procedure. To increase transparency about drug registration, EPARs provide a summary of the clinical trials used as a basis for approval. Also, the reasons for granting market approval are outlined (37). Regulations about new drugs extend into the post-marketing period. In particular, requirements for post-marketing surveillance have been developed in order to overcome methodologic limitations to identify adverse effects prior to marketing. Therefore, pharmaceutical companies are required to collect data about adverse effects from daily practice and inform the regulatory authorities about the findings.

A critical issue in the assessment of benefits and risks of drugs by regulatory authorities is the consideration that these properties have to be extrapolated to patients in medical practice who may have other characteristics than the patients included in pre-marketing trials. Information on this issue for practitioners and patients is provided in the summary of product characteristics and leaflets as precautions and measures to guide drug utilization. Furthermore, pharmaceutical companies promote the prescribing of new drugs by communicating the advantages and handling the risks. Above all, advances in medical science and practice form a constantly changing context in which new drugs have to be embedded. In particular, the development of evidence-based medicine and its application in practice guidelines have emphasized the need to establish the true value of therapies in daily practice (52). Generally, it is recommended that doctors limit prescription of new drugs until post-marketing safety data have accumulated and there is evidence of clinical and cost-effectiveness from large-scale data (27). Limitations in the applicability of trial results to medical practice thus demonstrate a gap that is relevant for all parties involved.

In the present study we focus on the gap between pre-marketing clinical research and medical practice in the context of drug regulation. We performed a qualitative study that aimed to identify the various opinions and ideas held in medical practice about this subject. Questions addressed are what is seen as: a) core issues regarding the gap between pre-marketing research and medical practice; b) possible changes in the process of drug regulation to bridge this gap; c) potential barriers to change; and d) possible actors involved in such changes. For this purpose, we selected physicians and pharmacists who were involved in one or more activities that are liaised to drug regulation, such as clinical research or

assessment of new drugs for treatment guidelines. This selection ensured that the interviewees were knowledgeable about the drug regulation process and/or the merits and limitations of pre-marketing research. Their opinions are expected to be relevant to regulatory authorities, pharmaceutical companies, clinical researchers, practitioners, and policy makers.

This paper is part of a larger study that focuses on discrepancies regarding age and sex distribution and patterns of comorbidity of patients involved in phase III pre-marketing trials and patients in daily practice using cardiovascular drugs (47;48;49;50). Because of this focus on cardiovascular drugs, all interviewees worked or were specifically interested in the cardiovascular field.

METHODS

Data Collection

Selection of Drug Class. Cardiovascular drugs were chosen for the study at large because they are widely used by younger and older patients, of whom the latter often present with comorbidity and comedication (38). Furthermore, there is an increasing prevalence of cardiovascular diseases among elderly female patients (51). Additionally, the cardiovascular field is subject to intensive research and thus forms an interesting area to study issues in drug regulation.

Selection of Respondents. During the period November 1998 to June 1999, interviews were held with 32 physicians and 15 pharmacists who were involved in various activities that are liaised with drug regulation. Selection criteria for the physicians were involvement in the development of national, regional, or local treatment guidelines or formularies, or in clinical research in the cardiovascular field. For the hospital and community pharmacists, the criteria were involvement in hospital or primary care drug and therapeutic committees and special interest in cardiovascular drugs. Cardiologists, specialists in internal medicine (internists), general practitioners (GPs), and community pharmacists were identified through key informants and publications. The hospital pharmacists were selected from the same hospitals as the specialists, which included six academic teaching hospitals and four regional hospitals throughout the Netherlands.

Fifty persons were asked to participate, of whom an internist, a cardiologist, and a GP refused because of time constraints. Five respondents (one cardiologist, two internists, and two GPs) were not involved in patient care. One of the physicians and three pharmacists were female. The mean age of the physicians was 51 (range, 37–62) and of the pharmacists, 42 years (range, 32–58). Professional affiliations and key characteristics of the respondents are shown in Tables 1 and 2. Information about the respondents' acquaintance with EPARs was available for 39 interviewees.

Interview Procedure. All interviews were conducted by the principal investigator (NW) at the offices of the respondents and varied in duration between 45 and 90 minutes. The interviewer had no affiliations to any of the respondents. In the semi-structured interviews, the issue of the gap between research and practice was addressed in general using data about discrepancies that were found in former parts of the study (48;49;50). The issue was also addressed in relation to specific case examples, for which two recently marketed cardiovascular drugs were selected (47). In these parts of the interview, a set of predefined questions was used. Following these questions, in both sections of the interview, open questions were used to elicit the personal views of the respondents about drug regulation. The subjects that were raised by the respondents and their ideas about possible changes were further explored. They were not asked to consider the economic implications of their proposals.

Table 1. Professional Affiliations of 47 Interviewed Physicians and Pharmacists

	Academic teaching hospital	Nonacademic hospital	Primary care practice
Internists[a]	9	3	
Cardiologists	7	3	
General practitioners	4		6
Hospital pharmacists	6	4	
Community pharmacists			5

[a]One internist worked primarily at a pharmaceutical company.

Table 2. Key Characteristics of Respondents

	Physicians (n = 32)	Pharmacists (n = 15)
Involvement in pre-marketing clinical research	20	9
Involvement in development of treatment recommendations or therapeutic committees	16	12
Present or past affiliation with regulatory authorities	2	1
Acquaintance with European Public Assessment Reports[a]	6	3

[a]Data missing for seven physicians and one pharmacist.

Methods of Analysis

The interviews were audiotaped and typed verbatim. The recording of two interviews failed, and for these cases notes were taken directly after the interviews. The transcripts of the interviews, and the case notes of these two interviews, were used for analysis. All statements concerning drug regulation were collected from the interviews by the principal investigator. This material was analyzed by two researchers, NW and JP, the latter being an experienced sociologist in the field of methodology and education. NW developed the analytical framework for data presentation. At various stages of development, both researchers reflected on this developmental process and the interpretation of data (4;28). Differences in opinion were worked out through discussion and reaching consensus.

Since there is no agreed-upon methodology to be applied, insights were used from two different approaches. First, data were analyzed using the grounded theory paradigm (41). A grounded theory is inductively derived from the data, without a pre-defined framework (30). During analysis the data were examined, for example, about the nature of the themes and issues regarding drug regulation the respondents were talking about. Thus, a cyclical process of coding and constant comparison of data was used to understand mechanisms in drug regulation that, according to the respondents, contribute to the gap between pre-marketing research and medical practice. This analysis generated six issues related to three different themes. Three issues were related to the regulatory requirements and standards, one was related to the basic principles of the current regulatory system, and two were related to possible conflicting interests between various parties involved.

In the second step, we applied our experience with so-called analytical evaluations (33). This methodology uses "reconstruction" as an analytical tool to identify changes and barriers to change in social systems. Using this procedure, the regulatory process, as seen by the respondents, was "reconstructed": which aims are to be achieved, which means are available, including organizational structures and actors, and which changes are needed? Therefore, the data were intensively scanned with regard to issues, actors, and barriers to change that regulate the actors' and organizations' behavior.

The two procedures were combined to triangulate the analysis. In both analytical procedures, the aim was to identify all different opinions. Respondents focused on different aspects of drug regulation, according to their varying professional backgrounds.

RESULTS

Core Issues, Aims, Actors, Changes, and Barriers

The six core issues regarding drug regulation are presented in the following section, including proposed changes, aims, actors, and potential barriers to change. The first three issues relate to regulatory requirements and standards, the fourth to the basic principles of the regulatory system, and the fifth and sixth to possible conflicting interests between parties involved. A summary of the results is provided in Tables 3 and 4.

1. ***Pre-marketing clinical trials are not sufficiently focused on patient groups and research issues relevant to medical practice***. The respondents distinguished two mechanisms that contribute to the lack of focus of pre-marketing trials on populations relevant to daily practice. First, the nature of trial design and performance generally leads to exclusion of subgroups that represent relevant patients in daily practice. Second, it was recognized that requirements for pre-marketing research are necessarily limited, because it was not considered reasonable to expect that all aspects of a drug can be studied prior to marketing. However, at the same time this means that there are insufficient data to use a new drug to its full extent. The following changes were suggested to meet these problems. In particular, pharmaceutical companies that design and conduct trials and regulatory authorities who set requirements should play a role to achieve the proposed changes.

Research Goals. The general opinion was that research questions concerning new drugs should focus more on patients and issues that are relevant in medical practice. It was suggested that the formulation of research questions could be more theory-driven than standard-driven. Also, large-scale efficacy and safety trials should allow for more basic mechanistic research questions to be answered. Comparative trials and determination of the contribution of a new drug in the context of multiple interventions, both lifestyle and therapeutic, were expected to become increasingly relevant. Redundancy of research should be limited, for example, on new drugs that belong to classes where a large body of knowledge already exists.

A barrier to changing the direction of clinical research was seen in the different interests between pharmaceutical companies and medical practice. It was noted that certain research, such as comparative studies or studying age-related differences of drugs, will not be performed unless the FDA requests it. On the other hand, it was also recognized that pharmaceutical companies need to study various patient populations if they want their products to be accepted by medical practice.

Patient Selection. Defensive patient selection based on the exclusion of risk factors such as fertility, older age, or comorbidity was recognized by the respondents as an important limitation of phase III trials. It was suggested that selection criteria should represent the patient groups that will use the drug in daily practice, based on epidemiologic data. Ethics committees should critically evaluate patient selection criteria, because it was considered unethical to design a clinically relevant study but to use defensive inclusion. Training of researchers was suggested to increase the inclusion of more complex patients into trials.

Studying elderly patients was not thought to have a large impact on the pre-marketing time frame. Therefore, regulatory authorities should strictly adhere to guidelines for research in elderly. Upper age limits should be abolished, or at least be considerably higher than 65 years in order to include more elderly patients. It was noticed that a shift is taking place

Table 3. Summary of the Core Issues, Aims, Actors and Proposed Changes to Bridge the Gap Between Pre-marketing Clinical Research and Medical Practice

Core issues and aims of proposed changes	Actors	Proposed changes
1. Trial design and performance lead to exclusion of subgroups of patients relevant to medical practice. Pre-marketing research is inevitably limited, but at the same time insufficient to use new drugs to the full extent. Proposed changes aim to increase the focus of pre- and post-marketing clinical research on issues and subgroups that are relevant in medical practice.	Regulatory authorities	Stimulate necessary research and limit redundancy Adhere to guidelines for inclusion of subgroups in trials Promote safety research in high-risk populations Develop requirements for post-marketing research and involvement of other parties Promote independent post-marketing research
	Pharmaceutical industry	Define research goals on other target populations Formulate research aims more theory than standard driven and include mechanistic research aims Develop less defensive patient selection criteria Extend research setting to primary care Analyze possible differences between subgroups with various characteristics
	Ethics committees	Critically evaluate selection criteria prior to conduct of trials
	Clinical investigators	Training of researchers to include more complex patients Training and certification of clinical researchers in primary care
	Practice researchers	Systematic collect and analyze data on utilization of new drugs in daily practice Develop methodology for analysis of data from practice databases
2. Cardiovascular drugs are approved on effects on surrogate endpoints, whereas the basis for patient treatment in practice refers to effectiveness on clinical endpoints. Proposed changes aim to develop regulatory policies to include demonstrating effectiveness on clinical endpoints.	Regulatory authorities	Develop requirements for conditional approval until clinical effectiveness is demonstrated Differentiate between drugs in classes with or without validated endpoints
	Professional organizations	Promote prescribing of products with proven long-term effectiveness

3. When drugs are prescribed for unapproved indications (off-label use), efficacy and safety have not been assessed. Proposed changes aim to develop policies to increase regulatory influence.	Regulatory authorities	Request safety documentation when off-label use can reasonably be expected
		Request documentation on unapproved indications and under-researched subpopulations for assessment
	Healthcare authorities	Limit reimbursement to approved indications
	Practitioners	Compile documentation on unapproved indications for assessment by regulatory authorities
	Professional organizations	Educate about the risks of off-label prescribing
4. Dutch and European regulatory authorities have limited possibilities for steering research and development of new drugs. Proposed changes aim to develop tools to guide research and development from the perspective of medical practice.	Regulatory authorities	Guide trial design to better focus on target populations in medical practice and consistent reporting on excluded or under-researched groups
		Develop criteria for definite registration involving requirements for post-marketing research following conditional approval
5. The confidential nature of assessment and decision making about drug registration limits the possibilities to verify the quality of the process. Proposed changes aim to improve public accountability of regulatory authorities.	Regulatory authorities	Develop policies for public debate, hearings, expert meetings, and voting in the process of drug approval
		Involve leading scientists in defining requirements for drug approval
6. Practitioners lack information to evaluate new drugs for application in practice. Proposed changes aim to increase awareness among practitioners about the limitations of pre-marketing research and provide tools to define which subgroups of patients are most likely to benefit from drugs.	Regulatory authorities	Provide more specified information, for example, about daily defined doses, or populations in-and excluded in trials
		Provide information about mechanisms and analyses in relationship to differences and equivalence in efficacy and safety in subgroups of patients
		Develop standardised formats to inform about relative and absolute benefits and harms of drugs
	Professional organizations and healthcare authorities	Always report the criteria used for therapeutic evaluations
		Increase the availability of independent continuing medical education

Table 4. Perceived Barriers to Change

Perceived barrier regarding:	Nature of the perceived barrier:
Changing the direction of clinical research	Different interests between pharmaceutical companies and medical practice in performing certain research
Including more elderly in trials	Larger time investment of researchers Unwillingness of elderly patients to participate
Developing research in primary care	Lack of research infrastructure and facilities in primary care, leading to logistically complex cooperation between primary and secondary care researchers
Developing requirements for post-marketing research	Public or private responsibility for funding of post-marketing research
Developing requirements to demonstrate clinical effectiveness	Within one class, approval of products according to different standards Balancing new requirements with realistic opportunities to earn back investments Balancing research to demonstrate clinical effectiveness with research into mechanisms of such effects
Increasing involvement of experts on behalf of regulatory authorities	Low status of the work and possible insufficient budgets
Developing strategies for steering research and development of new drugs	Inconsistencies between policies for stimulation of innovative research, requirements for drug approval, and reimbursement policies

toward higher inclusion of elderly in trials. A practical barrier was seen in the unwillingness of the elderly to participate, but other respondents noted the opposite.

Trial Setting. Pre-marketing clinical research should focus more on patients in primary care. To achieve this, training and certification of primary care physicians is required. A barrier to the development of research in primary care settings was observed in lacking infrastructure and facilities. Also, involvement of many GPs is required to match the number of patients who can be included through one outpatient clinic.

Analysis. Trial size is an important parameter for statistical power to study differences between subpopulations with varying effect-modifying factors such as age, sex, ethnic origin, comorbidity, or comedication. Applying experience from geriatrics in dealing with comorbidity and comedication in trial design and analysis to other research fields was considered useful. A number of suggestions were made to increase the learning from trials: a) meta-analysis of data from phase III trials, if justified methodologically; b) design of trials on differences between effect-modifying factors; and c) subgroup analyses in phase IV post-marketing trials when larger numbers of patients can be included.

Timing of Research. Respondents acknowledged that barriers to drug approval should not increase, but more emphasis should be put on post-marketing research. Also, some research, such as focusing on long-term use or withdrawal of medication, may not be feasible on beforehand, and should be performed after marketing. The following suggestions were made regarding post-marketing research:

- Improvement of systematic collection and analysis of efficacy and safety data, especially in subgroups excluded from pre-marketing trials. Protocols should standardize data collection, but can be lean in comparison to those used for double-blind trials.
- Further development of methodology for scientific analysis of patient data from large practice-based registrations.
- Stimulation by regulatory authorities that pharmaceutical companies perform safety studies in high-risk populations under well-controlled circumstances. Prior agreement should be reached about the

terms under which a safety profile could be acceptable. As a result, relevant data would become available without condemnation of the product.

- Involvement of representatives from medical practice, in addition to the pharmaceutical company and regulatory authorities, in the planning and evaluation of post-marketing research.
- Performance of independent post-marketing research, including surveillance of adverse effects.

A perceived barrier to developing requirements for post-marketing research was observed in funding. Some respondents argued that post-marketing research should be publicly funded if it is considered relevant for medical practice. Others were of the opinion that post-marketing research is an inextricable part of drug development, and practice-oriented research is also the companies' responsibility.

2. *Cardiovascular drugs are registered on the demonstration of effects on surrogate endpoints, such as blood pressure or cholesterol lowering, whereas patient treatment in medical practice is based on effects on clinical endpoints (morbidity and mortality).* We found general agreement that demonstrating effects on clinical endpoints, also referred to as studying effectiveness, should be a main issue in drug regulation. Several ideas were presented to improve the availability of clinical endpoint data, in particular of innovative therapies.

Ideally, effectiveness data should be present when marketing approval is granted, but this was generally not considered a realistic requirement. A differentiation in strategy was suggested for innovative and me-too products. An innovative product could be accepted without clinical endpoint data to meet needs in health care, but this argument would not apply to later products of the same class, in which case effectiveness should be documented prior to marketing. Different opinions existed regarding the need to demonstrate effectiveness for all cardiovascular drugs. It was thought to be reasonable to request effectiveness data when applying for reimbursement of preventive medicine, although this may lead to redundant research. In contrast, other respondents argued that the principle of class effects should be applied, and demonstration of equivalence with drugs with proven endpoints should be sufficient.

A strategy that was suggested to stimulate clinical endpoint studies is to request such studies conditional to granting initial marketing authorization.[1] Conditional approval should include requirements on the nature and planning of post-marketing research. Final registration is subsequently granted on disease-related and total morbidity and mortality data. The use of this strategy was exemplified by the initial approval of a cholesterol-lowering statin in Sweden. At that time, the company was requested to substantiate its long-term effectiveness. As a result, long-term studies were performed, and also research into models showing effectiveness within a relatively short time-span was highly stimulated.

With respect to the prescribing of new cardiovascular drugs, it was suggested to limit their prescribing until effectiveness data are present, a strategy that could be advocated by professional organizations.

Three limitations regarding the feasibility of the proposed changes were observed. First, an important question was raised about the introduction of new, far-reaching requirements, such as conditional approval. New products within existing classes would be marketed according to different requirements, thus leading to unequal competition with the older products. Second, it was mentioned that changes in requirements for research should be balanced against realistic opportunities for companies to earn back investments. Last, it was noticed that it might not be easy for regulatory authorities to find a balance between the commercial and scientific aspects of requirements. From a company's point of view, it is important to know whether an investment will be marketed if certain requirements have been met, whereas from a scientific point of view, research into mechanisms is relevant but more difficult to translate into requirements because of ongoing advances in medical science.

3. ***Drugs can be prescribed for unapproved indications, so-called off-label use. Regulatory assessment of the efficacy and safety of the drug in this situation has not been performed***. Different types of off-label use were recognized. First, products may be prescribed for unapproved indications where other products of the same class were granted approval. The second type refers to the prescribing of products for an indication without approval for any of the products from the same class. An example of the latter was recognized in the prescribing of losartan for heart failure. This first representative of the class of angiotensin-II antagonists was approved for hypertension only. Because of its resemblance to the class of ACE inhibitors, of which some products have also been approved for heart failure, it has been prescribed in the same way. It was suggested that in such situations where regulatory authorities can reasonably expect off-label use to occur, they should at least request to document the safety of the drug in patients with that indication. Additionally, it was thought to be reasonable for regulatory authorities to request a pharmaceutical company to substantiate a particular indication for assessment following certain developments in medical practice. Requirements to improve regulation of unapproved drug use were considered very important to balance situations where interests of pharmaceutical companies restrain conducting such research.

It was recognized that off-label prescribing occurs frequently in the Netherlands. Professional organizations were thought to play an active role in educating practitioners about the risks of off-label prescribing. Furthermore, the following strategies were suggested:

- Limit reimbursement of drugs to approved indications. This approach may positively stimulate companies to perform research into unapproved indications.
- Request medical and pharmaceutical specialists to substantiate a registration file with documentation on the efficacy and safety of unapproved indications and apply for assessment by regulatory authorities.

4. ***The current basic principles of the Dutch and European regulatory systems limit possibilities for steering research and development of new drugs***. At present, within the boundaries of European legislation, research and development involving new drugs are mostly directed by the pharmaceutical industry. For some issues, there is no basic principle included in the regulatory system. An example where respondents noticed a lack of steering possibilities for regulatory authorities refers to different strategies that are being used toward studies with children and pregnant patients, on the one hand, and elderly and patients with comorbidity on the other. When no research has been performed in the former groups, they are excluded as target populations for the use. It was suggested that developing comparable strategies for the elderly and patients with comorbidity might stimulate research into these patient groups.

The binary character of the decision regarding drug registration was considered not to be in concordance with the importance of post-marketing research and development of new drugs. Relevant issues can be defined at the moment of drug approval and may emerge during the further development of a new drug in medical practice and in advancing medical science. In both situations, it was considered desirable that regulatory authorities have opportunities to request additional research, other than pharmacovigilance, and assess the results under requirements of conditional approval.

Respondents noted that, from the perspective of practitioners, there is little need to market me-too products, but they observed little barriers for it. It was suggested that policy developments should focus on strengthening the dynamics of innovation, for example, by introducing requirements for post-marketing research of me-too products that aim to demonstrate the clinical relevance of claims of improvement, or identification of subgroups of patients that benefit most from the drug. A better balance should be found between

allowing a certain amount of me-too products to further develop in medical practice and stimulation of innovative research.

It was noted that the guidance of a process with multiple decisions requires different tools, strategies, and criteria than a system involving a single binary decision. Criteria for steering a developmental process imply valuation of this process and its outcomes, whereas for a single binary decision it is sufficient to assess only the outcomes of the process. Because of these differences, it was questioned whether guidance and assessment of research in the post-marketing phase should be performed by the same organization as the one performing the initial marketing approval. It was suggested that developments in drug regulation of this order may be feasible at a European level or may require transatlantic or global harmonization.

It was mentioned that an important aspect of developing strategies for steering research and development of new drugs is consistency of aims within the broad range of drug policies, involving the stimulation of innovative research, drug approval, and reimbursement strategies.

5. ***The confidential nature of assessment and decision making about drug registration limits the ability to verify the quality of the process***. Respondents expressed limitations in the present system, which is based on confidence in the expertise and independence of regulatory authorities. Transparency and public debate about requirements for approval were considered necessary to achieve a better connection with needs in medical practice. Also, debates, hearings, expert meetings, and voting should be made public. Current leading scientists should be involved in defining the body of knowledge that is required to guide drug registration. A barrier to increase the involvement of experts on behalf of the regulatory authorities was thought to lie in the low status of such work and possibly insufficient budgets. This implies that other resources need to be made available.

Respondents who compared characteristics of drug regulation between Europe and the United States attributed a higher level of professionalism and interaction with companies to the FDA. For example, it was stated that the FDA verifies many details of a registration file with the company during assessment. On the other hand, the high workload and possibly a limited capacity of regulatory authorities in Europe were also recognized.

It was noted that there is an inextricable network between the pharmaceutical industry and regulatory authorities. The position that all parties who genuinely strive for the development of innovative products would benefit from openness was not thought to be popular.

6. ***Physicians and pharmacists lack information (knowledge) to evaluate new drugs for application in daily practice.*** Professional organizations could increase awareness among practitioners about the limitations of pre-marketing research. Ideally, all data from clinical trials should be available for practitioners when new drugs are being marketed. Critical assessment of new drugs is relevant because of the increasing complexity of medicine. Therefore, articles in the Dutch Drug Bulletin should always report the criteria used to evaluate the therapeutic position of drugs. It was also noted that professional organizations and the government should undertake more efforts to increase the availability of independent continuing medical education.

A number of suggestions were given to improve the information about new drugs. Information in the summary of product characteristics (SPC, or document IB for drugs on the Dutch market) could be more specific to improve prescribing outside one's own area of specialisation. Information about subpopulations that were excluded from pre-marketing research and possible consequences for use in such patients is particularly useful when there is a rationale that data from trials may be less applicable to other patient groups (e.g., patients with comorbidity or patients of other ethnicities). The following changes were suggested to improve the applicability of trial data to medical practice:

- Provide information about the pathophysiologic mechanisms that characterize specific target populations and the relationships with differences in efficacy and safety of drugs;
- Provide information on analyses that were performed to study comparability or equivalence of effects between various subgroups of patients, such as between patients with and without comorbidity or patients of different ethnicity; and
- Develop a standardized format for presenting relative and absolute benefits and harms of drugs.

DISCUSSION

When asked about the gap between pre-marketing research and medical practice in the context of drug approval and regulation, the respondents in our study placed the issue in the broader perspective of drug development, clinical research, reimbursement, and prescribing. Our approach to interview medical and pharmaceutical practitioners, who were well-informed on different aspects of the drug regulation process, provided the opportunity to study core issues of the present system and possible changes.

This is an opinion-based study. One limitation is that we focused on views and opinions held in medical practice. The respondents were not explicitly asked to think about the economic implications of their proposals. Our results, however, will be discussed, together with views from regulatory authorities and the pharmaceutical industry, as found in the literature. Since this study was designed to identify the nature of different concepts that could be introduced in drug regulation in order to bridge the gap between research and practice, well-informed interviewees were selected. Their opinions should not be considered representative for all medical and pharmaceutical practitioners. The methods of analysis used in this study were selected for their suitability to identify ideas and concepts (33;41). It can be questioned how the choice of another drug class would influence the results. The cardiovascular field is highly competitive and subject to intensive research and debate, for example, regarding the limitations of surrogate endpoints for regulatory assessment (43). However, discrepancies between populations in research and practice were also found in other therapeutic areas (9;31;36;42;45). Also, only a limited part of our results refers to specific cardiovascular issues, whereas many general regulatory aspects were put forward. Therefore, it can be expected that the results of our study could contribute to the further development of the regulatory system at large.

Clearly, drug regulation is part of a complex system, not only involving policies and regulations at a national level, but also increasingly involving European and global regulations and developments. The interviewees recognized the complexity of the system and provided tools for a "reconstruction" of the process of drug regulation. Six core issues were identified that cover various fundamental aspects of the gap between pre-marketing research and medical practice. In general, these issues refer to the standards applied in drug regulation, the basic principles of the system, and conflicting interests.

From a historical perspective, Bodewitz et al. (5) have analyzed the origin and shaping of standards in drug regulation. They argue that during the 1960s, the interaction between regulatory authorities, the pharmaceutical industry, and medical scientists was essential in developing the scientific standards for drug registration regarding the quality, efficacy, and safety of drugs. At that time, a major shift in medicine was marked by the general acceptance of the double-blind controlled trial methodology as the scientific standard to demonstrate efficacy of drugs. This methodology was implemented in the process of drug regulation. Since then, the system has evolved, but this methodology still forms one of its basic principles.

An interesting question is why the gap between clinical trials and medical practice has become an important issue in medicine. The results of our study indicate that there is a need to focus the regulatory standards more on the present needs in medical practice. The

respondents raised two major subjects, i.e., variability in drug response and demonstration of clinical effectiveness. With respect to the first issue, it is well recognized that homogeneity of treatment groups may enhance the internal validity of trials but poses a problem to medical practice, where large variation exists between patients (26). Age, sex, ethnicity, comorbidity, and comedication are well known effect-modifying variables. Thus, an important debate within evidence-based medicine refers to defining subgroups of patients that are most likely to benefit from drugs (29). Increasingly, systematic methods are being developed and used in medical practice for applying evidence from trials to individuals and populations with other characteristics (32). These developments reflect important approaches in medical practice, aiming to bridge the gap between knowledge derived from clinical studies, and individual patient treatment. Within regulatory bodies, the need to study variability between patient groups has also been recognized. This has led to the approval of guidelines, for example, regarding the evaluation of differences in drug responses related to age in 1989 by the FDA, followed in 1993 by the EMEA (6;17). However, in the present European system, such guidelines have a nonobligatory status. The respondents of our study proposed a number of changes, including a shift in the focus of clinical trials on variability in drug responses and improvement of clinical information about variability.

The second issue, which was claimed to require a better implementation into regulatory standards, is the demonstration of effectiveness. The recognition that efficacy on surrogate endpoints does not necessarily lead to clinical benefit has fueled the development of evidence-based medicine and its application in treatment guidelines (16;24). Ongoing research, especially in the cardiovascular field, has shown that different relationships exist between surrogate endpoints and clinical effects, indicating the need for validation (15;43). Also, the expected increase in development and use of preventive medicine (35) illustrates the need, from the perspective of medical practice, to regulate the demonstration of effectiveness. At present, in a number of countries, policy developments have focused on the demonstration of cost-effectiveness, and the issue is linked to reimbursement regulations (23). The respondents in our study suggested that effectiveness should also be a guiding principle in drug approval, and several regulatory changes were proposed. A central aspect referred to a system of conditional approval prior to granting final registration on effectiveness studies. This concept differs from the present "approval under exceptional conditions," when marketing is granted without sufficient evidence of the quality, efficacy, or safety of the product according to guideline 75/318/EEG. This may be the case for orphan drugs. The concept of conditional approval, as proposed in our study, would involve the present requirements of evidence for initial marketing, followed by requirements for post-marketing research to demonstrate clinical effectiveness in relevant situations. Regulatory developments at present do not appear to be evolving in the proposed direction, since requirements for 5-year marketing authorization renewal will be abolished and replaced with tougher pharmacovigilance procedures (14). Furthermore, in our study it was suggested to accept the principle of class effects in order to reduce costly and redundant research. Although validation of surrogate endpoints, and demonstration of equivalence and class interchangeability are clearly complex issues (7;15;18), they are scientifically important and should be dealt with in terms of drug regulation in the pre- or post-marketing phase.

The results of our study suggest two strategies to achieve the proposed changes to improve the connection between pre-marketing research and medical practice: a) strategies that can be applied within the present system of drug regulation; and b) strategies affecting the basic principles of the present system. Regulatory authorities were identified as primary actors to initiate changes. Furthermore, the pharmaceutical industry, clinical investigators, ethics committees, practice researchers, governmental healthcare authorities, practitioners, and professional organizations need to be involved. A number of potential barriers to change

were identified. Dependent on the nature of changes in drug regulation that may be aimed for, these potential barriers need to be considered.

Strategies that can be applied within the present regulatory system typically involve policies aiming to increase the focus of clinical research on subgroups of patients relevant in practice. To improve adherence to research guidelines, a strategy for change may require a redefinition of the nonobligatory status of these instruments. Other suggested changes to optimize the present regulatory system aim to increase awareness among practitioners about limitations of pre-marketing research, improve information about new drugs, and limit the prescribing of new drugs. Within the present regulatory system, the EMEA is increasing communications with interested parties, such as consumer organizations. The public consultation on the procedure for transparency about opinions on applications forms an example (12). However, the differences in responses to the proposed procedure from various organizations, representing the pharmaceutical industry, healthcare providers, and patients, reflect the different positions in the field and may be indicative of the difficulties in balancing interests.

The second strategy introduces new basic principles to the process of drug regulation. One would be the introduction of an interactive post-marketing drug development process. This principle fits with the view that successful research and development of a new drug, leading to marketing authorization, form the beginning rather than the end of the developmental process. The history of medical innovation has shown numerous instances in which new indications have been discovered after drugs were marketed. Widespread use is often an essential precondition for the identification of new applications, and clinical practice itself is thus a particularly important source of medical innovation (34;46). From a methodologic point of view, pre-marketing trials include limited numbers of highly selected patients, which is not sufficient to fully reveal adverse drug reactions. Therefore, methodologic tools for pharmacovigilance become increasingly important (11). Additionally, clinical trials are designed to test a narrow hypothesis and consequently usually do not reveal unexpected benefits (20). These arguments imply that an important contribution to focusing drug research and development on issues relevant to medical practice lies in the post-marketing phase. However, apart from regulating post-marketing pharmacovigilance within the current systems, regulatory authorities lose their power to actively influence research and development after registration. The pharmaceutical industry has been criticized that its drive for profits can overshadow its social responsibilities, and a better balance between interests of shareholders and those of the public is needed (3). To achieve this, public interests need to be represented in defining the direction of post-marketing research.

An example of a public interest that is insufficiently met can be found in the lack of clinical trials in children, resulting in unapproved use (21;40). It has been claimed that companies are reluctant to conduct trials in children in particular because the pediatric population is considered to be of no commercial value (8). Also, they might be hesitant to expose a wide, vulnerable population to possible risks. To overcome this, regulatory authorities need tools that could force companies to conduct trials in populations that are generally excluded from research. An example is the extension of U.S. market exclusivity to encourage companies to conduct pediatric trials (40). From our study, it is concluded that such strategies should be developed in a broader context, including all off-label use.

The respondents in our study emphasized the importance of stimulating the development of innovative drugs over me-too products. Kanavos and Mossialos (22) argue that the present system of patent protection helps industry but may not necessarily encourage innovation. Therefore, strategies that enforce the conduct of innovative research may in principle be welcomed, although the pharmaceutical industry could also see this as increasing the

requirements that have to be met. Another position is that balancing pre- and post-marketing requirements may ease the burden to produce ever-increasing amounts of information prior to drug marketing. This was illustrated by Schmidt (39):

Information needed to approve a drug	+	Ability to get information after marketing	+	Ability to control usage after marketing	+	Ease of withdrawal of drug approval	=	A constant

Another fundamental principle to achieve the necessary changes is the development of a system in which more parties interact during the whole regulatory process, rather than just the regulatory authorities and pharmaceutical industry. This would include a more open exchange of information. To understand the origin of the confidential nature of European drug regulation, several researchers placed the development of legislation in its historical perspective, which is closely related to the development of modern pharmaceutical industry (5;10). A confidentiality clause was included in the 1962 law in the Netherlands to protect leaking of information from a manufacturer to its competitors. This Dutch model was often followed across Europe. The same argument opposing wider rights of access to information about drug testing and approval can be heard from industry nowadays (1). However, in the 1970s, drug regulators and safety experts expressed their concerns about the confidentiality of information, since they were unable to disclose data from registration files, which could have been helpful in cases of safety problems (10). In the course of history, many arguments have changed. At present, independent peer review is considered highly relevant for a reorientation of medical practice to scientific standards. In our study, the current lack of accountability of the regulatory authorities was clearly recognized as a problem.

In their study among representatives of regulatory authorities and pharmaceutical industries in Europe, Abraham and Lewis (1) showed that scientists from pharmaceutical companies themselves acknowledge that more freedom of information would benefit medical and pharmaceutical sciences. Their results suggest that increased openness is likely to stimulate innovative research and drug development, rather than to limit the developmental process. Another argument refers to the position of the European regulatory authorities. Openness would provide a forum in which they could increase their contribution to the medical debate with information about new drugs. This is likely to benefit medical practice. A positive aspect of openness and public accountability is an increased credibility of the regulatory authorities and pharmaceutical companies. Additionally, clinical researchers would become accountable for their contributions in the regulatory process (2).

Commitment of the EMEA to transparency is claimed by the introduction of EPARs on the Internet (37). EPARs and the Dutch NPARs include a summary of the clinical trials used as a basis for approval and reflect the considerations for granting approval. Providing this information is in itself a positive development, but based on our study it can only be valued in terms of a first step toward openness and public debate. Also, our findings revealed a substantial ignorance about the existence of EPARs. Because our interviewees were selected to be knowledgeable about the regulatory process, rather than to be representative for practice, our results can only be indicative of a low knowledge among practitioners of this source of information regarding new drugs.

POLICY IMPLICATIONS

The results of this study indicate that drug regulation should focus more on the needs in medical practice. This perspective is in line with the basic assumptions for drug regulation, which lie in protecting the patients' interests and facilitating safe and effective use of

drugs. It also places drug regulation in the broader reorientation of medicine involving the shift toward patients' needs and interests. The need for reorientation from a drug centered regulatory process toward a practice-oriented process is also recognized within the regulatory authorities (19;44). In particular, we recommend that regulatory authorities develop their influence on the post-marketing drug research process, together with other parties involved, to bridge the gap between pre-marketing research and medical practice.

NOTE

[1]This concept of conditional approval differs from the notice "approval under exceptional conditions" as defined in guideline 75/318/EEG.

REFERENCES

1. Abraham J, Lewis G. *Regulating medicines in Europe*. London: Routledge; 2000.
2. Angell M. Is academic medicine for sale? *N Engl J Med.* 2000;342:1516-1518.
3. Angell M. The pharmaceutical industry: To whom is it accountable? *N Engl J Med.* 2000;342:1902-1904.
4. Barbour RS. Checklists for improving rigour in qualitative research: A case of the tail wagging the dog? *BMJ*. 2001;322:1115-1117.
5. Bodewitz HJHW, Buurma H, de Vries GH. Regulatory science and the social management of trust in medicine. In: Bijker WE, Hughes TP, Pinch TJ, eds. The social construction of technological systems. Cambridge, Mass: The MIT Press; 1987:243-259.
6. Commission of the European Committee. *Studies in support of special populations: Geriatrics*. Brussels: European Community; 1993.
7. Committee for Proprietary Medicinal Products (CPMP). Points to consider on switching between superiority and non-inferiority. *Br J Clin Pharmacol.* 2001;52:223-228.
8. De Cremiers F. Proceedings of the 34th DIA Annual Meeting: Thinking globally: Product development, registration and marketing in the new millennium, June 7–11, 1998, Boston, Mass. *Drug Inf J*. 1999;33:585-600.
9. Diaz T, Chu SY, Sorvillo F, et al. Differences in participation in experimental drug trials among persons with AIDS. *J Acquir Immune Defic Synd Hum Retrovirol*. 1995;10:562-568.
10. Dukes MNG. Drug regulation and the tradition of secrecy. *Int J Risk Safety Med*. 1996;9:143-149.
11. Egberts ACG. *Pharmacoepidemiological approaches to the evaluation of antidepressant drugs*. University of Utrecht: 1997. Unpublished thesis.
12. EMEA. Outcome of public consultation on new EMEA transparency initiatives. Publication EMEA/D/16906/00. Available at: www.eudra.org/emea.html.
13. EMEA website. Available at: www.eudra.org.
14. English V. Networking at the EMEA. *Scrip Magazine*. 2001;10:41-45.
15. Fleming TR. Surrogate end points in cardiovascular disease trials. *Am Heart J*. 2000;139:S193-S196.
16. Fleming TR, DeMets DL. Surrogate end points in clinical trials: Are we being misled? *Ann Intern Med.* 1996;125:605-613.
17. FDA. *Guideline for the study of drugs likely to be used in the elderly*. Rockville, Md: Department of Health and Human Services; 1989.
18. Furberg CD, Herrington DM, Psaty BM. Are drugs within a class interchangeable? *Lancet*. 1999;354:1202-1204.
19. Garattini S, Bertele V. Adjusting Europe's drug regulation to public health needs. *Lancet*. 2001;358:64-67.
20. Gelijns AC, Rosenberg N, Moskowitz AJ. Capturing the unexpected benefits of medical research. *N Engl J Med*. 1998;339:693-698.
21. Impicciatore P, Choonara I. Status of new medicines approved by the European Medicines Evaluation Agency regarding paediatric use. *Br J Clin. Pharmacol*. 1999;48: 15-18.

22. Kanavos P, Mossialos E. Outstanding regulatory aspects in the European pharmaceutical market. *PharmacoEconomics*. 1999;15:519-533.
23. Kanavos P, Trueman P, Bosilevac A. Can economic evaluation guidelines improve efficiency in resource allocation? The cases of Portugal, the Netherlands, Finland, and the United Kingdom. *Int J Technol Assess Health Care*. 2000;16:1179-1192.
24. Kerridge I, Lowe M, Henry D. Ethics and evidence based medicine. *BMJ*. 1998;316:1151-1153.
25. Knottnerus JA, Dinant GJ. Medicine based evidence: A prerequisite for evidence based medicine. *BMJ*. 1997;315:1109-1110.
26. Leufkens HG, Urquhart J. Variability in patterns of drug usage. *J Pharm Pharmacol*. 1994;46(suppl 1):433-437.
27. Martin RM. When to use a new drug. *Australian Prescriber*. 1998;21:67-69.
28. Mays N, Pope C. Rigour and qualitative research. *BMJ*. 1995;311:109-112.
29. McAlister FA, Straus SE, Guyatt GH, Haynes B. Users' guide to the medical literature, XX: Integrating research evidence with the care of the individual patient. *JAMA*. 2000;283:2829-2836.
30. Miller SI, Fredericks M. How does grounded theory explain? *Qual Health Res*. 1999;9: 538-551.
31. Nadel MV. *Women's health: FDA needs to ensure more study of gender differences in prescription drug testing*. Washington, DC: US General Accounting Office; 1992.
32. O'Connell D, Glasziou P, Hill S. *How to use the evidence: Assessment and application of scientific evidence*. Canberra: National Health and Medical Research Council; 2000.
33. Peschar JL, Meijer CJW. *WSNS on track: The evaluation of the process of inclusion of special education into general education in the Netherlands*. Groningen: Wolters-Noordhoff; 1997.
34. Pieters T. *Biology meets drug development: The biography of a "miracle" drug, the interferons*. Maastricht University; 1999. Unpublished thesis.
35. RIVM. *Health care perspectives 2002: Background document—Medicines now and in the future*. Houten: Bohn Stafleu Van Loghum; 2001.
36. Rochon PA, Fortin PR, Dear KB, Minaker KL, Chalmers TC. Reporting of age data in clinical trials of arthritis: Deficiencies and solutions. *Arch Intern Med*. 1993;153:243-248.
37. Sauer F. European Medicines Evaluation Agency is ahead of national licensing authorities. *BMJ*. 1998;317:1078.
38. Schellevis FG. *Chronic diseases in general practice: Comorbidity and quality of care*. Katholieke Universiteit Nijmegen: 1993. Unpublished thesis.
39. Schmidt AM. The politics of drug research and development. In: Wechsler H, Lamont-Havers RW, Cahill GF, eds. *The social context of medical research*. Cambridge: Ballinger Publishing Group; 1981:233-262.
40. Schofield I. Regulators' response to public health concerns in Europe. *Scrip Magazine*. 2001;10:8-11.
41. Strauss AL, Corbin J. *Basics of qualitative research: Techniques and procedures for developing grounded theory*. 2nd ed. Thousand Oaks: Sage Publications, Inc; 1998.
42. Svensson CK. Representation of American blacks in clinical trials of new drugs. *JAMA*. 1989;261:263-265.
43. Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs? *JAMA*. 1999;282:790-795.
44. Toering DJ. Interview with the director of the Dutch Medicines Evaluation Board. *Pharmaceutisch Weekblad*. 2001;136:251-253.
45. Trimble EL, Carter CL, Cain D, et al. Representation of older patients in cancer treatment trials. *Cancer*. 1994;74:2208-2214.
46. Vos R. *Drugs looking for diseases: Innovative drug research and the development of the beta-blockers and the calcium antagonists*. Dordrecht: Kluwer Academic Publishers; 1991.
47. Wieringa NF, Denig P, de Graeff PA, Vos R. Assessment of the position of new cardiovascular drugs in the therapeutic regimen: Relationships between considerations, professional characteristics, and prescribing. *Int J Technol Assess Health Care*. 2001;17:559-570.
48. Wieringa NF, de Graeff PA, van der Werf GT, Vos R. Cardiovascular drugs: Discrepancies in demographics between pre- and post-registration use. *Eur J Clin Pharmacol*. 1999;55: 537-544.

49. Wieringa NF, Vos R, van der Werf GT, de Graeff PA. Inclusion of patients with co-morbidity and co-medication in pre-marketing trials of cardiovascular drugs. *Drug Develop Res*. 2000;51:159-168.
50. Wieringa NF, Vos R, van der Werf GT, van der Veen WJ, de Graeff PA. Co-morbidity of "clinical trial" versus "real-world" patients using cardiovascular drugs. *Pharmacoepidemiol Drug Saf*. 2000;9:569-579.
51. Witteman JC. *Women and cardiovascular diseases in the Netherlands*. Den Haag: Nederlandse Hartstichting; 1994.
52. Yusuf S, Teo KK. The gap between reliable evidence and adoption of therapies. *Eur Heart J*. 1999;20:637-638.