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Economics of Fixed-Dose Combination Drugs Approved in the United States

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ECONOMICS OF FIXED-DOSE COMBINATION DRUGS APPROVED IN THE UNITED STATES

A Dissertation Presented

by

JING HAO

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

September 2015

Public Health

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ECONOMICS OF FIXED-DOSE COMBINATION DRUGS APPROVED IN THE UNITED
STATES

A Dissertation Presented

by

JING HAO

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ABSTRACT

ECONOMICS OF FIXED-DOSE COMBINATION DRUGS APPROVED IN THE UNITED STATES

SEPTEMBER 2015

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Patent is the most important form of intellectual property protection for new drugs. Patent extension and market exclusivity currently serve as major regulatory incentives to promote new drugs. Combination drug, or fixed-dose combination (FDC) are formulations that contain two or more active ingredients in a single pill. FDCs, especially combinations of single drugs that are already in the market, are common strategy for brand-name drug companies to extend the patent and exclusivity life. The substitution of single drug products that soon have generic alternatives with newer, brand-name combinations lead to potential increases in pharmaceutical expenditures and raises concerns on economic burden. The study found that the effective patent life increased overtime during the past three decades; however the effective patent life length was not significantly associated with an increase in the number of approved new molecular entities (NMEs), which often represent innovative new drugs. Other incentives, besides the patent life, need to be considered as effective incentives to stimulate pharmaceutical innovations. The

findings support hypothesis that the number of FDC approvals increased overtime from 1980s to 2012, while the approval number of the NME and new therapeutic Biologics License Applications decreased during last decade. The findings also support hypothesis that the pharmaceutical company market FDC drugs shortly before the generic versions of the single ingredients enter the market extending the patent and marketing exclusivity life of drugs included in the combination. In regard to the economic concern of the FDC, the study found that the FDC average wholesale price (AWP) unit price increased significantly over time 1980-2012 and that pharmaceutical companies set FDC AWP, at the same level of the costliest single active ingredient in the combination as pricing strategy to shift demand from single active ingredients facing generic competition toward new FDC drugs. The price difference between FDC and single ingredient drugs varied by therapeutic class, the year the FDC entered into the US market and the number of single drugs in the combination that have generic drugs at FDC market entry.

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INTRODUCTION

Innovative new drugs are important to advance population health care by presenting new treatment options for patients. However, the number of innovative new drugs (estimated by drugs approved by the FDA as New Molecular Entity, NME) has decreased in the 2000s, compare to previous decades¹. The economics behind the pharmaceutical industry's new drug research and development (R&D) are complex, including considerations of patent life, market size, public funding, economics of scale of selected therapeutic classes, prevalence of disease, and status of scientific development, and these considerations do not necessarily always address the needs of patients^{2,3}. For example, given the growing public health threat of antibiotic resistance and calls for innovative new antibiotics, pharmaceutical companies are curtailing their R&D on innovative new antibiotics because of economic disincentives, i.e., that the profit return is low^{4,5}.

A patent is the most important form of intellectual property protection for new drugs. Under a patent, the brand-name drug pharmaceutical company can charge a high drug price and earn above-normal profit. When a patent expires, generic drugs normally enter the market and bring the medication price down. Earlier studies indicate that patent protection is important for

¹ Kaitin KI, DiMasi JA. Pharmaceutical innovation in the 21st century: new drug approvals in the first decade, 2000-2009. *Clin Pharmacol Ther.* 2011;89(2):183-8.

² Boots I, Sukhai RN, Klein RH, Holl RA, Wit JM, Cohen AF, et al. Stimulation programs for pediatric drug research--do children really benefit? *Eur J Pediatr.* 2007;166(8):849-55.

³ Love J. Pharmaceutical research and development and the patent system. *Int J Health Serv.* 2005;35(2):257-63.

⁴ Nelson R. Antibiotic development pipeline runs dry. New drugs to fight resistant organisms are not being developed, experts say. *Lancet.* 2003;362(9397):1726-7. Sonderholm J. Wild-card patent extensions as a means to incentivize research and development of antibiotics. *J Law Med Ethics.* 2009;37(2):240-6.

⁵ Sonderholm J. Wild-card patent extensions as a means to incentivize research and development of antibiotics. *J Law Med Ethics.* 2009;37(2):240-6.

advancing pharmaceutical innovations, and the absence of patent protection would affect the innovation efforts of pharmaceutical companies⁶.

Currently, both patent extension and market exclusivity serve as the focus of policy proposals and regulatory incentives to promote R&D by pharmaceutical companies⁷. For example, the Waxman-Hatch Act (WHA) enacted in 1984 allows sponsors of FDA-approved new drug applications (NDA) to recover the time that the FDA spent on the pharmaceutical application review and half of the patent time the sponsor dedicated to clinical trials and administrative activities required for FDA approval⁸.

Pharmaceutical companies use a variety of strategies, other than developing innovative new drugs, to extend patent and market exclusivity life of their products⁹. A fixed-dose combination (FDC) drug, which is the formulation of two or more active ingredients in a single tablet, is one example. A drug introduced for the first time in the US market as an FDC may contain only NMEs or a mix of NMEs and already-marketed products (i.e., NME & New Combination), or only already marketed products (i.e., New Combination). The use of combinations of products that are already marketed in the US has been a common strategy for brand-name drug companies to extend the patent and exclusivity life of individual drugs,

⁶ Cohen W, Nelson RR, Walsh JP. Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not). National Bureau of Economic Research. 2000. <http://www.nber.org/papers/w7552.pdf>. Accessed March 14th 2015.

⁷ Kesselheim AS. Using market-exclusivity incentives to promote pharmaceutical innovation. *The New England journal of medicine*. 2010;363(19):1855-62.

⁸ Grabowski H, Vernon J. Longer patents for increased generic competition in the US. *The Waxman-Hatch Act after one decade*. *PharmacoEconomics*. 1996;10 Suppl 2:110-23.

⁹ Bhat VN. Patent term extension strategies in the pharmaceutical industry. *Pharmaceuticals Policy and Law* 2005;6:109-22.

especially since implementation of the WHA, which lowered the barrier for generic entry^{10,11}. Importantly, over the last decade, prescribing patterns led to an increased utilization of FDC drugs, which has raised concerns about their economic burden¹².

Existing literature examines the association of a specific regulatory change with effective patent life and/or drug innovation. However, to the authors' knowledge, there is no evidence on whether an increase in effective patent life protection is effective in bringing more innovative new drugs to the market. Further, no empirical analysis has been conducted to assess the approval and extension of patent and exclusivity life of FDCs. Existing studies assessing price differences of FDCs and single ingredient drugs included in the combination focus on specific FDCs of a few therapeutic classes, such as antihypertensive and respiratory medications^{13,14}. However, no published study has assessed the pricing structure of all FDA-approved FDC drugs at the time of their first launch into the US market compared to all single ingredient drugs included in the combination, to estimate overall price differences between FDCs and single ingredient drugs, and by therapeutic class. A full literature review is presented within each chapter.

¹⁰ Bhat VN. Patent term extension strategies in the pharmaceutical industry. *Pharmaceuticals Policy and Law* 2005;6:109-22.

¹¹ Hong SH, Shepherd MD, Scoones D, Wan TT. Product-line extensions and pricing strategies of brand-name drugs facing patent expiration. *Journal of managed care pharmacy. JMCP*. 2005;11(9):746-54.

¹² Hong SH, Wang J, Tang J. Dynamic view on affordability of fixed-dose combination antihypertensive drug therapy. *Am J Hypertens*. 2013;26(7):879-87.

¹³ Friedman HS, Eid NS, Crespi S, Wilcox TK, Reardon G. Retrospective claims study of fluticasone propionate/salmeterol fixed-dose combination use as initial asthma controller therapy in children despite guideline recommendations. *Clin Ther*. 2009;31(5):1056-63.

¹⁴ Brixner DI, Lenhart G, Young DC, Samuelson WM. The effect of fixed combination of fluticasone and salmeterol on asthma drug utilization, asthma drug cost, and episodes of asthma exacerbations. *Curr Med Res Opin*. 2007;23(11):2887-95.

Thus, the goal of this dissertation, containing three manuscripts/chapters, is to investigate the economics of FDC drugs. Specifically, in chapter I, we explore whether a longer effective patent life is associated with more NME approvals and whether current regulatory changes are associated with an increase in NME approvals. Chapter II aims to provide empirical evidence on the approval trend of FDC drugs from 1980 to 2012, to assess the market-entry timing of the FDCs, and to evaluate whether FDCs represent an effective patent life extension, compared to the single active ingredients included in the combination. In chapter III, we compare the Average Wholesale Price (AWP, i.e., listed drug price for pharmaceutical products sold by wholesalers to retail pharmacies and nonretail providers and commonly used as a drug price benchmark) difference between all FDCs of new drugs approved by the FDA in the period 1980-2012 and single active ingredients included in the combination, and investigate the factors that are associated with the price difference of FDC drugs and single active ingredients included in the combination.

CHAPTER 1

ARE PATENTS AND MARKET EXCLUSIVITIES AN EFFECTIVE STRATEGY TO STRENGTHEN PHARMACEUTICAL INNOVATION?

Abstract

Patents and market exclusivities serve as regulatory incentives to promote pharmaceutical innovation. This study assessed associations between major US regulatory changes enacted in the last three decades, and the effective patent life and FDA approved New Molecular Entities (NMEs) from 1980-2009. The Waxman Hatch Act (WHA) was associated with a 3.64 years increase in the maximum effective patent life ($p=0.01$). The Prescription Drug User Fee Act (PDUFA) was associated with a 1.1 year increase in the minimum effective patent life ($p=0.03$). The number of approved NMEs increased 45.7% ($p=0.02$) and 37.1% ($p=0.04$) 6 and 7 years, respectively, after the WHA enactment. Likewise, the number of approved NMEs increased 42.4% ($p=0.007$), 65.8% ($p<0.0001$) and 51.3% ($p=0.0008$) 2, 3 and 4 years, respectively after PDUFA enactment, and 76.1% ($p=0.0006$) after the enactment of the Uruguay Round Agreements Act. Conversely, the number of FDA approved NMEs decreased 43.5% ($p<0.0001$), 30.0% ($p=0.01$) and 30.4% ($p=0.02$) 1, 2 and 4 years, respectively after the enactment of the Food and Drug Administration Modernization Act. The effective patent life length was not associated with an increase in the number of approved NMEs. Other incentives, besides the patent life, need to be considered to stimulate pharmaceutical innovation.

Keywords: Effective Patent Life, New Molecular Entities, Drug Regulation, Drug Approvals, Food and Drug Administration, Patents, Exclusivities

Introduction

Intellectual property (IP) law promotes scientific progress and facilitates the transfer of technology by requiring public disclosure of inventions [1]. However, intellectual property regulation also limits competition and increases the cost of patented products[1]. A patent, granted by the United States (US) Patent and Trademark Office (USPTO), is “a right for a limited period of time to exclude others from making, using, or selling an invention” [2]. A patent is the most important form of intellectual property regulation for new pharmaceuticals [3, 4].

In the U.S., the Uruguay Round Agreements Act (URAA), enacted on June 8, 1995, established a 20-year patent term (i.e., patent statutory term) from the filing date of a patent application before the USPTO. Before this enactment, patentees received 17 years of patent life from the date of patent issued by the USPTO. The FDA approval review process requires extensive preclinical and clinical studies. Thus, the effective patent term (i.e., effective patent life) left after the FDA approval is shorter than the regulatory patent term [4]. The USPTO grants pharmaceutical patent extensions [5, 6] which partially restore the patent time spent in clinical trials and patent application review time [7, 8]. The FDA grants market exclusivity rights to sponsor companies upon approval of certain drug applications [9]. The FDA cannot approve a generic application for a drug until the exclusivity expires.

Major regulatory changes occurred during the last 30 years in the US patent and drug regulatory systems which include: the Drug Price Competition and Patent Restoration Act (Waxman-Hatch Act -WHA) in 1984, the Prescription Drug User Fee Act (PDUFA) in 1992, and the Food and Drug Administration Modernization Act (FDAMA) in 1997. The WHA allows sponsors of FDA-approved new drug applications (NDA) to recover, with certain limits, the time

spent by the FDA on a pharmaceutical application review and half of the patent time the sponsor dedicated to clinical trials and administrative activities required for FDA approval [10]. PDUFA authorizes the FDA to collect fees from companies that produce certain human drug and biological products [11, 12]. FDAMA provides an additional 6 months of market exclusivity attached to any existing exclusivity or patent protection on a drug addressing pediatric studies [6, 7].

Both patent extensions and market exclusivity periods serve as regulatory incentives for pharmaceutical companies to conduct research and development (R&D) [12-18]. Patent extensions and market exclusivities are currently the focus of policy proposals to promote innovation [6]. Therefore, it is important to examine the effectiveness of these regulations on enhancing patent life and promoting approvals of new molecular entities (NMEs).

Prior research has examined the association between specific regulatory changes, drug approvals and the effective patent life of pharmaceuticals [4, 8, 10, 12, 18]. The increase in the average effective patent life resulting from the WHA extension was estimated around 2 years [10]. In addition, although PDUFA reduced the FDA review time by more than 1 year [12], the impact on increasing pharmaceutical spending on R&D remains unknown [6]. Almost half of all patents filed before the USPTO by US applicants after URAA enhancement through 2007 benefited from the use of the 20-year patent statutory term [4]. FDAMA enactment resulted in an increase in the drug studies conducted in the pediatric population; nevertheless, FDAMA did not lead to an increase in the approval of pharmaceuticals indicated for children [19].

No study has examined the association between the length of the effective patent life and the number of NMEs approved by the FDA. Thus, there is need to empirically assess the effectiveness of the changes in regulation affecting drug patents and exclusivities of FDA

approved NMEs. The specific aims of this study are 1) to assess the association between main pharmaceutical regulatory changes enacted in the US in the last three decades and the effective patent life of NMEs approved by the FDA, 2) to determine if the length of the effective patent life is associated with the number of FDA approvals of NMEs, and 3) to evaluate whether patent and drug regulatory changes are associated with changes in the number of approvals of NMEs.

Data and Methods

Data were collected from electronic versions of the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book, OB) from 1980 to 2009 and from the FDA's website. Patent information was abstracted from the U.S. Patent and Trademark Office (USPTO) website. Data were updated through December 31, 2009. This study included all NMEs approved in the U.S. between 1980 and 2009. The following information was extracted: drug name, Anatomical Therapeutic Chemical (ACT) code, therapeutic class, NDA approval date, patent expiration date, market exclusivity and generic competition data, and product marketing status.

This study followed the conceptual model used in prior research to calculate the effective patent life (i.e., time period from NME NDA approval to market exclusivity and patent expiration) [20]. The study included FDA designated NMEs that were listed as the first NDA approved by the FDA for the NME. NMEs were excluded from the analysis if they were never marketed after FDA approval, discontinued or withdrawn from the market, or found not to have at least one patent listed in the OB at some point during the period of analysis. NMEs were categorized into an anatomical main group following the Anatomical Therapeutic Chemical (ATC) classification system maintained by the World Health Organization Collaborating Centre for Drug Statistics Methodology.

The unit of analysis was the first NDA and the first NDA Product Number for each NME approved by the FDA during the study period. The FDA review time was estimated as the difference between the NDA approval date and the NDA received day. The effective patent and market exclusivity life includes the period from the NDA approval to market exclusivity and patent expiration. Patents with the minimum and the maximum effective patent life were used to estimate the minimum (first patent) and maximum (last patent) effective patent and market exclusivity life when several patents were listed in the OB for a NME.

Summary descriptive statistics were computed for variables included in the analysis. Wilcoxon-Sum Rank tests were computed to assess associations between the minimum/maximum effective patent life and regulatory changes enacted during the study period. The study period was divided into five regulatory periods (1) 1980- WHA(1984); (2) WHA(1984) -PDUFA(1992); (3) PDUFA(1992) – URAA(1995); (4) URAA(1995)– FDAMA(1997); (5) FDAMA(1997) - 2009 to assess the association between the patent and exclusivity life and each regulatory measure compared to previous regulatory policy measure.

Poisson regression models were performed to assess the association between the number of FDA approved NMEs and the minimum/maximum effective patent life controlling for drug therapeutic class and the five regulatory changes included in the analysis. Poisson regression models also controlled for a 1-10 year time delay in the effect of regulatory changes and effective patent life length changes on the pharmaceutical company R&D stage to the USPTO filing and FDA approval. All analyses were performed using SAS 9.4 statistical software for Windows (SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at 0.05.

Poisson Regression Models:

$$\log \left(E(Y_{ti+j}) \right) = \beta_0 + \beta_1 X_{1ti} + \beta_2 X_2 + \beta_3 X_{3ti} + \beta_4 X_{4ti} + \beta_5 X_{5ti} + \beta_6 X_{6ti}$$

$$\log \left(E(Y_{ti+j}) \right) = \beta_0 + \beta_1 X'_{1ti} + \beta_2 X_2 + \beta_3 X_{3ti} + \beta_4 X_{4ti} + \beta_5 X_{5ti} + \beta_6 X_{6ti}$$

Where Y = Total number of NME NDA approvals for each therapeutic category by year

X_1 = Minimum effective patent life for each therapeutic category by year

X'_1 = Maximum effective patent life for each therapeutic category by year

X_2 = Therapeutic class

X_3 = WHA

X_4 = PDUFA

X_5 = URAA

X_6 = FDAMA

j denotes a time delay factor, $j=1, 2, 3, \dots, 10$ (years) and

$\beta_3=0$ if $ti < 1984$, $\beta_3=1$ if $ti \geq 1984$

$\beta_4=0$ if $ti < 1992$, $\beta_4=1$ if $ti \geq 1992$

$\beta_5=0$ if $ti < 1995$, $\beta_5=1$ if $ti \geq 1995$

$\beta_6=0$ if $ti < 1997$, $\beta_6=1$ if $ti \geq 1997$

Results

In the study period, the FDA approved 739 NMEs; the number of NMEs approved increased from the 1980s ($n=217$) to the 1990s ($n=311$) and decreased in the period 2000-2009 ($n=211$). The patent life analysis included 581 NDA NMEs; and excluded 158 NDA NMEs that did not have patent life information listed in the OB. In the study period, the average minimum effective patent life was 10.25 ± 3.94 years (median=10.27 years; IQR 6.97) and the average maximum effective patent life was 13.56 ± 5.72 years (median=14.00 years; IQR 7.62).

The WHA was significantly associated with a 3.64 years increase in the maximum effective patent life. The median of the maximum effective patent life increased from 9.00 years (IQR 9.00) before the enactment of the WHA to 12.64 years (IQR 7.50) after the enactment of WHA and before PDUFA ($p=0.011$) (Table 1). PDUFA was significantly associated with an increase in the minimum effective patent life. The median of the minimum effective patent life was 9.63

(IQR 7.59) years after the enactment of the WHA and before the enactment of PDUFA; the median of the minimum effective patent life increased to 10.73 (IQR 7.36) years after PDUFA implementation and before the enactment of URAA ($p=0.0283$). However, the minimum effective patent life decreased significantly after enactment of FDAMA, compared to the period prior to FDAMA and after the enactment of URAA (median 10.44 years (IQR6.37) and 12.36 years (IQR 6.54), respectively ($p=0.014$)(Table 1, Figure1).

The association between the FDA approved NMEs and the minimum and maximum effective patent life controlling for the therapeutic class and regulatory measure was not statistically significant with the exception of a 2.5% decrease in number of approvals when modeling a one year time delay in the effect of changes in the maximum patent life length ($p=0.0087$) (Table 2, Table 3).

There is a statistically significant association between the approvals of NMEs by the FDA and the specific regulatory measures enacted during the study period. Parameter estimates revealed that the WHA was significantly associated with an increase in the FDA approved NMEs 6-7 years after its enactment. The number of FDA approved NMEs 6 years after the enactment of WHA increased 46.09% ($p=0.0154$) and 45.71% ($p=0.0183$) in models controlling for the minimum and maximum effective patent life, respectively and the therapeutic class. Likewise, the number of FDA approved NMEs 7 years after the implementation of the WHA increased 38.32% ($p=0.0305$) and 37.07% ($p=0.0391$) for the minimum and maximum effective patent life, respectively(Table 2, Table 3).

PDUFA was significantly associated with an increase in the FDA approved NMEs immediately following its enactment. The number of FDA approved NMEs 2 years after the enactment of PDUFA increased 41.31% ($p=0.0089$) and 42.43% ($p=0.0070$) for the minimum

and maximum effective patent life, respectively. The number of FDA approved NMEs peaked 3 years after the implementation of the PDUFA increasing 64.70% ($p < 0.0001$) and 65.81% ($p < 0.0001$) for the minimum and maximum effective patent life, respectively. The number of FDA-approved NMEs 4 years after the implementation of the PDUFA increased 49.32% ($p = 0.0014$) and 51.32% ($p = 0.0008$) for the minimum and maximum effective patent life, respectively. In addition, PDUFA was associated with a significant decrease in the approvals of NMEs 8 to 10 years after its enhancement; FDA-approved NMEs decreased 32.82% ($p = 0.0102$) and 30.69% ($p = 0.0169$) for the minimum and maximum effective patent life, respectively 10 years after its enactment (Table 2, Table 3).

Likewise, URAA was significantly associated with an increase in the FDA approved NMEs. One year after the implementation of URAA, the approvals of NMEs went up 72.24% ($p = 0.001$) and 76.10% ($p = 0.0006$) for the minimum and maximum effective patent life, respectively. Conversely, FDAMA was significantly associated with a decrease in the FDA approved NMEs. One year after the enactment of FDAMA, the approval of NMEs was 44.12% ($p < 0.0001$) and 43.47% ($p < 0.0001$) lower for the minimum and maximum effective patent life, respectively than the prior year (Table 2, Table 3).

Discussion

Major regulatory changes in the U.S. patent system and drug regulatory system occurred in the past three decades. One of the purposes of the patent system is to stimulate research and development in the US. This study assessed to which extent regulatory changes implemented in the US in the last 30 years are associated with changes in the number of FDA approved NMEs and the effective patent life of pharmaceuticals.

Study results corroborate prior research regarding secular trends in the FDA approval of NMEs [21, 22]. Study findings reveal that there is a statistically significant positive association between the WHA and PDUFA enactment and the length of the effective patent life. These findings are consistent with prior research [4, 8, 10, 12, 18].

The assumption that stronger patent protection will stimulate innovation is contentious [5]. This study evidences that the association between the length of the effective patent life and the approvals of NMEs is not statistically significant. Thus, other factors such as market size, public funding and status of scientific development may explain the number of FDA approved NMEs [23-26].

Study findings also evidence a statistically significant increase in the number of FDA approved NMEs six to seven years after the enhancement of the WHA. The WHA substantially increased the patent and exclusivity protection periods and it was enacted with the specific goal of balancing the need for innovation and access to generic drugs.

This study revealed a statistically significant increase in the number of FDA approved NMEs two to four years after the enhancement of PDUFA. PDUFA allowed the FDA to collect fees from companies that sponsor new drug applications for certain human drug and biological products, using those fees to hire more drug reviewers and shorten the time for pharmaceuticals to reach the market [12]. The number of full-time equivalent FDA staff devoted to the drug application review process nearly doubled from 1,277 in 1992 to 2,503 in 2004 [27]. Before the enactment of PDUFA, the average FDA drug application review time in the period 1990-1992 was 31.0 months; after PDUFA 1993-1996 the FDA review time decreased to 14.5 months[12] in spite of the backlog of NDAs awaiting FDA review in 1992 [28]. Thus, the association between the enactment of PDUFA and the increase in the approvals of NMEs may be

confounded by the fact that PDUFA created an incentive for the FDA to approve more pharmaceuticals in exchange for resources from the pharmaceutical companies.

In addition, while URAA contain general incentives to promote research and development, the observed increase in the approvals of NMEs one year after the enactment of URAA in 1995 may reflect a PDUFA spillover effect. The positive association between PDUFA enactment and the FDA approved NMEs does not remain in the mid- or long-term.

There was a declining pace in the pharmaceutical innovation in the 2000s [29, 30]. Study findings confirm the decrease in the number of NMEs approved after the enactment of FDAMA and through the 2000s compared to the number of approvals in the 80s and 90s. In fact, in the 2000s, new indications, new formulations, and new combinations of previously marketed products accounted for a large proportion (48.8% in 2006 alone) of the approvals[31]. This decreased in the number of NMEs approved by the FDA support our findings that significantly fewer NME approvals were observed eight to ten years after enactment of the PDUFA or one, two and four years after the implementation of FDAMA.

In summary, study findings evidence that the extension of patents and market exclusivities alone does not effectively translate into pharmaceutical innovation. Thus, further researcher is needed to discern other factors behind the research and development of new drugs.

Limitations

Study findings must be considered with a few caveats in mind. This study focuses on the patent and market exclusivity life of the first NDA of the NME. The study included first and last patent listed in the OB and excluded other patents listed in the OB and patents not listed. The average time for pharmaceutical preclinical development is estimated around 5 years and the median time for clinical trial and regulatory review periods are estimated at 5.1 and 1.2 years,

respectively (Hondegem et al. 2007; Keyhani et al. 2006). While the regression models estimate the effects of a regulatory change holding the impacts of other regulatory changes constant, overlapping policy and regulatory effects may still exist.

Conclusion

PDUFA was associated with a statistically significant increase in the minimum effective patent life; and the WHA was associated with a statistically significant increase in the maximum effective patent life. In addition, the WHA, PDUFA and URAA were associated with a statistically significant increase in the NMEs approved by the FDA. The effective patent life length was not associated with a statistically significant increase in the number of approved NMEs. Research is needed to further elucidate effective regulatory and policy measures to incentivize pharmaceutical innovation.

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Figure 1. Regulatory Changes and Effective Patent Life of FDA approved NMEs, 1980-2009

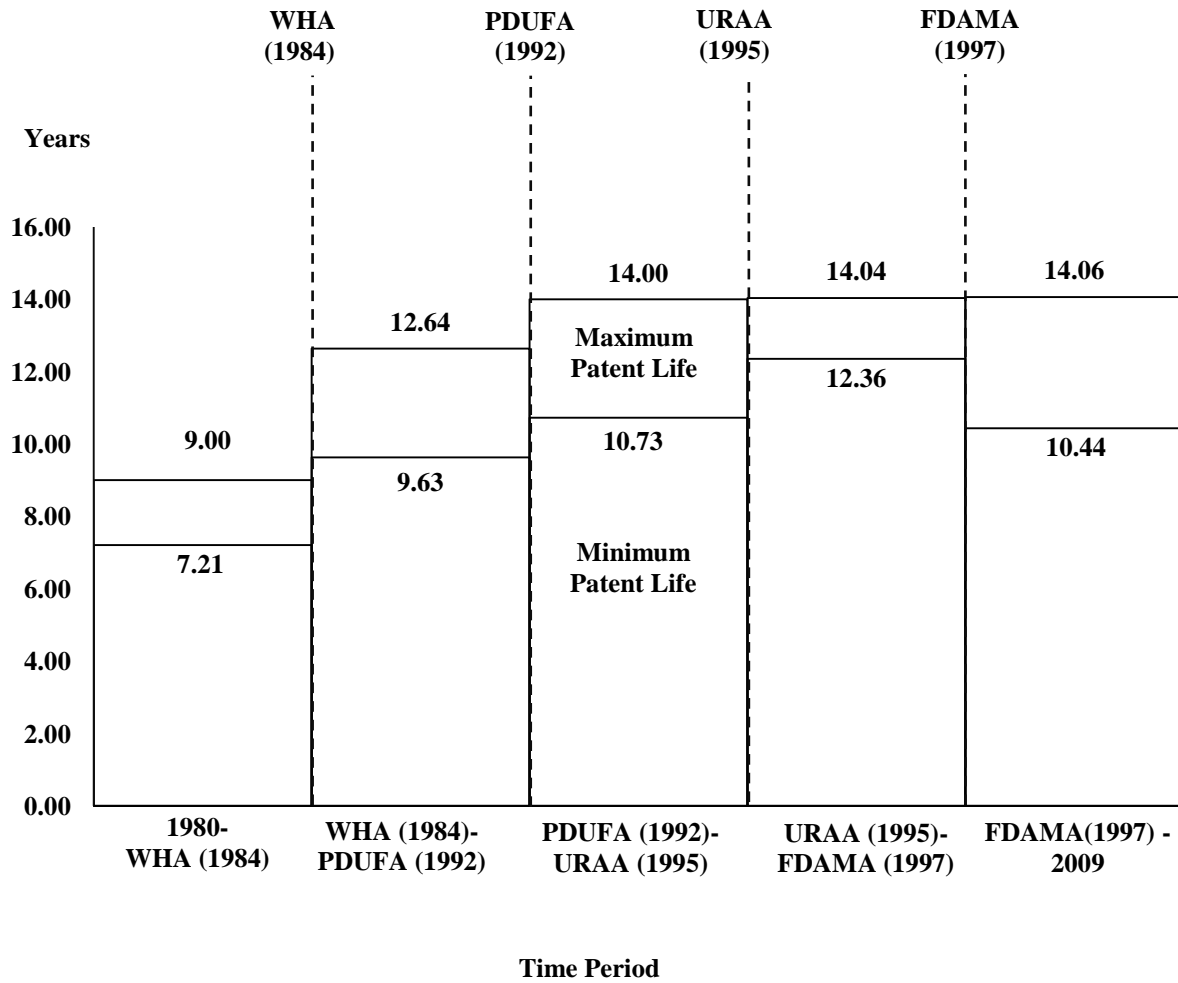


Table 1. Effective Patent Life of FDA Approved NMEs by Regulatory Period

Regulatory Measure	Patent and Pediatric Exclusivity Life in Years Minimum Effective Patent Life		Patent and Pediatric Exclusivity Life in Years Maximum Effective Patent Life	
	Mean(Std)	Median (IQR)	Mean(Std)	Median (IQR)
1. 1980-WHA(1984)	9.14 (4.68)	7.21 (6.82)	10.59 (6.09)	9.00 (9.00)
2. WHA(1984) – PDUFA(1992)	9.80 (3.95)	9.63 (7.59)	12.73 (6.56)	12.64 (7.50)‡
3. PDUFA(1992) – URAA(1995)	10.75 (4.15)	10.73 (7.36)*	13.48 (6.27)	14.00 (9.69)
4. URAA(1995) – FDAMA(1997)	11.45 (4.21)	12.36 (6.54)	14.69 (5.38)	14.04 (6.92)
5. FDAMA(1997)-2009	10.28 (3.59)	10.44 (6.37) _F	14.26(4.81)	14.06 (5.36)
FDAMA(1997)- 2004	10.63 (3.65)	11.16 (6.86)	14.69 (5.10)	15.06 (6.25)
2005-2009	9.45 (3.32)	9.09 (4.95)	13.20 (3.83)	13.61 (3.92)
1980-2009	10.25(3.94)	10.27(6.97)	13.56(5.72)	14.00 (7.62)

Note: *denotes statistically significant difference between the minimum effective patent life of policy periods 2. WHA(1984) – PDUFA(1992) and 3. PDUFA(1992)-URAA(1995) (p-value 0.0283).

_F denotes statistically significant difference between the minimum effective patent life of policy periods 4. URAA(1995) – FDAMA(1997) and 5. FDAMA(1997)-2009 (p-value 0.014).

_Edenotes statistically significant difference between the maximum effective patent life of policy periods 1. 1980-WHA(1984) and 2. WHA(1984) – PDUFA(1992) (p-value 0.011).

Table 2. FDA approved NMEs and Minimum Effective Patent Life, Regulatory Measure

Years after Enactment	Estimate	IRR	95% CI	p-value
Minimum Effective patent life				
1	-0.0143	0.9858	(-0.0425, 0.0140)	0.3227
2	0.0077	1.0077	(-0.0215, 0.0369)	0.6048
3	0.0008	1.0008	(-0.0289, 0.0305)	0.9588
4	0.0106	1.0107	(-0.0195, 0.0407)	0.4894
5	0.0079	1.0080	(-0.0227, 0.0385)	0.6109
6	0.0295	1.0300	(-0.0024, 0.0615)	0.0703
7	0.0015	1.0015	(-0.0306, 0.0336)	0.9262
8	0.0020	1.0020	(-0.0322, 0.0361)	0.9105
9	0.0097	1.0098	(-0.0244, 0.0439)	0.5761
10	0.0239	1.0242	(-0.0112, 0.0591)	0.1816
WHA (1984)				
1	-0.0176	0.9826	(-0.3334, 0.2982)	0.9131
2	-0.1066	0.8989	(-0.4002, 0.1869)	0.4765
3	-0.0546	0.9468	(-0.3572, 0.2479)	0.7234
4	-0.0083	0.9918	(-0.2927, 0.2762)	0.9546
5	0.2116	1.2356	(-0.0832, 0.5063)	0.1596
6	0.3790	1.4609*	(0.0725, 0.6856)	0.0154
7	0.3244	1.3832*	(0.0304, 0.6183)	0.0305
8	0.1780	1.1948	(-0.1063, 0.4622)	0.2197
9	0.1410	1.1514	(-0.1367, 0.4187)	0.3197
10	0.2284	1.2566	(-0.0588, 0.5157)	0.1191
PDUFA (1992)				
1	0.0446	1.0456	(-0.2444, 0.3336)	0.7622
2	0.3458	1.4131**	(0.0868, 0.6047)	0.0089
3	0.4990	1.6470*****	(0.2539, 0.7440)	<.0001
4	0.4009	1.4932**	(0.1554, 0.6465)	0.0014
5	0.1173	1.1245	(-0.1373, 0.3720)	0.3665
6	-0.1255	0.8821	(-0.3924, 0.1414)	0.3567
7	-0.1370	0.8720	(-0.4141, 0.1401)	0.3326
8	-0.4543	0.6349**	(-0.7687, -0.1399)	0.0046
9	-0.4433	0.6419**	(-0.7452, -0.1414)	0.0040
10	-0.3980	0.6717*	(-0.7018, -0.0941)	0.0102

Table 2. (Continued)

Years after Enactment	Estimate	IRR	95% CI	P Value
URAA (1995)				
1	0.5437	1.7224**	(0.2197, 0.8678)	0.0010
2	-0.0344	0.9662	(-0.3568, 0.2879)	0.8342
3	-0.2913	0.7473	(-0.6109, 0.0283)	0.0741
4	-0.2382	0.7880	(-0.5636, 0.0872)	0.1514
5	-0.2864	0.7510	(-0.6525, 0.0798)	0.1253
6	-0.3795	0.6842	(-0.7821, 0.0230)	0.0646
7	-0.3661	0.6935	(-0.7825, 0.0503)	0.0849
8	0.1121	1.1187	(-0.3037, 0.5280)	0.5972
9	0.0679	1.0703	(-0.3480, 0.4839)	0.7489
10	-0.0402	0.9606	(-0.4767, 0.3962)	0.8567
FDAMA (1997)				
1	-0.5820	0.5588****	(-0.8351, -0.3289)	<.0001
2	-0.3531	0.7025*	(-0.6376, -0.0687)	0.0150
3	-0.2642	0.7678	(-0.5632, 0.0347)	0.0832
4	-0.3526	0.7029*	(-0.6614, -0.0438)	0.0252
5	-0.1009	0.9041	(-0.4449, 0.2432)	0.5655
6	0.1136	1.1203	(-0.2630, 0.4901)	0.5545
7	0.1755	1.1919	(-0.2145, 0.5656)	0.3778
8	-0.0922	0.9119	(-0.4671, 0.2827)	0.6298
9	-0.0368	0.9639	(-0.4336, 0.3600)	0.8558
10	-0.0068	0.9932	(-0.4454, 0.4317)	0.9756

Note: *p<0.05, **P<0.01, ***p<0.001, ****p<0.0001; IRR=incident rate ratio.

Table 3. FDA approved NMEs and Maximum Effective Patent Life and Regulatory Measure

Years after Enactment	Estimate	IRR	95% CI	p-value
Maximum Effective patent life				
1	-0.0253	0.9750**	(-0.0442, -0.0064)	0.0087
2	-0.0096	0.9904	(-0.0284, 0.0092)	0.3150
3	-0.0113	0.9888	(-0.0306, 0.0080)	0.2523
4	0.0040	1.0041	(-0.0144, 0.0225)	0.6674
5	-0.0065	0.9935	(-0.0252, 0.0122)	0.4961
6	0.0064	1.0065	(-0.0122, 0.0251)	0.4977
7	0.0031	1.0031	(-0.0156, 0.0217)	0.7479
8	0.0024	1.0024	(-0.0169, 0.0216)	0.8079
9	0.0012	1.0012	(-0.0177, 0.0202)	0.8986
10	0.0081	1.0081	(-0.0116, 0.0277)	0.4197
WHA (1984)				
1	0.0408	1.0416	(-0.2780, 0.3596)	0.8020
2	-0.0689	0.9334	(-0.3676, 0.2297)	0.6510
3	-0.0281	0.9723	(-0.3337, 0.2775)	0.8569
4	-0.0144	0.9858	(-0.3039, 0.2752)	0.9226
5	0.2372	1.2677	(-0.0632, 0.5377)	0.1218
6	0.3765	1.4571*	(0.0636, 0.6893)	0.0183
7	0.3153	1.3707*	(0.0158, 0.6149)	0.0391
8	0.1715	1.1871	(-0.1186, 0.4617)	0.2466
9	0.1421	1.1527	(-0.1423, 0.4265)	0.3275
10	0.2149	1.2398	(-0.0788, 0.5086)	0.1515
PDUFA (1992)				
1	0.0321	1.0327	(-0.2552, 0.3194)	0.8265
2	0.3536	1.4243**	(0.0966, 0.6107)	0.0070
3	0.5056	1.6581****	(0.2630, 0.7483)	<.0001
4	0.4142	1.5132***	(0.1716, 0.6568)	0.0008
5	0.1280	1.1365	(-0.1239, 0.3798)	0.3193
6	-0.0894	0.9145	(-0.3535, 0.1747)	0.5070
7	-0.1351	0.8737	(-0.4074, 0.1373)	0.3311
8	-0.4511	0.6370**	(-0.7633, -0.1389)	0.0046
9	-0.4310	0.6499**	(-0.7297, -0.1323)	0.0047
10	-0.3666	0.6931*	(-0.6673, -0.0659)	0.0169

Table 3. (Continued)

Year after Enactment	Estimate	IRR	95% CI	P Value
URAA (1995)				
1	0.5659	1.7610***	(0.2412, 0.8905)	0.0006
2	-0.0193	0.9808	(-0.3423, 0.3036)	0.9065
3	-0.2761	0.7587	(-0.5962, 0.0439)	0.0908
4	-0.2370	0.7890	(-0.5626, 0.0887)	0.1539
5	-0.2738	0.7605	(-0.6405, 0.0930)	0.1435
6	-0.3704	0.6904	(-0.7732, 0.0324)	0.0715
7	-0.3687	0.6916	(-0.7854, 0.0480)	0.0829
8	0.1093	1.1155	(-0.3071, 0.5258)	0.6069
9	0.0753	1.0783	(-0.3400, 0.4906)	0.7222
10	-0.0312	0.9693	(-0.4676, 0.4053)	0.8887
FDAMA (1997)				
1	-0.5705	0.5653****	(-0.8223, -0.3186)	<.0001
2	-0.3550	0.7012*	(-0.6390, -0.0710)	0.0143
3	-0.2637	0.7682	(-0.561, 0.0336)	0.0821
4	-0.3630	0.6956*	(-0.6708, -0.0553)	0.0208
5	-0.1058	0.8997	(-0.4493, 0.2378)	0.5463
6	0.0971	1.1020	(-0.2795, 0.4737)	0.6132
7	0.1715	1.1871	(-0.2189, 0.5619)	0.3891
8	-0.0938	0.9105	(-0.4682, 0.2806)	0.6234
9	-0.0442	0.9568	(-0.4403, 0.3520)	0.8271
10	-0.0098	0.9902	(-0.4482, 0.4285)	0.9649

Note: *p<0.05, **P<0.01, ***p<0.001, ****p<0.0001; IRR=incident rate ratio.

CHAPTER 2

FIXED-DOSE COMBINATION DRUG APPROVALS, PATENTS AND EXCLUSIVITIES COMPARED TO SINGLE ACTIVE INGREDIENT PHARMACEUTICAL

Abstract

Background Fixed-dose combinations (FDC) contain two or more active ingredients. The effective patent life of FDC compared to single active ingredient has not been assessed.

Objectives Trends in FDA approved FDC in the period 1980-2012 and time lag between approval of FDC and single active ingredients in the combination were assessed, and the effective patent life of FDC was compared with their single active ingredients.

Methods New molecular entities (NMEs), new therapeutic biologics license applications (BLAs) and FDC data were collected from the FDA Orange Book and Drugs@FDA. Analysis included FDC containing one or more NMEs or BLAs at first FDA approval (NMEs-FDC) and only already marketed drugs (Non-NMEs-FDC). Descriptive, Kruskal-Wallis and Wilcoxon Rank Sum analyses were performed.

Results During the study period, the FDA approved 28 NMEs-FDC (3.5% of NMEs) and 117 non-NMEs-FDC. FDC approvals increased from 12 in the 1980s to 59 in the 2000s. Non-NMEs-FDC entered the market at a median of 5.43 years (interquartile range 8.57) after first FDA approval of single active ingredients in the combination. The Non-NMEs-FDC entered the market at a median of 2.33 years (9.94) before single active ingredient generics approval. Non-NME-FDC added a median of 9.70 (13.49) years to the patent and exclusivity life of the single active ingredients in the combination.

Conclusion FDC approvals significantly increased over the last twenty years. Pharmaceutical companies market FDC drugs shortly before the generic versions of the single ingredients enter the market extending the patent and marketing exclusivity life of drugs included in the combination.

Key words: Fixed-dose combination drugs, drug approvals, patent and exclusivity life, FDA

Introduction

Patents are the most important form of intellectual property protection for new drugs [1-5]. In the US, the Uruguay Round Agreements Act (URAA), enacted in June 8, 1995, established a 20-year patent term (i.e. patent statutory term) from the filing date of a patent application before the United States Patent and Trademark Office (USPTO). Before URAA, patentees had 17 years of patent life upon the date when the patent was issued by the USPTO. Patent extensions are granted by the USPTO to partly restore the time spent on clinical trials and FDA review and market exclusivity are granted by the FDA upon approval of certain drug applications [6-8]. Pharmaceutical products do not face generic competition during the effective patent life period thus, pharmaceutical companies set up prices of new drugs to maximize profits [5,9]. Once the patents and exclusivities expire, generic drugs may enter the market driving down pharmaceutical prices.

Fixed-dose combination drugs (FDCs) are formulations that contain two or more active ingredients in a single dosage [10]. According to the FDA, “two or more drugs may be combined in a single dose when each component makes a contribution to the claimed effects, and the dosage of each component (i.e., amount, frequency, and duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy” [11].

A new molecular entity (NME) and a new biologic license application (BLA) are drugs containing active substances that have never before been approved for marketing in the US. Some new drugs are first introduced as a FDC in the US market (i.e. NME-FDC). A NME-FDC may contain only NMEs or a mix of NMEs and other already marketed drugs. A Non-NME-FDC is a new combination that contains only already marketed drugs (Figure 2). The development and marketing of FDCs have been a strategy for brand-name drug companies to extend the drug

patent and exclusivity life of pharmaceuticals in the US, particularly after the enactment of the Waxman-Hatch Act (WHA) in 1984 [12, 13].

If a FDC is novel, non-obvious, and useful, it can be patented and the exclusion of competitors from the market can be enforced (Figure 3). In this case, the sponsor company is able to add patent and exclusivity time to the combination of individual products included in the FDC, for which patents and exclusivities may be expired or close to expire. The FDA provides three years of market exclusivity to new NME-FDC when the application contains new clinical investigations. If the new FDC is not patentable, the patent and exclusivity life of the FDC will typically be equal to the three year market exclusivity or the longest patent and exclusivity life of its individual components. FDC drugs allow patent holders to maintain the market share for products included in the combination, to expand their patent and exclusivity protection, and to shift the demand from single active ingredients to the FDC as patent expiration of single active ingredients looms [13,14]. The substitution of less-expensive single drug products with newer, high-priced, combinations leads to increases in pharmaceutical expenditures [15].

To the best of authors' knowledge, no empirical analysis has been conducted to assess the extent to which FDC drugs expand the effective patent and exclusivity life of pharmaceuticals. Due to the growing number of FDC approved by the FDA and the difference in cost between FDC and single active ingredients, there is a need for an in-depth analysis of trends in FDC drugs approvals and the effective patent and exclusivity life of FDC compared to single active ingredients included in the combination. Thus, the objectives of this study were: 1) to assess trends in FDCs and single active ingredients approved by the FDA in the period 1980-2102; 2) to estimate the time lag between the first approval of single active ingredients and the FDC drugs containing those active ingredients; 3) to estimate the time lag between the first FDC approval

and the approval of abbreviated new drug applications (ANDAs) for the active ingredients included in the combination; and 4) to estimate the effective patent life of FDC drugs compared to the single active ingredients included in the combination.

Data and Methods

Data were derived from the electronic versions of the FDA Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book, OB) and the Drug@FDA database from 1980 to 2012. The study included all FDA approved NMEs and BLAs during the study period.

Information collected for each FDA-approved pharmaceutical product included the NDA number, product number, generic name, trade name, dosage form/route of administration, Anatomical Therapeutic Chemical (ATC) code, National Drug Code (NDCs), market status (i.e., prescription, over-the-counter or discontinued), NDA approval date, patent expiration date, and market exclusivity data. Therapeutic category information was extracted from the ATC classification system maintained by the World Health Organization Collaborating Centre for Drug Statistics Methodology.

Using FDA data, a dataset with all NDAs and BLAs approved by the FDA during the study period was created. All NMEs and BLAs approved during the study period, and all FDCs containing at least one of those NMEs and BLAs were selected. The analysis was broken down into two groups; FDCs containing at least one NME/BLA at first FDA approval (NME-FDC) and FDCs containing single active ingredients approved for the first time during the study period (non-NME-FDC). The units of analysis were the first NDA/BLA of all NMEs, BLAs, NME-FDCs, and non-NME-FDCs approved for the first time by the FDA during the study period.

The effective patent and exclusivity life is the time period from the FDA approval of the new drug application (NDA) to the expiration of all pharmaceutical patents and market exclusivities [16]. The time lag from the last approval of the single active ingredients and the first approval of FDCs containing those active ingredients was calculated. The time lag from the first ANDA approval of the single active ingredients and the first approval of FDCs containing those active ingredients was also calculated.

When a FDC had a generic alternative, the time difference in the patent and exclusivity life of the FDC and the single active ingredients included in the combination was estimated as the time between the dates of FDC first ANDA approval and the single active ingredients ANDA approvals. When a FDC did not have a generic alternative in the market, the difference in the patent and exclusivity life was estimated as the time between the FDC last patent and market exclusivity expiration date and the single active ingredients ANDA approval dates. The analysis was stratified by pharmaceutical sponsors that marketed both the single active ingredients and the corresponding FDC drugs, and by sponsors that marketed FDC drugs but not the single active ingredients.

A descriptive analysis of the variables included in the study was performed. Differences among therapeutic categories were tested using Kruskal-Wallis test and two groups Wilcoxon Rank Sum tests. Differences between non-NME-FDC and the single active ingredients sponsored by the same company and those sponsored by different companies were tested by Wilcoxon Rank Sum tests. Inferential analyses, which employ probability theory and test significances, were performed on therapeutic classes that had 5 or more FDC drugs. Significance level was set at 0.05. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

FDA-approved FDC drugs

In the period 1980-2012, the FDA approved 901 new drugs, including 811 NMEs and 90 BLAs. NME-FDC drugs represented 3.5% of the FDA-approved NMEs (n=28). The FDA did not approve any combination for BLAs. In the study period, 7 (25%) of the 28 NME-FDC drugs were discontinued. The largest number of NME-FDC drugs were antiinfectives (n=7), genitourinary system and sex hormones (n=6), and dermatologicals (n=4). The majority (5 out of 7) of the FDC antiinfectives was approved in the 1980s and 1990s (Table 4).

In addition, the FDA approved 117 non-NME-FDC drugs (i.e. 115 NMEs and 2 BLAs) that had at least one single active ingredient approved by the FDA during the study period. The non-NME-FDC drugs approved in the study period included 156 different single active ingredients with an average of 2.1 active ingredients per combination. A total of 23 (20%) of the 117 non-NME-FDC drugs were discontinued from the market as of December 31, 2012. Non-NME-FDC drugs approved by the FDA increased over time from an average of 1.2 approvals per year (n=12) in the 1980s to 2.5 (n=25) in the 1990s and 5.9 (n=59) in the 2000s. During the period 2010-2012, the FDA approved an average of 7.0 (n=21) non-NME-FDC drugs per year. The percentage of NME/BLA and non-NME-FDC increased from 5.5% in 1980s to 25.0% during the period 2010-2012. The ATC classes with the largest number of non-NME-FDC approved by the FDA were cardiovascular diseases (n=41), alimentary tract and metabolism (n=26), respiratory system (n=10), and antiinfectives (n=10).

Overall, 10.4% (n=12) of the 117 non-NME-FDC, were approved by the FDA using the priority review procedure (i.e., a review process applied by the FDA to drugs considered improvements over already marketed therapeutic alternatives). The percentage of priority review

approvals was highest for non-NME-FDC of antiinfectives for systemic use (50.0% of total FDA approvals).

Market Entry and Effective Patent Life

Non-NME-FDC entered the market at a median of 5.43 years (interquartile range, IQR 8.57 years) after the first approval of the single active ingredients included in the combination (Table 5). This time lag significantly varied by therapeutic class ($p=0.0146$). Antiinfectives and cardiovascular system non-NME-FDC entered the market significantly sooner (median 1.89 years, IQR 5.41) compared to the nervous system (7.23, IQR 14.32), respiratory system (9.34, IQR 4.15) and sensory organs (10.73, IQR 4.86)) ($p<0.05$).

The difference in market entry between non-NME-FDC and the single active ingredients sponsored by the same company and those sponsored by different companies was statistically significant. When the non-NME-FDC and the single active ingredient were sponsored by the same company, the FDC entered the market at a median of 4.50 years (IQR 6.19) after the first approval of the single active ingredients included in combination; whereas, when the applicant of the non-NME-FDC and the single active ingredient were different, the non-NME-FDC entered the market at a median of 10.31 years (IQR 12.04) after the first approval of the single active ingredients in the combination ($p=0.0112$) (Table 5).

Non-NME-FDC drugs entered the US market at a median of 2.33 years (IQR 9.94) before the generic alternative of the single active ingredient included in the combination reached the market; the time difference did not significantly varied by therapeutic class ($p= 0.0965$) (Table 6). When a non-NME-FDC and the single active ingredients were sponsored by the same company, the non-NME-FDC entered the market at a median of 5.05 years (IQR 7.51) before the first generic approval of the active ingredients; whereas, when the sponsor of the non-NME-FDC

and the single active ingredients were different, the non-NME-FDC entered the market 1.85 years (IQR 7.17) after the generic single active ingredients reached the market ($p < 0.0001$).

Non-NME-FDC drugs added a median of 9.70 years (IQR 13.49) of patent and market exclusivity protection to the effective patent life of the single active ingredients included in the combination; being the difference by therapeutic class not statistically significant ($p = 0.1535$) (Table 7). The difference in the effective patent life between non-NME-FDC and the single active ingredients sponsored by the same company and those sponsored by different companies was statistically significant. When the sponsor of the non-NME-FDC was the same as the single ingredient drug, the non-NME-FDC added in median 7.73 years (IQR 10.29) to the patent and market exclusivity life of the single active ingredient. Furthermore, when the sponsor of the non-NME-FDC and the single ingredient drug were different, the non-NME-FDC added a median of 11.48 years (IQR 13.48) of patent and market exclusivity protection ($p = 0.0048$).

Discussion

This study analyzed trends in all FDA approved FDCs in the period 1980-2012 and assessed the extent to which FDC drugs expand the effective patent life of previously marketed single active ingredient drugs. Study findings reveal that approval of FDC increased significantly over the last twenty years and varied by therapeutic class; the largest number of FDC approvals were for the treatment of highly prevalent conditions (i.e. cardiovascular and respiratory system drugs).

Antiinfective FDC drugs entered the market relatively soon after the approval of the single active ingredient drug NMEs. This strategy may be related with the significantly longer effective patent life of antiinfectives, compared to other therapeutic classes, and the high demand of antiinfective drugs [17, 18]. FDC drugs for cardiovascular diseases also entered the market

relatively soon after the approval of the single active ingredient drug NMEs, and represent a significantly shorter increase in the effective patent life.

Study findings also evidence that pharmaceutical companies market FDC drugs shortly before the generic version of the single active ingredient drug enters the US market thus, extending the patent and marketing exclusivity protection of the single drugs included in the combination. In addition, approximately 80% of non-NME-FDC drugs were sponsored by the same applicant of at least one single ingredient drug included in the combination. Shifting the demand to FDC drugs as patents and exclusivities of single active ingredients expire may impose a financial burden on public and private health programs and patients [19-22].

The time lag between approval of the single active ingredient drug NMEs and the FDC and the increase in the effective patent life of non-NME-FDC drugs differed significantly between those non-NME-FDC sponsored by the same company and those sponsored by different companies. When sponsored by different companies, FDC drugs cannot enter the market before the expiration of the patents and exclusivities of the single active ingredients. Whereas, when sponsored by the same company, the pharmaceutical company can market their FDC drugs prior to generic entry, expanding the patent and market exclusivity protection of the active ingredients included in the combination.

Pharmaceutical companies often advertise FDC drugs as pharmaceutical products that are convenient to the patient [23, 24]. Research is needed to assess the cost-effectiveness of FDC compared to single active ingredient pharmaceuticals.

Limitations

Study results must be considered with a few caveats in mind. The study analyzed NMEs and BLAs; other biologic products including blood, vaccines, allergenics, tissues, and cellular and gene therapies were excluded from the analysis. The study includes the last patent listed in the OB for the first product number of the first NDA of each NME and excludes successive NDAs (e.g. line extensions). Study data used in the analysis are right censored. The effective patent life of NMEs can increase due to new patents listed by the sponsor's company, patent extensions and pediatric exclusivity.

Conclusion

Approvals of FDC drugs significantly increased over the last twenty years and varied by therapeutic class. The large majority of FDC includes at least one single active ingredient first approved by the FDA in the period of 1980-2012. A small percentage of FDC was approved using the FDA priority review procedure.

The time lag between first approval of the single active ingredients and FDC drug approval significantly varied by therapeutic class and sponsor's company of the pharmaceutical product. Likewise, the time lag in the market entry between the FDC and single generic drugs vary significantly depending on whether the sponsor of the FDC and the single active ingredients included in the combination are the same or different. Pharmaceutical companies market FDC drugs shortly before the generic alternative of the single active ingredient in the combination reaches the market, thus effectively extending the patent and marketing exclusivity life of the single drugs included in the combination. The difference in the effective patent and exclusivity life between FDC and single ingredient drugs vary significantly depending on the therapeutic

class and whether the sponsor of the FDC and the single active ingredients included in the combination were the same or different.

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Table 4. FDA-Approved FDC drugs by Therapeutic Category, 1980-2012

	1980s	1990s	2000s	2010-2012	Total
NME-FDC					
Alimentary tract and metabolism	1	0	1	1	3
Antiinfectives for systemic use	3	2	1	1	7
Antineoplastic and immunomodulating	0	0	1	0	1
Antiparasitic products, insecticides and repellents	1	0	0	0	1
Cardiovascular system	0	0	0	0	0
Dermatologicals	1	1	2	0	4
Genito urinary system and sex hormones	1	1	3	1	6
Musculo-skeletal system	0	0	0	0	0
Nervous system	0	0	1	0	1
Respiratory system	0	2	0	0	2
Systemic hormonal preparations	0	0	1	0	1
Various	1	0	1	0	2
Total NME-FDC	8	6	11	3	28
Single Active Ingredient BLAs and NMEs	217	333	240	83	873
Total NME-FDC and Single Active Ingredient BLAs and NMEs	225	339	251	86	901
Non-NME-FDC					
Alimentary tract and metabolism	2	2	14	8	26
Antiinfectives for systemic use	2	2	5	1	10
Antineoplastic and immunomodulating	0	1	2	1	4
Antiparasitic products, insecticides and repellents	0	0	1	0	1
Cardiovascular system	7	13	15	6	41
Dermatologicals	0	1	4	0	5
Genito urinary system and sex hormones	0	0	1	2	3
Musculo-skeletal system	0	1	2	0	3
Nervous system	0	0	5	0	5
Respiratory system	1	2	5	2	10
Sensory organs	0	3	3	1	7
Various	0	0	2	0	2
Total Non-NME-FDC	12	25	59	21	117

Table 5. Time Lag between Approval of Single Active Ingredient NME and FDC

Therapeutic Class	FDC and Previously Approved Single Drug NME Same Applicant			FDC and Previously Approved Single Drug NME Different Applicant			Total		
	No. of FDC	Mean(Std)	Median (IQR)	No. of FDC	Mean(Std)	Median (IQR)	No. of FDC	Mean(Std)	Median (IQR)
Alimentary tract and metabolism	15	5.18(3.02)	6.12 (4.81)	7	15.13(7.08)	15.56 (18.01)	22	8.34(6.55)	6.31 (8.18)
Antiinfectives for systemic use	9	4.50(5.18)	1.91 (4.54)	1	0.22	0.22	10	4.07(5.07)	1.89 (5.41) ¹
Antineoplastic and Immunomodulating Agents	4	10.12(11.95)	5.59 (14.83)	0			4	10.12(11.95)	5.59 (14.83)
Antiparasitic products, insecticides and repellents	1	7.63	7.63	0			1	7.63	7.63
Cardiovascular system	33	3.90(3.57)	2.68 (4.31)	8	7.75(5.68)	7.47 (9.35)	41	4.65(4.27)	3.48 (5.89) ¹
Dermatologicals	1	12.52	12.52	1	27.34	27.34	2	19.93(10.48)	19.93 (14.82)
Genito urinary system and sex hormones	1	8.56	8.56	0			1	8.56	8.56
Musculo-skeletal system	1	9.52	9.52	2	12.35(4.16)	12.36 (5.89)	3	11.41(3.37)	9.52 (5.89)
Nervous system	4	9.53(7.66)	6.84 (8.95)	1	24.73	24.73	5	12.57(9.50)	7.23 (14.32) ₁
Respiratory system	6	7.18(4.93)	6.11 (5.71)	3	10.47(1.71)	9.63 (3.09)	9	8.27(4.31)	9.34 (4.15) ¹
Sensory organs	4	11.15(3.40)	11.39 (4.38)	2	6.82(4.93)	6.82 (6.98)	6	9.70(4.10)	10.73 (4.86) ₁
Various	1	0.00	0.00	0			1	0.00	0.00
Total	80	5.64(5.04)	4.50 (6.19)*	25	11.60(7.58)	10.31 (12.04)	105	7.06(6.25)	5.43 (8.57)

Notes: ¹ Statistically significant difference among therapeutic classes: Antiinfectives for systemic use compared to nervous system (p=0.0275), respiratory system (p=0.0412), and sensory organs (p=0.0301), respectively. Cardiovascular system compared to nervous system (p=0.0274), respiratory system (p=0.0209), and sensory organs (p=0.0183), respectively. Note that the statistical significance does not hold when Bonferroni Correction was applied.

* Statistically significant difference between FDC and single drug NME same and different applicant (p= 0.0112).

IQR=Interquartile Range.

Table 6. Time Lag between FDC Drug Approval and Single Drug Generic Market Entry

Therapeutic Class	FDC and Previously Approved Single Drug NME Same Applicant			FDC and Previously Approved Single Drug NME Different Applicant			Total		
	No. of FDC	Mean(Std)	Median (IQR)	No. of FDC	Mean(Std)	Median (IQR)	No. of FDC	Mean(Std)	Median (IQR)
Alimentary tract and metabolism	11	(-5.08)(4.12)	(-5.99) (5.69)	9	6.43(3.89)	5.18 (5.47)	20	0.10(7.06)	(-0.20)(10.31)
Antiinfectives for systemic use	6	(-7.24)(6.16)	(-6.07) (4.89)	0			6	(-7.24)(6.16)	(-6.07)(4.89)
Antineoplastic and Immunomodulating Agents	2	2.91(16.20)	2.91 (22.90)	2	2.17(2.85)	2.18(4.03)	4	2.54(9.50)	(2.18)(13.47)
Antiparasitic products, insecticides and repellents	1	(-10.50)	(-10.50)	0			1	(-10.50)	(-10.50)
Cardiovascular system	18	(-8.12)(5.34)	(-8.42)(7.69)	17	(-1.13)(5.53)	1.42(9.33)	35	(-4.72)(6.42)	(-5.12)(11.79)
Dermatologicals	1	(-1.48)	(-1.48)	1	12.27	12.27	2	5.40(9.73)	5.40(13.75)
Genito urinary system and sex hormones	1	(-0.52)	(-0.52)	0			1	(-0.52)	(-0.52)
Musculo-skeletal system	2	(-1.82)(1.43)	(-1.82)(2.02)	1	2.49	2.49	3	(-0.39)(2.69)	(-0.81)(5.32)
Nervous system	4	(-0.30)(6.56)	0.78(9.34)	1	11.27	11.27	5	(-2.01)(7.68)	2.39(7.19)
Respiratory system	7	(-1.52)(5.61)	(-3.72)(6.41)	2	(-1.24)(1.54)	(-1.24)(2.18)	9	(-1.46)(4.89)	(-2.33)(3.90)
Sensory organs	2	0.96(4.91)	0.96(6.93)	3	(-2.33)(10.80)	(-6.33)(20.45)	5	(-1.02)(8.22)	(-2.51)(10.75)
Various	0			0			0		
Total	55	(-4.83)(6.25)	(-5.05)(7.51) ***	36	1.66(6.46)	1.85(7.17)	91	(-2.27)(7.06)	(-2.33)(9.94)

Notes:

*** Statistically significant difference between FDC and single drug NME same and different applicant, $p < 0.0001$.

IQR=Interquartile Range

Table 7. Effective Patent Life: FDCs Compared to Single Active Ingredient Included in Combination

Therapeutic Class	FDC and Previously Approved Single Drug NME Same applicant			FDC and Previously Approved Single Drug NME Different Applicant			Total		
	No. of FDC	Mean(Std)	Median (IQR)	No. of FDC	Mean(Std)	Median (IQR)	No. of FDC	Mean(Std)	Median (IQR)
Alimentary tract and metabolism	9	8.70(4.80)	9.70(3.63) ^{††}	9	17.84(8.05)	21.51(14.03)	18	13.27(7.97)	11.29(13.78)
Antiinfectives for systemic use	4	5.77(2.37)	6.04(3.67)	0			4	5.77(2.37)	6.04(3.67)
Antineoplastic and immunomodulating agents	0			0			0		
Antiparasitic products, insecticides and repellents	1	0.00	0.00	0			1	0.00	0.00
Cardiovascular system	10	2.34(3.29)	1.05(2.74) ^{††}	15	10.05(6.31)	10.84(7.40)	25	6.97(6.49)	6.98(9.99)
Dermatologicals	1	17.13	17.13	1	23.85	23.85	2	20.49(4.76)	20.49(6.72)
Genito urinary system and sex hormones	1	5.72	5.72	0			1	5.72	5.72
Musculo-skeletal system	2	13.80(4.03)	13.80(5.70)	1	17.03	17.03	3	14.88(3.41)	16.65(6.08)
Nervous system	4	7.61(7.62)	6.86(12.38)	1	29.60	29.60	5	12.01(11.84)	10.88(13.88)
Respiratory system	7	9.22(8.96)	10.97(18.02)	2	9.97(14.06)	9.97(19.89)	9	9.39(9.22)	10.97(18.02)
Sensory organs	2	17.13(3.56)	17.13(5.04)	3	9.17(8.41)	10.99(16.53)	5	12.36(7.59)	14.61(5.54)
Total	41	7.42(6.54)	7.73(10.29)**	32	13.41(8.47)	11.48(13.48)	73	10.05(7.98)	9.70(13.49)

Notes:

†† Statistically significant difference between Cardiovascular System and Alimentary Tract and Metabolism (p=0.0053)

** Statistically significant difference between FDC and single drug NME same and different applicant (p=0.0048)

IQR=Interquartile Range

Figure 2. Classification of FDC at First Approval

NME & New Combination (NME-FDC)

- FDC of 2 or more NMEs
- FDC of 1 or more NMEs and 1 or more already marketed products

New combination not containing a NME (Non-NME-FDC)

- FDC of 2 or more already marketed single drug products

Figure 3. Potential Patent and Exclusivity Protection of FDC

Patents and exclusivities of single products

- Patents of single products
- Market exclusivity of single products

Patents and exclusivities of the FDC

- Patents of the new combination
- Market exclusivity of the new combination

CHAPTER 3

FIXED-DOSE COMBINATION AND SINGLE ACTIVE INGREDIENT DRUGS: A COMPARATIVE COST ANALYSIS

Abstract

Background: Fixed-dose combination (FDC) drugs are formulations of two or more active ingredients.

Objectives: To assess the pricing structure and price difference of all FDA approved FDCs and single drugs included the combination.

Methods: Data were collected from the FDA Orange Book and Drugs@FDA. Average Wholesale Price (AWP) unit price data were derived from The Red Book.

Results: The FDA approved 117 FDC. The average AWP difference percentage between the FDC and the sum of the single drugs in the FDC is 84.9% \pm 26.2% and varied by therapeutic class ($p < 0.01$). The FDC AWP averaged 83.3% \pm 23.4% of the single drug AWP sum when there are no generics, and 95.1% \pm 42.3% ($p < 0.01$) when there are 2 generic single active ingredients in the FDC.

Conclusions: The price difference between FDC and single active ingredients in the combination is correlated with the therapeutic class, the year of FDC approval, and the number of single ingredients in the combination that have generics.

Key Words: Fixed-dose combination drugs; Average Wholesale Price; Drug Approvals; Food and Drug Administration.

Introduction

Combination drugs, or fixed-dose combination (FDC) drugs, are formulations of two or more active ingredients in a single tablet [1]. According to the U.S. Food and Drug Administration (FDA), two or more drugs may be combined into a single dose when each component makes a contribution to the claimed effects and the dosage of each component (i.e., amount, frequency, and duration) produces a safe and effective treatment for a significant patient population requiring such concurrent therapy [2]. FDC drugs are used to treat a range of medical conditions including asthma, diabetes, and cardiovascular diseases, and infectious diseases, such as HIV/AIDS, and tuberculosis [3, 4].

FDC drugs became a popular marketing strategy of the pharmaceutical industry to extend the life cycle of pharmaceuticals, especially after implementation of the Drug Price Competition and Patent Term Restoration Act in 1984 (i.e., Waxman Hatch Act -WHA), which facilitates faster entry of generic drugs into the market [5-8]. Pharmaceutical companies introduced FDC drugs to expand their patent and exclusivity periods and to shift the demand to combination drugs as patents and exclusivities of single active ingredients expire [8, 9]. The approval of FDC drugs allows the pharmaceutical industry to maintain at least part of the sales of the single ingredient products experiencing generic competition. The substitution of old less-expensive prescription drugs with new costly pharmaceutical products accelerated the growth in prescription drug spending [10]. Further, over the last decade, prescribing patterns led to an increased utilization of FDC drugs [11-15]. The increasing utilization and cost of FDC drugs has raised concerns about its economic burden and overall health benefits for the patient [12, 16].

Previous studies assessed differences in the cost of FDC drugs and single-active ingredients included in the combination using a convenience sample of FDC. Studies focused on

few therapeutic classes such as antihypertensive medications [14, 17-23] and respiratory drugs [11, 24-27]. Rabbani and Alexander (2008) compared drug costs of 27 most commonly prescribed FDC antihypertensive drugs and the cost of their generic single active ingredients using the Medical Expenditure Panel Survey (MEPS). The total monthly prescription cost was lower for 23 of the 27 FDC antihypertensive drugs examined [17]. Hong, Wang and Tang (2013) assessed the cost of 26 antihypertensive FDC drugs also using MEPS data [14]. Authors found that the FDC drug cost was similar to the non-generic single active ingredients but higher than the generic version of single active ingredients [14]. Likewise, study results for respiratory system drugs evidenced that on average, the total monthly prescription drug cost of FDC exceeds the cost of the single active ingredients included in the combination [11, 24, 27].

In summary, previous studies were a retrospective analysis of commercial or public insurance claims data based on reimbursement rates by patients and third party payers. Studies' findings were mixed and inconclusive with regards to cost differences between FDC drugs and single active ingredients. Some studies estimated that the FDC average annual prescription drug cost per patient was higher than the cost of single active ingredients included in the combination [11, 23-26], whereas, other studies found the opposite [18-21]. Ten out of 13 peer-reviewed studies found through a literature review, were sponsored by the drug manufacturer.

This study builds on prior research to assess the pricing structure of all FDC drugs at the time of their first launch into the US market, and compare the prices of the FDC and the single active ingredient drugs included in the combination by type of approval and therapeutic class. Thus, the specific objectives of the study were to assess the price difference between all FDC of new drugs approved by the FDA in the period 1980-2012 and single active ingredients included in the combination; and to analyze the association between the price difference of FDC drugs

and single active ingredients included in the combination and the therapeutic class, the FDA approval year of the FDC, and generic availability of single active ingredients included in the combination.

Data and Methods

Data for all FDA approved new molecular entities (NMEs –i.e., a new drug containing an active ingredient that has never before been approved for marketing in the US), new therapeutic biologic license applications (BLAs –i.e., a new biologic license application approved by the FDA Center for Drug Evaluation and Research), FDC drugs, and the single active ingredient drugs included in the combinations were derived from electronic versions of the FDA Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book-OB), and Drugs@FDA. Pharmaceutical prices data were extracted from Thomson Micromedex’s Red Book online. The Red Book is a reference source for pharmacists for prescription and over-the-counter drug prices [28]. It includes pricing history and comprehensive drug information for all FDA approved and marketed brand and generic prescription drugs, and over-the-counter drugs. The Red Book provides current and historical information of the Average Wholesale Price (AWP -i.e., listed drug price for pharmaceutical products sold by wholesalers to retail pharmacies and nonretail providers) [28, 29]. The Red Book also contains information about the Federal Upper Limit (FUL –i.e., a Federal program that limits Medicaid reimbursement rate for certain multiple source drugs when generics are available in the US market). Last, therapeutic category data are derived from the Anatomical Therapeutic Chemical (ATC) classification system maintained by the World Health Organization Collaborating Centre for Drug Statistics Methodology. Data sets were combined by matching the drug National Drug Code (NDC), drug product trade name, and active ingredient.

The study included all FDC drugs approved by the FDA in the period 1980-2012 that had at least one single drug approved as a NME or BLA during the study period. The study also included all single active ingredient pharmaceutical products included in the FDC. This study followed the FDA classification of FDC drugs at the time of FDA first approval which includes NME & new combination (i.e., new combination includes a mix of already marketed products and at least one FDA approved NME), and new combination (i.e., all active ingredients in the combination are already marketed products).

Data collection for each FDC drug and single active ingredients included the following information: drug product trade name, active ingredient, dosage/strength, form/route of administration, package size, unit dosage, application number, product number, drug formulation (i.e., FDC drugs, single active ingredient drugs), approval date, NDC, drug applicant, AWP unit price and effective date, and FUL unit price and effective date. AWP data were collected for all first New Drug Application (NDA) of NMEs & new combinations, and new combinations at the time of first drug market entry. The unit of analysis combined the active ingredient(s), route, form, and strength for each FDC drug or single active ingredient.

The study included the first NDA of all FDA approved NMEs & new combinations, first NDA of new combinations containing at least one drug product previously approved by the FDA as a NME or BLA in the study period, and all single active ingredient drugs included in the combination. The analysis excluded repackages and unit-dose products. When several package sizes were available for a FDC or single active ingredient at the first entry date, the package size closer to 100 units was used for the analysis. If several generic products were available for a single active ingredient, the estimated average price for the single active ingredient generic drug with package size closest to the units contained in the FDC was used for the analysis. When there

were no generics of the single active ingredients included in a FDC in the US market at the time the FDC drug first enters the market, the AWP unit price of the single active ingredients brands were used in the analysis.

The price analysis was performed based on the price difference percentage between the FDC drug AWP and the AWP sum of the single drugs included in the combination. When several strengths were available for the same active ingredient the price difference percentage was calculated based on the average percentage for all strengths. All prices were adjusted to 2013 dollars using the all items, not seasonally adjusted, US city average consumer price index.

Descriptive analyses were performed to estimate and compare FDC drug AWP and the AWP sum of the single drugs included in the combination. The price difference percentage between the FDC drug AWP and the AWP sum of the single drugs included in the combination was estimated over the study period, and analyzed by therapeutic class.

Price differences between FDC and single drug groups were assessed using the Wilcoxon Signed-Rank test. Price differences among time periods and drug characteristic groups were assessed using Wilcoxon Rank-Sum test. ANOVA was used to test the differences of the price difference percentage of the combination drug AWP and the AWP sum of the single drugs among decades, and drug characteristic groups. A multiple linear regression model was performed to evaluate the association between the price difference percentage of the combination drug AWP and the AWP sum of the single drugs included in the combination, and the study explanatory variables. Independent variables were the number of active ingredients in the combination, the number of single active ingredients that had generic competition at the first FDC market entry, the first AWP effective year for the FDC drug, and the FDC therapeutic class.

Wilcoxon Signed-Rank test, Wilcoxon Rank-Sum test, and multiple linear regression analyses were performed on therapeutic classes that had 5 or more FDC drugs.

Descriptive statistics were also performed using the FUL unit price for single generic drugs when available. A t-tests analysis was performed to compare the FUL and the AWP of the price difference percentage of the FDC drugs and the price sum of the single drugs included in the combination. All analyses were performed using SAS 9.2 statistical software. Significance level was set at 0.05.

Results

In the period 1980-2012, the FDA approved 901 new drugs, including 811 NMEs and 90 BLAs. New combinations containing at least one NME represented 3.5% of the FDA approved NMEs (n=28). The FDA did not approve any combination for BLAs. In addition, the FDA approved 117 new combinations that have at least one single active ingredient previously approved by the FDA as a NME or BLA. These FDC drugs include 115 NMEs and 2 BLAs. Overall, 10.4% (n=12) of the 115 FDC drugs including a NME were approved by the FDA using priority review (i.e., a review process applied by the FDA to drugs considered improvements over the already marketed therapeutic alternatives). The percentage of priority review approvals was highest for antineoplastic systemic use FDC (50.0% of total FDA approvals). The number of FDC drug approvals increased over time from 12 in the 1980s, to 25 in the 1990s, and 58 in the 2000s. In the period 2010-2012, the FDA approved 22 FDC drugs. The 117 FDC drugs approved in the period 1980-2012 include a total of 156 different single active ingredients with an average of 2.1 active ingredients per combination.

The price analysis excluded 22 FDC not marketed in the US as of December 31, 2013, and 29 FDC without complete active ingredient, strength, route of administration, approval date, and price information. The final analytical sample for the price analysis included 66 FDC drugs.

The average AWP unit price difference percentage between the FDC drugs and the average AWP unit price sum of the single drugs included in the combination is on average 84.9% \pm 26.2% (Table 8). The average AWP unit price difference percentage between the FDC and the single drugs included in the combination varies by therapeutic class ($p = 0.0022$). The FDC average AWP unit price percentage of cardiovascular system drugs was significantly higher than the average AWP unit price percentage of alimentary tract and metabolism drugs (86.7 \pm 23.7 and 67.4 \pm 20.5%, respectively; $p = 0.012$). Likewise, the FDC average AWP unit price percentage of alimentary tract and metabolism drugs was significantly lower than the average AWP unit price percentage of anti-infectives for systemic use (67.4 \pm 20.5% and 105.8 \pm 16.9%, respectively; $p = 0.0008$). The difference in the FDC average AWP unit price percentage of cardiovascular drugs and anti-infectives for systemic use was not statistically significant (Table 8).

FDC AWP unit price significantly increased during the study period from a median of US\$1.40 (IQR US\$ 0.71) in the 1980s, to US\$ 1.92 (IQR US\$0.70) in the 1990s ($p = 0.0263$), US\$3.38 (IQR US\$3.19) in the 2000s ($p = 0.0019$), and US\$5.78 (IQR US\$7.64) in the period 2010–2012 ($p = 0.0014$). Overall, the average AWP unit price difference percentage between the FDC and single active ingredients included in the combination decreased over time from 119.3 \pm 29.2% in the 80 s to 86.7 \pm 23.2% in the 00 s ($p < 0.05$; Table 9).

The average AWP unit price difference percentage between the FDC and the single active ingredients in the combination increases with the number of single active ingredients in

the combination. The percentage average AWP unit price difference was, on average, $84.7 \pm 27.1\%$ when the FDC contains two single active ingredients, up to $86.0 \pm 15.0\%$ when the combination contains three active ingredients, although the difference was not statistically significant (Table 9).

The average AWP unit price difference percentage also increases with the number of active ingredients in the combination that have generic competition. The FDC average AWP unit price was on average $83.3 \pm 23.4\%$ of the single drug average AWP unit price sum when there were no generic versions in the market. This average AWP unit price difference percentage increases to $95.1 \pm 42.3\%$ ($p < 0.01$) when there were two single active ingredients in the combination that have generic versions in the market at the time the FDC drugs enters into the US market (Table 9).

The average AWP unit price difference percentage between the FDC and the single drugs in the combination was significantly associated with the FDC drug therapeutic class ($p < 0.001$), the year when the FDC first enters into the US market ($p < 0.001$), and the number of single drugs in the combination that have generic competition at the time of the FDC market entry ($p < 0.05$; Table 10). The association between the average AWP unit price percentage difference and the number of active ingredients included in the combination was not statistically significant.

There were 13 generic single drugs that have FUL price data available at the time the FDC first enters the market. The price difference percentage between the FDC and the single active ingredient drugs using the average FUL prices, instead of the AWP, was even larger. The mean price difference percentage between the FDC and the price sum of single drugs in the combination was $104.2 \pm 51.2\%$ compared with $78.7 \pm 35.2\%$ for the FUL and AWP ($p < 0.01$), respectively. This price difference also varies by therapeutic class. The price difference

percentage between AWP of cardiovascular FDC and single drugs was $108.2 \pm 16.9\%$ and $71.4 \pm 8.7\%$ for FUL and AWP ($p < 0.001$), respectively. Likewise, the price difference percentage between alimentary tract and metabolism FDC and single drugs was $71.7 \pm 31.6\%$ and $62.8 \pm 27.8\%$ for FUL and AWP ($p < 0.05$), respectively (Table 11).

Discussion

This study assesses the AWP per unit for all FDC drugs approved by the FDA in the period 1980-2012 compared to the sum of the AWP per unit of the single active ingredients included in the combination at the time the FDC drug first enters the US market. FDC drug AWP unit prices are, on average, lower than the AWP per unit sum of the single drugs in the FDC. However, the price difference varied significantly by therapeutic class. In addition, this study reveals that the price difference percentage between FDC and single drugs increases with the number of single drugs that have generic competition. Study results corroborate previous research regarding pharmaceutical companies FDC drugs marketing strategy [14, 17, 22]. Pharmaceutical companies market FDC drugs to maintain market share as more single active ingredient drugs lose patent protection over time and more generic drugs enter the market increasing competition, and driving prices down.

Novel study findings provide evidence that pharmaceutical companies' pricing strategy varies by therapeutic class and FDA review process. The AWP per unit of cardiovascular and alimentary tract and metabolism FDC drugs at first market entry is lower than the AWP sum of the single active ingredients indicating that companies reduce the FDC AWP unit price in therapeutic classes with high utilization and large number of drug competitors in the market. In addition, cardiovascular and alimentary tract and metabolism FDC drugs are not granted priority review status by the FDA at the time of approval, indicating that those FDC drugs do not represent an improvement over the already marketed single active ingredient drugs. Conversely,

the AWP unit price of antinfectives for systemic use is higher for the FDC than the AWP per unit sum of the single active ingredients in the combination. Antinfective FDC drugs represent the highest percentage of FDA priority review FDC drug approvals in the study period. Furthermore, antinfective FDC drug approvals include indications for diseases, such as HIV and hepatitis C, that typically have fewer formulary restrictions hence, allowing pharmaceutical companies to setup a premium price for the combination.

Further, study results evidence that pharmaceutical companies' pricing strategy for cardiovascular and alimentary track and metabolism FDC drugs is based on setting up FDC AWP unit price below the price sum of the individual products included in the combination to signal the market that the combination is cheaper. Pharmaceutical companies setup the FDC drug price at market entry at the same level of the costliest single active ingredient in the combination to shift demand from single active ingredients facing generic competition towards new FDC drugs.

Pharmaceutical companies often advertise FDC drugs as pharmaceutical products that are convenient to the patient, with lower copayments and pharmacy dispensing fees associated with dispensing a FDC drug instead of multiple single ingredients [20, 21, 30-33]. Prior research also explored the clinical evidence on the differences between FDC drugs and single active ingredient regimens. FDC drugs reduce the complexity of treatment regimens and increase treatment adherence and persistence [34-39]. However, research is needed to assess whether those advantages outweigh the potential risk of exposing patients to higher dosage of pharmaceuticals and to estimate the cost-effectiveness of FDC drugs compared to single active ingredients included in the combination.

The AWP is the most commonly used unit price in the US market to estimate the drug product acquisition cost that is used to setup payments and reimbursement rates. The AWP does not represent actual transaction market prices; pharmaceutical companies setup a high AWP unit price to later on provide substantial discounts and rebates to pharmacies, managed care companies and health care payers. Study analysis using FUL prices, instead of AWP, further evidence that the AWP overestimate the actual final drug acquisition prices. The price difference percentage between the FDC and the single active ingredient drugs using the FUL prices further evidences that the actual market transaction prices for cardiovascular FDC drugs may be in fact higher than the price sum of the single ingredients when there are generic drugs in the US market.

Limitations

This study used the AWP unit price to proxy prices of FDC and single ingredient drugs. The AWP is an essential data resource for payers, decision makers, and stakeholders and it is commonly used as a drug price benchmark by state Medicaid programs, Pharmacy Benefit Managers (PBMs), and health plans. The AWP pricing history for almost all FDA approved drugs allows price comparison analyses and trends evaluation at the drug population level. However, the AWP does not represent the actual transaction price or reflect any discounts or rebates [29]. In addition, third-party payers use other methods to manage drug prices such as Medicaid Federal Upper Limit (FUL) for multiple-resource drugs [40]. Thus, price differences between FDC and single drugs may be overestimated.

The analysis is conducted based on the AWP at the time the FDC drug enters the US market. Generic drug market entry may lead to decreases in drug prices over time [41]; hence,

the price difference percentage between FDC and generic versions of the single active ingredients in the combination may become larger over time.

Study findings may not be representative of the combination drug market. The study includes 66 FDC drugs with complete information. Price data availability including rebates and discounts, and completeness of the information remains a challenge limiting the transparency in the pharmaceutical market. Last, analysis is based on the AWP unit price since defined daily dose data are not available for FDC drugs. Further research is needed to assess FDC drug utilization, actual drug acquisition prices after rebates and discounts, and costs of FDC drugs compared to the single active ingredients included in the combination.

Conclusions

The AWP price difference percentage between FDC and single active ingredient drugs included in the combination is correlated with the therapeutic class, the year of first FDA approval of the combination, and the number of single drugs in the combination that have generic versions at FDC market entry.

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Table 8. FDC and single active ingredient drugs AWP unit price by therapeutic class

Therapeutic Class	N	Percentage of FDC AWP over sum AWP of single ingredients (%)	
		Mean (Std)	Median (IQR)
Cardiovascular System	34	86.7%(23.7%)*	85.6 % (28.9%)
Alimentary Tract and Metabolism	14	67.4%(20.5%)* ^{††}	70.1 % (28.2%)
Antinfectives for Systemic Use	6	105.8%(16.9%) ^{††}	100.0 % (2.1%)
Sensory Organs	3	98.4%(38.2%)	97.9 % (76.4%)
Dermatologicals	2	133.3%(33.8%)	133.3 % (47.9%)
Musculo-Skeletal System	2	87.7%(21.0%)	87.7 % (29.8%)
Nervous System	2	74.6%(3.8%)	74.6 % (5.4%)
Respiratory System	2	68.8%(15.4%)	68.8 % (21.8%)
Genito Urinary System and Sex Hormones	1	49.1%	49.1%
Total	66	84.9%(26.2%)	84.6 % (31.7%)

Note: Analysis includes therapeutic classes that have 5 or more FDC drugs.

* Denotes statistically significant difference of AWP unit price difference percentage between the FDC and the single drugs between cardiovascular system and alimentary tract and metabolism (p=0.0127);

^{††} Denotes statistically significant difference of AWP unit price difference percentage between the FDC and the single drugs between alimentary tract and metabolism and antiinfectives for systemic use (p=0.0008); IQR=interquartile range.

Table 9. FDC and single active ingredient drugs AWP by selected characteristics of the combination

Characteristics	N	Percentage of FDC AWP over sum AWP of single ingredients (%)	
		Mean (Std)	Median (IQR)
FDC AWP at first market entry			
1980s	5	119.3%(29.2%)*	110.9%(9.4%)
1990s	14	84.9%(14.9%)	91.4%(23.8%)
2000s	28	86.7%(23.2%)	84.0%(30.0%)
2010-2012	19	73.0%(28.8%)	65.8%(30.4%)
Active ingredients included in combination			
2	60	84.7%(27.1%)	84.7%(32.5%)
3	6	86.0%(15.0%)	77.7%(31.8%)
Active ingredients that have generic competition			
0	19	83.3%(23.4%)	84.8%(36.4%)
1	40	83.8%(24.3%)	85.4%(28.1%)
2	7	95.1%(42.3%)**	72.9%(48.1%)

Notes:* Denotes statistically significant difference between the percentage of FDC AWP over the sum AWP of single ingredients and decade of FDC AWP at first market entry -1980s reference. Indicates statistically significant at $p < 0.05$

** Denotes statistically significant difference between the mean of the percentage of FDC AWP over the sum of single active ingredients in combinations that have generic version for 2 of the single active ingredients in the combination at the time the FDC drugs entered into the US market compared to combinations that did not have any generic in the combination. Indicates statistically significant $p < 0.01$

Table 10. Correlations between the percentage of FDC AWP over sum AWP of single active ingredients and FDC drug characteristics

Characteristics	Estimate	Standard Error	p value
Therapeutic class			0.0002
Anti-infectives for Systemic Use	-11.5%	6.5%	0.0833
Alimentary Tract and Metabolism	46.7%	10.8%	<0.0001
Cardiovascular System	ref		
FDC AWP effective year at first US market entry	-1.5%	0.4%	0.0002
Active ingredients included in combination			0.144
2	ref		
3	-16.8%	11.3%	0.144
Active ingredients that have generic competition			0.0193
0	ref		
1	13.5%	7.0%	0.0601
2	32.0%	11.1%	0.006

Note: The regression model includes therapeutic classes that have 5 or more FDC drugs. Number of observations is 54; $R^2=0.53$; ref=reference group

Table 11. Percentage of FDC AWP over single active ingredient prices: AWP and FUL

Therapeutic Class	N	Percentage of FDC over sum prices of single active ingredients			
		Single active ingredient AWP		Single active ingredient FUL	
		Mean (Std)	Median (IQR)	Mean(Std)	Median (IQR)
Cardiovascular System	5	71.4%(8.7%)	69.1% (40.1%)	108.2%(16.9%)***	81.8% (45.5%)
Alimentary Tract and Metabolism	5	62.8%(27.8%)	68.8% (83.2%)	71.7%(31.6%)*	103.0% (16.6%)
Dermatologicals	1	157.3%	157.3%	157.8%	157.8%
Respiratory System	1	57.9%	57.9%	64.9%	64.9%
Sensory Organs	1	136.8%	136.8%	232.7%	232.7%
Total	13	78.7%(35.2%)	69.3% (24.5%)	104.2%(51.2%)**	96.8% (31.1%)

Note: Statistically significant difference between the percentage of FDC over sum of single drug prices based on the AWP and FUL, respectively. *, ** and *** indicates statistically significant at the 0.05, 0.01 and 0.001 levels, respectively.

CONCLUSION

The findings of the studies support previous evidence that effective patent life of pharmaceutical products has increased since the 1980s. The increase in effective patent life length, however, was not significantly associated with an increased number of FDA-approved NMEs. Meanwhile, the approval of FDC drugs, especially FDC drugs including at least one previously marketed single ingredient drug, increased over the last three decades. Though varying depending on the therapeutic class, on whether the sponsor of the FDC and the single drug included in the combination was the same or different, and on the generic market entry of single drugs included in the combination, pharmaceutical companies marketed FDC drugs shortly before the generic alternative of the single active ingredient included in the combination reached the market, and effectively extended the patent and marketing exclusivity protection of the single drugs included in the combination.

These results indicate that, given the importance of patent protection to pharmaceutical products, longer patent time alone did not contribute significantly to bringing more innovative new drugs to the market. Alternative incentives and regulations should be considered by policy- and decision-makers for the purpose of encouraging more innovative new drugs. Further, based on the entire body of FDA-approved FDC drugs from 1980 to 2012, the study provides empirical evidence on the economics behind the development and approval of FDC drugs and the statement that FDC drugs of products that are already marketed has been a common strategy for brand-name drug companies to extend the patent and exclusivity life of single ingredient drugs with an expiring patent.

In regard to the economics of the FDC drug pricing, the study found that the FDC average wholesale price unit price increased significantly over time and that pharmaceutical

companies set FDC AWP, at the same level of the costliest single active ingredient in the combination as pricing strategy to shift demand from single active ingredients facing generic competition toward new FDC drugs. However, the price difference between FDC and single ingredient drugs varied by therapeutic class, the year the FDC entered into the US market and the number of single drugs in the combination that have generic drugs at FDC market entry.

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