Is Excess Regulation Responsible For Soaring Pharmaceutical Prices?

Mary J. Ruwart, Ph.D. (AAPS2004@spamex.com)

Sci-Com, Burnet, TX and Department of Biology, University of North Carolina, Charlotte, NC

Abstract

Purpose: To quantify the costs and benefits of the 1962 Kefauver-Harris Amendments and their impact on prescription drug expenditures by consumers.

Methods: Published data were used to calculate the impact of the amendments on drug development time, lives lost by development delays, lives saved through improved drug safety, consumer savings due to improved drug quality, research and development (R&D) costs per new chemical entity (NCE), and prescription drug expenditures.

Results: Drug development time, which had been stable since the 1930s, rose an additional 9.8 years from 1962-1999, primarily due to the amendments. R&D costs per NCE had increased slowly with time prior to the 1960s. After amendment passage, the rate of increase rose 13-fold. Had pre-amendment trends continued, the capitalized cost of putting a new drug on the market might have been as low as 8% of what it is today. R&D/NCE was highly correlated with prescription drug expenditures, suggesting a link between soaring pharmaceutical prices and the amendment-driven increases in drug development costs. These costs exceeded savings to consumers from ineffective new drugs, estimated to be less than 10% of new introductions prior to the amendments. The amendments probably saved as many as 40,000 lives by improving drug safety, but the longer development times caused about 4.7 million premature deaths due to delayed introduction of life-saving drugs. Drugs abandoned because of amendment-driven costs or shortened patent lives cost an estimated 4.7-16.8 million lives as well. Thus, about 20-33% of disease-related deaths from 1963-1999 might have been prevented in the absence of the amendments.

Conclusions: Both monetary and human costs of the amendments appear to exceed benefits. In addition, the soaring cost of prescription drugs may result from amendment-driven increases in new drug R&D.

Introduction

The 1962 Kefauver-Harris Amendments, passed in the wake of the thalidomide tragedy, impacted dramatically on pharmaceutical manufacturing, labeling, advertising, and development. Manufacturers had to demonstrate clinical efficacy, as well as safety. The FDA had to approve applications, rather than simply objecting to those it found wanting. Consequently, the FDA began requiring more studies, both clinical and pre-clinical, in an effort to insure both safety and effectiveness.

Regulatory requirements have opposing effects on drug safety. The added testing can result in early detection of side effects. However, the accompanying delays in getting a life-saving drug to market can result in unnecessary deaths. The added monetary cost of regulations may also limit the number of drugs which can be developed, while increasing the prices of those which do reach the market. This study constructs an approximate cost/benefit ratio of these tradeoffs for the 1962 amendments and their impact on new drugs, i.e., new chemical entities (NCEs).

Benefits

The amendments were expected to guard against drug toxicity. In the 12 years prior to amendment passage, drug casualties (death or serious injury) of 100 or more were reported in the U.S. for four drugs (Table 1). Thus, the maximum protection that could be afforded by the amendments was to prevent ALL such toxicity. ***Using this assumption of total eradication of side-effects, about 7000 lives could have been saved from 1963 to 2003.***

Table 1: Pre-Amendment Drug Deaths and Serious Injuries

Drug	Actual
Chlorampencicol	753
MER-29	500
Cutter vaccine	215
Orabilex	100
Total	1568
Total/decade	1206
Total without amendments (1963-2003)	4825
Population Adjusted	6994

Drug casualty data from Gieringer (1985).

Table 2: Consumer Waste from Ineffective NCEs

Prior to amendment passage, manufacturers had to show that their drugs were safe for their intended use. Because the amendments demanded rigorous efficacy testing as well as safety testing, they were expected to protect the consumer from wasteful spending on ineffective drugs.

The FDA asked the National Research Council for an efficacy evaluation of pre-amendment drugs. In addition, other researchers reported on how medical professionals, such as doctors, formularies, and pharmacies, evaluated pre-- and post-amendment NCEs (Table 2).

Study Author	% Ineffective
Natl. Research Council (1969)	**7**
Jondrow (1972)	**9**
Peltzman (1974) pharmacies	**0**
Peltzman (1974) formularies	**0**
Peltzman (1974) physicians	**10**

Had the amendments eliminated ALL wasteful spending from inefficacious drugs, the maximum savings expected would be 10% of NCE purchases.

Costs

Figure 1. Estimated Temporal Regulatory Burden

The amendment-driven regulatory demands greatly increased development time, defined as the interval between compound synthesis and FDA approval, for NCEs. Development times had been stable or declining slightly for 25 years prior to the amendment's introduction into Congress (Figure 1), making this increase especially noteworthy.

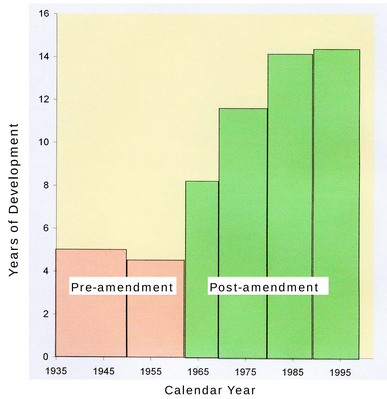

Figure 1. Pre-amendment development times (years between synthesis and approval) shown in pink from Schnee (1970). Post-amendment development times shown in green (Hansen (1979); DiMasi et al. (1991); DiMasi et al. (2003)).

By the 1990s, the average development time for NCEs was 14.2 years compared to 4.4 years in the 1950s, suggesting that the temporal regulatory burden was 69%. In 1984, the Waxman-Hatch bill recognized this regulatory burden in an attempt to restore part of the lost patent life for new drugs. In doing so, the bill defined a "regulatory review period" that estimated the total temporal regulatory burden in the 1980s at 84%. Thus, only 15% of the temporal regulatory burden can be ascribed to pre-amendment legislation.

Development times peaked in the 1990s, primarily due to the Prescription Drug User Fee Act (PDUFA) of 1992. Approval times dropped by one year, but were offset by other increases. Total development time for the 1990s would have been 15.2 years without PDUFA.

Table 3. Lives Lost From Extended Development Times

Lichtenberg (1999) estimated that each NCE saves about 11,200 life-years/year, based on U.S. population levels in 1991. This translates to about 767 lives/NCE/year, based on the weighted average of life years lost when a person dies from heart disease, stroke, or cancer (Statistical Abstracts of the United States (2003). ***Thus, the number of lives lost by the amendment's prolongation of development times can be estimated at 4.7 million lives (Table 3).***

Time Periods	1963-1969	1970-1979	1980-1989	1990-1999
Number of NCEs Approved	83	173	204	290
Mean Development Time (Yrs)	8.1	11.6	14.1	14.2
Years due to Amendments	3.7	7.2	9.7	9.8
Population Relative to 1991	0.778	0.851	0.94	1.04
Lives Lost due to Delays	**183,284**	**813,155**	**1,426,905**	**2,267,371**

Total Lives Lost	**1963-1999**	**4.7 million**

Figure 2. Impact of the Amendments on New Drug R&D

Prior to amendment passage, R&D costs per NCE were rising slowly with time. After amendment passage, development costs for new drugs rose steeply (Figure 2). The trend line established by Equation 1 for post-amendment development costs suggests that out-of-pocket R&D/NCE in 2003 was $500 million (inflation-adjusted dollars). Had pre-amendment trends continued, Equation 3 predicts that R&D/NCE in 2003 would have been a mere $69 million or about 14% of what it is today. The monetary regulatory burden of the amendments (86%) is somewhat higher than the temporal one (69%), suggesting that manufacturers spend more on R&D than they otherwise would in an attempt to compress lengthy development time lines.

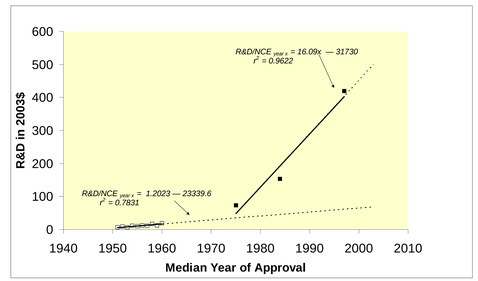

Figure 2. Post-amendment (closed squares; Hansen (1979), DiMasi et al. (1991), and DiMasi et al. (2003)) and pre-amendment (open squares; Schnee (1970) and Bailey (1972)) out-of-pocket development costs as a function of median approval time.

Capitalizing costs widen the gap between pre-- and post--amendment extrapolations, because of longer development times post-amendment (14.2 in the 1990s vs. 4.4 years in the 1950s). For example, today's $500 million out-of-pocket costs become $1,209 million when capitalized at 11%. Had pre-amendment trends continued until today, the $69 million out-of-pocket costs predicted by Equation 3 would become $92 million.

In summary, had pre-amendment trends continued, today's out-of-pocket R&D/NCE would be 14% of what it currently is. Capitalized R&D/NCE would be a mere 8% of what it is today.

Figure 3. Impact of the Amendments on Pharmaceutical Expenditures

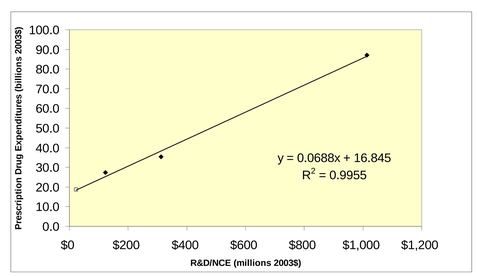

Figure 3. Inflation-adjusted prescription drug expenditures in billions of 2003 dollars (Statistical Abstracts of the United States, 2002) as a function of pre-amendment (1960; open square) and post-amendment (1975, 1984, and 1997; closed squares) capitalized new drug R&D (millions of 2003 dollars). Regression line includes all four data points.

R&D costs correlate closely ($r^2 = 0.99$) with prescription expenditures by consumers, whether out-of-pocket (data not shown) or capitalized costs (Figure 3) are used. Such a correlation might at first seem surprising, since pharmaceutical companies spent no more than 22% of each domestic sales dollar on U.S. R&D. However, the amendments impacted greatly on manufacturing, labeling, and advertising as well as drug development. Thus, new drug R&D may act as a surrogate, at least in part, for the impact of the amendments on these other expenses.

In addition, it is common business practice to price products as a multiple of costs. Since R&D is the largest single cost for NCEs, it might be a convenient yardstick by which to price new pharmaceuticals. Although further work is needed to clarify these relationships, Figure 3 implies that a reduction in new drug R&D would reduce our pharmaceutical expenditures proportionately.

Thus, prescription drug costs, reported to be $162 billion in 2003 (PhRMA, 2003), might have been as low as $24 billion had pre-amendment R&D trends continued. Expenditures on prescription drugs would then be only 15% of what they are today.

Table 4. Impact of the Amendments on Innovation

High R&D forces manufacturers to channel funds into development and away from innovation. Consequently, fewer NCEs reach the public. Wiggins (1981) estimated that the amendments decreased new introductions by 57% (or 47% if we assume that 10% of the decrease was due to the amendments' exclusion of inefficacious NCEs (see Table 2)). More recent decreases in new introductions can be calculated from the data of DiMasi (2001), who measured the number of NCEs dropped from late-stage testing for "economic reasons." DiMasi's estimates did not include compounds dropped for economic reasons prior to selection as a drug candidate or early in the development process. Thus, the innovative loss, calculated as a weighted average of the Wiggins and DiMasi's estimates (Table 4), is probably larger than 50%.

In other words, without the long development times and the resultant high cost of developing NCEs, we'd have more than twice as many innovative new drugs as we do today.

Years	Loss of NCEs	Study Source
1963-1969	47%	assumed from Wiggins (1981)
1970-1976	47%	Wiggins (1981)
1977-1980	47%	assumed from Wiggins (1981)
1981-1986	48%	DiMasi (2001)
1987-1992	54%	DiMasi (2001)
1993-1999	54%	assumed from DiMasi (2001)
Weighted Average	**50%**	**Loss of innovative NCEs**

Table 5. Cost of Innovation Losses

Loss of innovation is costly to the consumer, because every dollar spent on new pharmaceuticals yields $2.11 in other health care savings and $0.91 in savings from leisure and work time that would otherwise be lost to illness (Lichtenberg, 1996). In addition, Lichtenberg estimates that every 10% increase in new drug approvals reduce disease-related mortality by 5%. Thus, the lives lost when innovation decreases can also be estimated (Table 5). The actual losses depend on how potent the lost innovations would have been compared to drugs currently on the market. Since true innovations are more costly and difficult to test, drugs that would have saved many lives and much money are likely to have been abandoned early in development. If so, Table 5 may greatly underestimate the impact of the amendments.

Depending upon the potency of the lost innovations, their absence has cost us somewhere between $48-$483 billion in unnecessary health care costs and lost time. Approximately 2.5-25% of disease-related deaths in the past 40 years might have been prevented by these innovations. Instead, somewhere between 1.6 and 16 million people died prematurely.

	Potency of Lost Innovations		
Compared to Marketed Drugs	**100%**	**50%**	**25%**
Health Care Losses (billions $)	337.6	168.8	84.4
Leisure/Work Time Losses (billions $)	145.6	72.8	36.4
Total Cost in Money	**483.2**	**241.6**	**724.8**
Total Cost in Lives			
% of disease-related deaths	**25**	**12.5**	**8.2**
millions of disease-related deaths	**16.5**	**8.2**	**4.1**

Table 6. Summary of Cost and Benefits

Table 6 summarizes the costs and benefits of the 1962 amendments. ***Depending upon which assumptions are used, monetary costs appear to exceed benefits by a factor of 100 or more. In terms of lives lost, costs appear to exceed benefits by at least 900 to 1.***

Costs	in billions of $		in 1000s of Lives	
	Minimum	Maximum	Minimum	Maximum
Prescription Drug Costs	114	138		
Health Care Costs	84	338		
Leisure/Work Costs	36	146		
Development Delays			4700	4700
Innovation Losses			1600	16500
Total Costs	**234**	**622**	**6300**	**21200**
Savings from less waste		2.5		
Lives Saved				7
Total Benefits		**2.5**		**7**
Cost/Benefit Ratio	**94**	**249**	**900**	**3029**

Discussion

The amendments impose additional costs which are not addressed here, notably the taxpayers' cost of enforcing them. In addition, because manufacturers are rarely able to profitably promote generic or natural products for new indications, they choose instead to develop new prescription drugs which enjoy patent exclusivity. Many inexpensive compounds that prevent or alleviate disease are underutilized or chemically reconfigured into a more costly prescription medication.

Thus, even though these estimates are not be exact, it's likely that they underestimate, rather than overestimate, the detrimental impact of the amendments. This is hardly surprising, since most drug toxicity, even in pre-amendment times, was largely a result of drug sensitivity in small subsets of the population rather than manufacturer negligence. Even had thalidomide been tested in pregnant rats and dogs, it's toxic effects would have remained undetected, since they are generally restricted to primates. Thus, in terms of safety, the regulations could, at best, make minor improvements.

Marketplace discipline had already limited consumer waste from lack of efficacy to about 10% of NCE approvals. Thus, the amendments had little room for improvement. To eliminate that 10%, the regulations increased the price of pharmaceuticals about 600-700%, hurting instead of helping consumers.

The largest cost of the amendments is in loss of life through the delayed availability of life-saving drugs and shifting of resources from innovation to development. This loss of life invariably shifts costs to health care, since standard medical procedures, which are more expensive, are often substituted.

Work by previous investigators (Grabowski, et al. (1978); Jadlow (1970); Peltzman (1973); Sarett (1974); Wardell and Lasagna (1975)) also suggested that the monetary and human cost of the amendments exceeded benefits. Their work was largely ignored by legislators since the data sets used for quantification in this study were not yet available. ***Somewhere in the neighborhood of 20-33% of people who died disease-related deaths from 1963-1999 paid the ultimate price for this excess regulation.***

Had the amendments not become law, this analysis predicts that some 10-20 million people would have lived longer and healthier lives. Capitalized new drug R&D might be as little as 8% of what it is today. We'd have at least twice the number of innovative pharmaceuticals, yet prices would be about 15% of what they are now. Even if pharmaceutical expenditures doubled with the increase in the number of new drugs, we'd still pay only 30% of what we do today. Health care costs, including pharmaceuticals, might be lowered by as much as 28%.

Like all analyses of social impact, these estimates lack the rigor of a controlled scientific experiment. However, even with their limitations, they present compelling evidence that the national debate on pharmaceutical pricing and health care costs should include a focus on the unintended consequences of regulation.

Conclusion

The costs, in both lives and money, of the 1962 Kefauver-Harris amendments likely exceed benefits by a factor of 100 or more.

These costs include pharmaceutical prices 6-7 times what they otherwise would be, 10-20 million premature deaths, loss of more than half our potential life-saving innovation, and double-digit increases in health care costs.

The national debate on pharmaceutical prices and health care costs should include a rigorous examination of the impact of excess regulation.

Acknowledgements/References

This study could not have been undertaken without the critical research cited below. The author would like to acknowledge those who put so much effort into documenting the nuances of drug development. A special thanks goes to Frank Lichtenberg for his kind sharing of unpublished FDA listings of NCEs.

Bailey MN. Research and development costs and returns: the U.S. pharmaceutical industry. *J Political Economy* 1972; 80:70-85.
DiMasi, JA. Risks in new drug development: approval rates for success rates for investigational drugs. *Clin Pharmacol Ther* 2001b; 69:297-307.
DiMasi JA, Hansen, RW, Grabowski, HG, Lasagna, L. Cost of innovation in the pharmaceutical industry. *J Health Economics* 1991; 10:107-142.
DiMasi JA, Hansen, RW, and Grabowski, HG. The price of innovation: new estimates of drug development costs. *J Health Economics* 2003; 22:151-185.
Grabowski HG, Vernon JM, and Thomas LG. Estimating the effects of regulation on innovation: an international comparative analysis of the pharmaceutical industry. *J Law Economics* 1978; 21:33-163.
Gieringer DH. The safety and efficacy of new drug approval. *Cato J* 1985;5:177-201.
Hansen RW. "The pharmaceutical development process: estimates of current development times and effects of regulatory changes," in Robert I. Chien's *Issues in Pharmaceutical Economics*. Lexington, Mass: Lexington Books; 1979.
Jadlow, JM Jr. The economic effects of the 1962 amendments [dissertation]. Charlottesville, VA: University of Virginia, 1970
Jondrow J. A measure of the monetary benefits and costs to consumers of the regulation of prescription drug effectiveness [dissertation]. Madison, WN: University of Wisconsin, 1972.
Lichtenberg, FR. Do (more and better) drugs keep people out of hospitals? *Am Econ Rev*, 1996; 86:384-88.
Lichtenberg, FR. Pharmaceutical innovation, mortality reduction, and economic growth. *NBER Working Paper #w6569*. Washington, DC: National Bureau of Economic Research; 1999.
National Research Council's Drug *Efficacy Study: Final Report to the Commissioner of Food and Drugs.* Washington, DC: National Academy of Sciences; 1969.
Sam Peltzman's *Regulation of pharmaceutical innovation: the 1962 amendments*. Washington, DC: American Enterprise Institute for Public Policy Research; 1974.
Pharmaceutical Research and Manufacturers of America (PhRMA)'s *Pharmaceutical Industry Profile 2003*. Washington, DC: PhRMA, 2003, p. 33.
Sarett, LH. FDA regulations and their influence on future R&D. Research Management, March: 18-20; 1974.
Schnee JE. Research and technological change in the ethical pharmaceutical industry [dissertation]. Philadelphia: University of Pennsylvania, 1970.
U.S. Census Bureau's *Statistical Abstract of the United States*. Washington, DC: US Government Printing Office; 2002, Table No. 112, p. 91.
U.S. Census Bureau's Statistical *Abstract of the United States*. Washington, DC: US Government Printing Office; 2003, Table No. 125, p. 99.
William M. Wardell and Louis Lasagna's *Regulation and Drug Development*. Washington, D.C.: American Enterprise Institute for Public Policy Research, 1975).
Wiggins, SN. Product quality regulation and new drug introductions: some new evidence from the 1970s. *Rev Econ Statistics* 1981;63:615-619.