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Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program

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Abstract

Context—In 1997, Congress authorized the Food and Drug Administration (FDA) to grant 6 month extensions of marketing rights through the Pediatric Exclusivity program if industry sponsors complete FDA-requested pediatric trials. The program has been praised for creating incentives for studies in children; it has been criticized as a "windfall" to the innovator drug industry. This critique has been a substantial part of Congressional debate on the program, which is due to sunset in 2007.

Objective—To quantify the economic return to industry for completing Pediatric Exclusivity.

Design—Cohort study of programs conducted for Pediatric Exclusivity. We selected 9 drugs that were granted Pediatric Exclusivity. From the final study reports submitted to FDA, we obtained key elements of the clinical trial design and study operations. We estimated the cost of performing each study and converted these into estimates of after-tax cash outflows. We obtained 3-year market sales and converted these into estimates of after-tax cash inflows based upon 6 months of additional market protection. We then calculated the net economic return (cash inflows less outflows) and ratio net return to costs (net economic return divided by cash outflows) for each product.

Main Outcome Measures—Net economic return and ratio of net return to cost.

Results—The indications studied reflected a broad representation of the program: asthma, tumors, attention deficit disorder, hypertension, depression/generalized anxiety disorder, diabetes, gastroesophageal reflux, bacterial infection, and bone mineralization. The distribution of net economic return for 6 months of exclusivity varied substantially among products [net return ranged from (−)$8.9 million to (+)$507.9 million; ratio of return to cost ranged from −0.68 to 73.6]

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Publisher's Disclaimer: The Views expressed in the paper are those of the authors and not necessarily those of the Food and Drug Administration or any other federal agency. No official endorsement by the Food and Drug Administration is provided or should be inferred. Dr. Li had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript are independent of any funding organization.

Conclusions—The economic return for pediatric exclusivity is highly variable. Pediatric Exclusivity, as an incentive to complete much-needed clinical trials in children, can generate lucrative returns, but more frequently produces more modest return on investment.

Introduction

Historically, only 25% of approved drugs marketed in the United States have sufficient pediatric data to support approval of product labeling by the US Food and Drug Administration (FDA) for dosing, safety, or efficacy in children. [1] Inadequate dosing and safety information places children at risk for adverse events and denies them potential therapeutic benefits. [2, 3]

In 1994, the FDA encouraged sponsors to obtain more pediatric drug data; however, new studies were not required, and the number of new studies was minimal. [4] In 1997, Congress passed the Food and Drug Administration Modernization Act (FDAMA). [5] Section 505A of FDAMA, known as the Pediatric Exclusivity Provision, provided an additional 6 months of patent protection, or marketing exclusivity, in return for performing studies specified by the FDA. The Best Pharmaceuticals for Children Act of 2002 extended the economic incentives provided by Pediatric Exclusivity. [6] This program has been successful from many perspectives resulting in a substantial increase in pediatric drug research compared to the very limited amount of such research prior to Pediatric Exclusivity. To date, the program has generated over 300 pediatric studies and over 115 products have undergone labeling changes for pediatric use. Despite this increase in pediatric drug studies, the Pediatric Exclusivity program has critics who contend that it has given a big “windfall to the prescription drug industry” because the profits enjoyed by the companies from the patent extensions are perceived to greatly exceed the cost of conducting the studies [7]. Several revised components of the Pediatric Exclusivity Program legislation have thus been proposed. These include disbanding the program altogether, varying the lengths of marketing protection based on annual sales, and reducing the marketing protection from 6 months to 3 months.

Precise data on study costs have not been available and estimates vary considerably. The National Institute of Child Health and Development has estimated that a safety and efficacy study may cost between $1 million and $7.5 million while the cost of a pharmacokinetic study can cost from $250,000 to $750,000 per age group.[3] The Pharmaceutical Research and Manufacturers of America (PhRMA) has estimated higher study costs ranging from $5 million to more than $35 million. [3] In another study, based on a survey of drug companies, the cost of pediatric studies was estimated to average $3.87 million per written request. [8]. The “Written Request” is issued by the FDA to the company and contains the required elements of the studies for Pediatric Exclusivity: the indication, number of studies, sample sizes, and trials design.

The Best Pharmaceuticals for Children Act will expire and face renewal by Congress in 2007. In addition to determining the costs of pediatric trials, we sought to determine if the incentives provided by the law are disproportionate to the costs of studies.

Methods

We identified the clinical trials performed for Pediatric Exclusivity though the “Written Request”. Although Pediatric Exclusivity was initiated in 1997, we evaluated studies for which the data were submitted from 2002–2004 (inclusive) because these data were available and presented to FDA uniformly under the electronic submission process, summaries from these studies are publicly available,[9] economic data are current, and the decisions regarding the granting of exclusivity were complete. During this period, data from 59 products were submitted to FDA. We selected the products to study using the following algorithm. We subdivided the program into the following areas: allergy/immunology (6 products), cancer

(n=9), central nervous system (n=8), cardiovascular (n=9), psychiatry (n=5), endocrine (n=6), gastro-intestinal (n=4), infectious disease (n=10), and other (n=2). We selected one product from each area, using the most recent application for which data were most complete in the 'electronic document room' of FDA. The electronic document room is a repository in which all components of submissions have been stored since 2002.

For each product, we estimated the net economic return to industry from participation in the Exclusivity program, and calculated the resulting net return to cost ratio. We use the following definitions: *net economic return* is the difference between after-tax cash inflows and outflows associated with the additional period of patent exclusivity; *cash inflows* represent estimates of product sales (net of production, marketing, and distribution costs) during the period of extended patent exclusivity; and *cash outflows* are estimates of the costs of performing pediatric studies. Cash inflows and outflows for each product were adjusted to 2005 after-tax values and adjusted to their present values as of June 30, 2005 using a discount factor comparable to the pharmaceutical industry's expected return from investment.

To estimate cash outflows, we used the final study report to estimate the cost of the trials, including investigative site costs, contract research organization costs, pharmaceutical company costs, and core laboratory costs. We partnered with two organizations to assist us in our estimates, Fast Track Systems, Inc. (Conshohocken, PA) and Covance Central Laboratory Services (Indianapolis, IN).

Fast Track Systems provided access to three separate global cost and procedure benchmarking databases drawn from over 240,000 negotiated investigator agreements, 25,000 finalized protocols in 800 indications and 3,000 contract research organizations[10]. Investigative site, coordinating center, and internal pharmaceutical costs were estimated based on input of trial parameters including: trial phase, indication, trial locations, number of sites, screen failure percentage, number of enrolled patients, study procedures, overhead costs, document preparation, pre-study preparation and recruitment, investigator meetings, site initiation visits, site monitoring, site close-out, site management, project management and administration, data entry, data clean-up, database programming and transfers, generation and review of tables, statistical plan and analysis, integrated clinical/statistical report, regulatory audits, and drug distribution.

When clinical trials required the use of a central core laboratory, we obtained an estimate from Covance Central Laboratory Services[11] internal pricing tool, which provides costs in an 8 service template including: database construction services, investigator training, collection services, transportation services, laboratory services, data services, clinical trials management, and specimen management. Drug shipment costs were included in the price of the trials, but costs for drug manufacturing and drug packaging were not.

Trial costs were estimated in 2005 dollars and did not require price adjustment. To adjust these cash outflows to after-tax values, we assumed that cash outflows (study costs) would be allowable expenses in income tax computation and that they would be taxed at the industry's average rate (30%) [12], which was varied between 25% and 35% in sensitivity analyses. Yearly sales data for each drug product was obtained from IMS Health, Inc (Fairfield, CT)[13] from pharmaceutical sales data audits. [14] Data were obtained from either 2002–2004, or the last three years before patient exclusivity expired.

We used contribution margin [15] (sales revenue less variable costs) which represents funds available to support fixed costs and profit to estimate the incremental after-tax cash inflows accruing from investments in pediatric clinical trials. (e.g. a 45% contribution margin means that to sell an additional dollar worth of product, it costs the company an additional 55 cents in variable costs) To estimate net cash inflows from average annual IMS sales, we assumed a

10% sales discount rate, a 50% contribution margin, and a 30% tax rate. IMS reports gross sales and does not include discounts to managed care, we therefore adjusted the IMS data to reflect a 10% discount from gross sales (90% net sales). The contribution margin averages 45% in the pharmaceutical industry[12]. However, the products in this study were nearing the end of their patent lifecycles and would be expected to have lower marketing and administrative costs. Thus, we assumed a 50% contribution margin (varied between 40% and 60% in sensitivity analyses). We assumed that cash inflows would be taxed at the industry average rate (30%, 25%–35% in sensitivity analyses).[12]

To avoid bias, we adjusted cash inflow and outflow estimates to account for differences in the timing of events. We used 2005 as our reference year and assumed that FDA final submissions for all products would occur on June 30th, 2005. Cash outflows were adjusted for the time interval between the midpoint of each study's duration and the reference date; and cash inflows were adjusted for the time interval between the reference date and the end of patent exclusivity. We selected a discount rate of 8% (0%–20% in sensitivity analyses) that is reflective of return on investment expectations in the pharmaceutical industry. A lower cost of capital of 8 % is used for the 2002–04 period because of lower interest rates on debt capital and lower returns on equity capital than was prevalent in the 1990s.[12] As cash outflows occurred before the reference date, their values were inflated to account for the company's lost opportunity costs. Conversely, because cash inflows occurred after the reference date, their values were deflated. We calculated the net economic return per Written Request by subtracting the discounted after-tax cash outflows from the discounted after-tax cash inflows associated with an additional 6 months of exclusivity. The net return to cost ratio was obtained by dividing the net economic return by the discounted after-tax cash outflow. Estimates were also calculated for 3 months of exclusivity.

We contacted companies to confirm estimates of costs and received validation on the condition that their product and the company were not identified. We did not include the cost of regulatory filing of the drug with the FDA, the costs of any pre-clinical work including juvenile animal toxicology studies, or the costs of developing a liquid formulation for pediatric use.

Results

The 2002–2004 Cohort

From 2002 to 2004, data from 59 therapeutic agents were submitted in response to the Pediatric Exclusivity Program. For these 59 agents, 137 trials were completed; 22,991 children were enrolled in these trials. The largest trial enrolled 795 children; the smallest enrolled 10. The median trial enrollment was 116 children. The median number of clinical trials completed for an agent was 2. The number of trials per product ranged from 1 to 8. Of these products, 13 products had annual sales of >$1,000,000,000 (Table 1), and the median annual sales of the 59 products submitted in the 2002–2004 cohort was $181,254,000. As noted in Table 1, 22% of the products studied between 2002–2004 fall into the "blockbuster" category of over $1,000,000,000 in annual sales.

The Products Selected

For this analysis, we obtained the final study reports from 9 drugs in a broad range of therapeutic areas under the algorithm described (Table 2). 8 of the 9 drugs underwent a labeling change as a result of the studies. Twenty seven clinical trials were completed: 16 evaluated efficacy, 4 were multi-dose pharmacokinetic, 6 were single-dose pharmacokinetic, and 1 was a safety study. Study sample size ranged from 18 to 1088 patients.

The median number of patients enrolled was 140 (range: 13, 1088), the median number of sites was 16, (range: 1, 118), and most trials were primarily conducted in the United States (Table 3). Nearly half (48%) of the trials took more than two years to complete. Most of the trials collected detailed data: the median number of case report forms for a trial was 73 (25th% was 59 pages and 75th% was 166 pages collected), and the median number of tables, listings, and figures for the Final Study report was 81 (Table 3).

The estimated costs of conducting each trial with coordinating center costs, sponsor management costs, site payments, central lab payments, and total costs had considerable variability (Table 4). Estimates of clinical trial costs are provided with a low estimate and a high estimate. However, our experience from multicenter clinical trials in children suggests that the high estimate is a more accurate reflection of the costs of conducting clinical trials in children [16–19]. Using this estimate, the median cost per written request was $12.34 million dollars (range $5.13 to $43.8 million dollars). The median cost for a single-dose pharmacokinetic study was $894,941 (range $ 655,139 to $ 7,114,220); median multi-dose pharmacokinetic study cost was $ 2,297,250 (range $ 655,829 to $20,967,287); and median efficacy study cost was $ 6,464,921 ($1,770,566 to $12,948,325). Five of the 9 products in this cohort would be considered “blockbuster” drugs with yearly US sales exceeding $1 billion dollars (Table 1). This is substantially higher than the 2002–2004 cohort for which 22% (13/59) of the products were “blockbuster” drugs (p=0.027). Thus, this group of 9 drugs is heavily weighted with products with a very high expected rate of return on sales.

The economic return estimates are based on assumptions of 6 months and 3 months of exclusivity (Table 5). The cash outflow amount (investment) is derived from the high estimate of after-tax cash outflows. The benefit is derived from the additional after-tax cash inflows associated with increased US sales during the time period (6 or 3 months). Median cash inflows were $140,447,244 (range $4,284,363 to $514,797,478) assuming 6-months of exclusivity, and decreased proportionately when the exclusivity period was reduced to 3 months. Median cash outflows were $10,362,062 (range $3,694,886 to $34,748,863). Assuming 6 months exclusivity, the median net benefit was $134,265,456 (range −$8,946,033 to $507,899,374). With 3 months exclusivity, the median net benefit was reduced to $64,041,833 (range −$11,088,214 to $250,500,635). These changes in net economic benefit are reflected in the ratios of net return to cost (Table 6).

Figures 1 and 2 show the change in net return to cost ratios associated with variations in contribution margin and discount rates. Products with larger cash inflows (e.g., Drug 6) were more sensitive to variation in contribution margin; whereas, products with lower cash inflows (e.g., Drug 5) were less sensitive. With regard to the discount rate, products with longer time lags between their clinical studies and the beginning of market exclusivity were more sensitive to changes (e.g., Drug 7); while those will short time lags were less sensitive (e.g., Drug 9).

Discussion

The development of therapeutics is based on ownership of pharmaceutical discoveries by for-profit businesses. [20] Drug development is enormously expensive because of the high attrition rate of potential products as they proceed through laboratory, animal, and human trials. The pharmaceutical industry recovers its expenses through charging a high price for the drug, based on exclusivity rights under patent. When the patent expires, the average market price decreases through competition with generic drugs. [21] The Pediatric Exclusivity Program was designed to give a financial incentive of 6 months of patent extension or marketing rights to pharmaceutical companies that conduct studies requested by FDA. Outside of the Exclusivity Program, the FDA is limited in the number and scope of studies for which it can require pediatric data for existing products on the market. The Exclusivity Program, therefore,

represents a unique opportunity to expand our knowledge of the safety and efficacy of products used in children.

We have estimated of the costs and economic benefits to pharmaceutical companies of a cohort of products submitted to FDA for approval. One might expect only those products with high yearly sales would be evaluated by the industry. We found, however, that products with a wide range of sales and with a variable return on investment were evaluated. We found that a very high rate of return is realized by blockbusters with annual sales of over $1,000,000,000; however, a much lower rate of return was likely realized by most products in the overall 2002–2004 cohort. Several products that submitted data for exclusivity in the overall 2002–2004 cohort may have been close to break-even with respect to financial return on investment. In fact, one product may have been studied at a negative return on sales.

The US General Accounting Office data have shown that most products that participate in the program have annual sales of <$200,000,000 [3]. Another study demonstrated that most medicines awarded Pediatric Exclusivity are not among the 200 top selling drugs [22]. The median annual sales of the 59 products submitted in the 2002–2004 cohort was $181,254,000 and 23/59 products had annual sales <$150,000,000.

Limitations

These data have several limitations, most of which underestimate the cost of submitting the data to FDA and thus serve to overestimate the return on sales on average. We did not have access to juvenile animal data that may have been required to conduct these trials. We did not have access to the costs associated with making special formulations —e.g., chewable tablets or liquid preparations— and the costs of required bioequivalence and stability testing. Our sample included an over-representation of products with high annual sales; 5/9 products had annual sales >$1,000,000,000.

The software we used to estimate the costs of conducting trials is used most frequently in adult trials, and pediatric trials are usually more expensive. At the Duke Clinical Research Institute, we are the data coordinating center for both adult and pediatric trials conducted under FDA guidance [16–19] and it has been our experience that pediatric studies cost more per patient than adult studies for both the coordinating center and the site investigator. We therefore used the higher study cost estimate for our analysis.

We focused on the economic incentives to industry of completing Pediatric Exclusivity. We did not account for the economic costs to health care incurred by the delay in generic versions of these products appearing on the US market. We did not evaluate improved treatment and reduced adverse events resulting from better labeling. We did not measure the potential liability to industry of discovering previously unreported (or undetected) adverse events in a pediatric study that may jeopardize sales to the entire product. As an example, the FDA joint advisory committee voted to recommend a “black-box” warning for certain antidepressant medications indicating that they increase the risk of suicidal thinking and behavior among pediatric patients. These data were derived mostly from studies of antidepressants performed for Pediatric Exclusivity [23–25]. Lastly, we did not measure the clinical benefits to children, their families, and our society from having pharmaceuticals tested in pediatric populations

Application of data

The Pediatric Exclusivity Program has been a success from the perspective of conducting trials for labeling in children. Between the start of the program in 1997 and the time of this writing, over 115 products have had a labeling change. Nearly 1/3rd of these labeling changes showed

an important difference in the pediatric dosing, safety, or efficacy compared to adult patients. This new information will likely result in long-term health benefits for children.

The Pediatric Exclusivity Program, and much of the pediatric reform Congress enacted in 1998 and 2002, is set to expire in 2007. Congressional debate regarding the renewal of the program includes the financial benefits granted to companies for their participation —namely the incentive in the form of 6 months market protection. Critics contend that obtaining Pediatric Exclusivity affords some manufacturers enormous returns.

In consideration of the large amount of information obtained for childhood health in the Pediatric Exclusivity Program, we contend that it would be a tragedy to "throw the baby out with the bathwater." These data suggest that if marketing protection is universally reduced from 6 months to 3 months, products that are likely to see small profit margins may not be submitted for pediatric testing. These may include medications for conditions such as bacterial infections (Drug 5) and, hypertension (Drug 2), which have a profound public health importance for children. Reduction in the amount of marketing protection will likely not change the study of drugs which are already widely used in children and adolescents [such as those with an indication for attention deficit hyperactivity disorder (Drug 8)]. These data also are relevant to the recent European legislation in which a nearly identical program has been developed and adopted by the European Union. It is not clear, however, how comparable these findings will be in the European model of drug pricing.

This discussion has focused on efforts to quantify both the cost of pediatric drug development trials and the expected economic benefit derived from 6 months of additional marketing exclusivity. We have not attempted to provide an economic analysis of projected benefits. Labeling changes resulting from pediatric studies for the drugs in this cohort have been impressive; 20/59 products had one or more of the following changes to the label: 5 had dosing changes, 9 had new pediatric safety information, and 12 products were not effective. [26] Of the 9 drugs evaluated in this study, all led to labeling changes. Importantly, several were associated with substantial safety concerns and lack of effectiveness in the pediatric population.

Using the numbers from the labeling information from the cohort of the 59 drugs, 34% (20/59) of the time that physicians prescribed the drugs from this cohort prior to 2002, they were making a dosing error or placing a child at risk of adverse events with limited therapeutic benefit. Administration of safe drugs that works, and at an appropriate dosage, is critical to public health. An analysis of the costs and benefits of this program to society, while extremely important, was beyond the scope of this study and would involve projection of the long-term clinical and economic outcomes associated with preventative measures which are difficult to ascertain such as the economic benefits of lives saved, unnecessary hospitalizations prevented, and avoidance of unnecessary therapies and improper treatment of diseases or conditions. These costs and benefits to society may be difficult to estimate with precision due to data limitations, but this area certainly represents an important subject for future study.

From the policy perspective, our study shows that the Pediatric Exclusivity Program overcompensates blockbuster products for performing clinical trials in children while other products have more modest returns on investment under this program. Further understanding and modeling is necessary to ascertain what constitutes adequate economic return to manufacturers in return for their risk. Clearly, however, the greatest return in the Pediatric Exclusivity Program are the benefits derived in obtaining new information relevant and applicable towards the care of children and this benefit should not be compromised.

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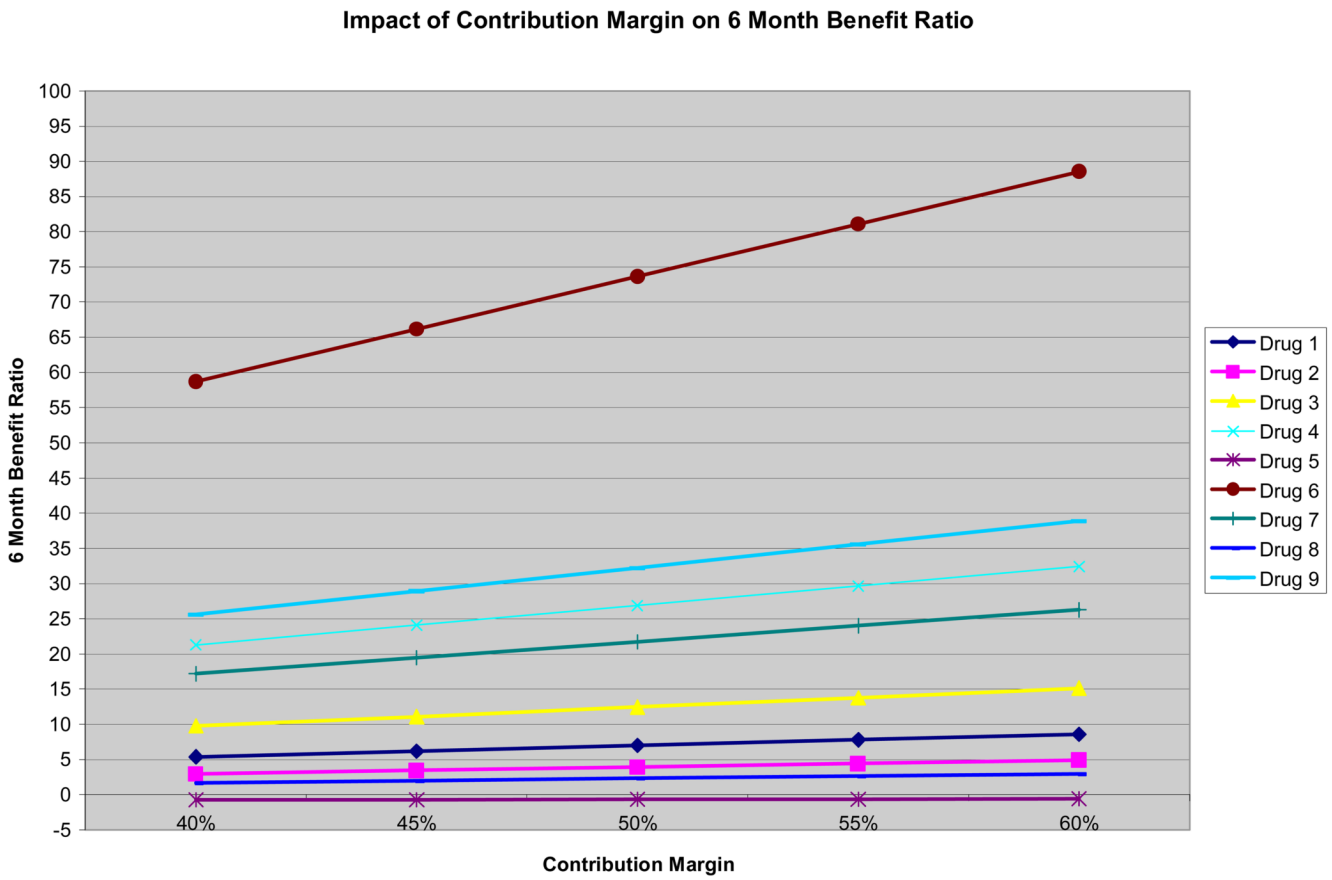

Figure 1.

The change in net return to cost ratio associated with variations in contribution margin for each evaluated drug is shown. The Y-axis denotes the impact on the 6 month benefit ratio as a percentage of the total. The X-axis denotes the percent contribution margin.

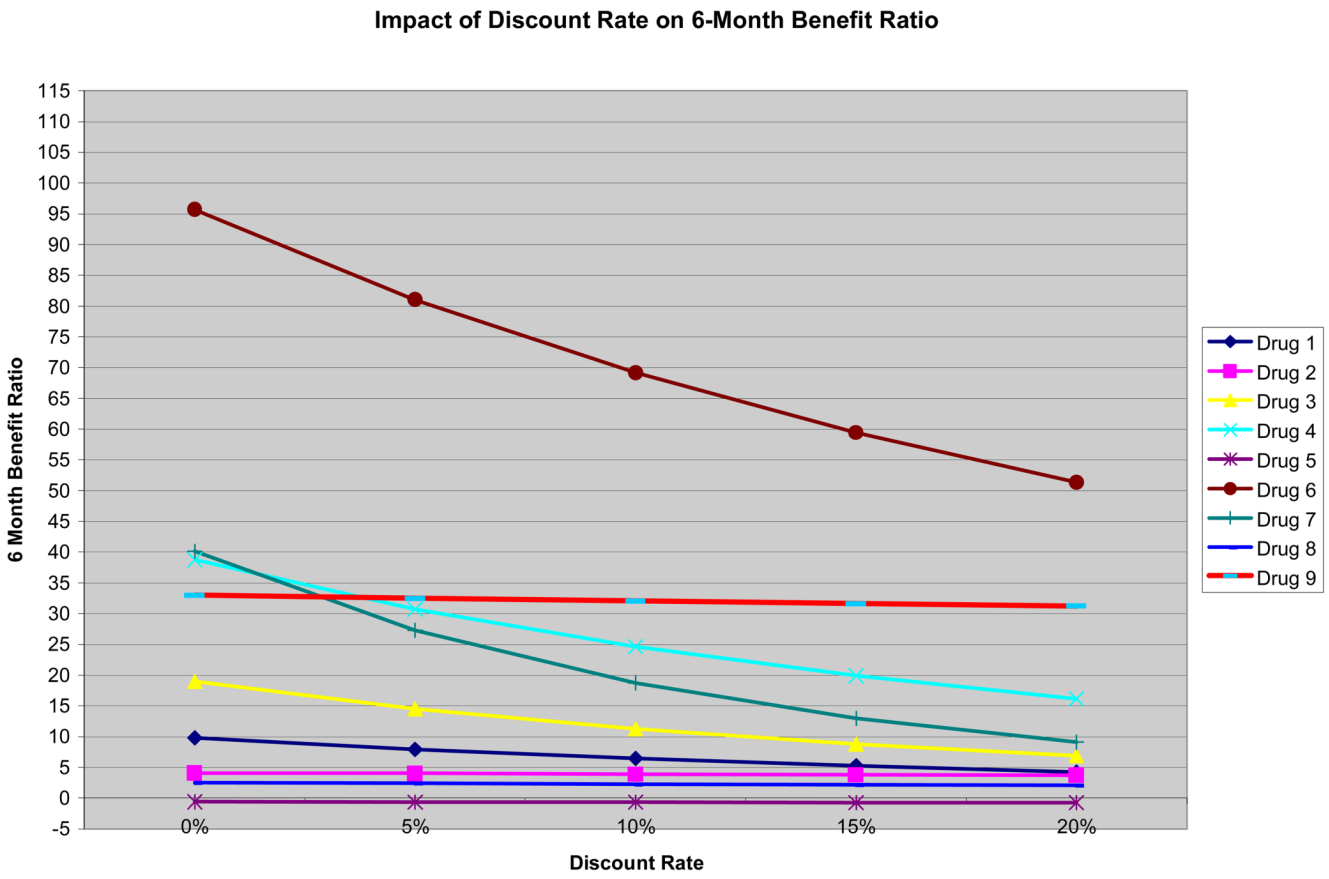

Figure 2.

The change in net return to cost ratio associated with variations in discount rate for each evaluated drug is shown. The Y-axis denotes the impact on the 6 month benefit ration as a percentage of the total. The X-axis denotes the percent discount rate.

Table 1

Annual sales for the cohort included in this analysis and for all drugs submitted 2002–2004

Annual Sales Estimate ($)	This cohort (N=9)	2002–2004 cohort (N=59)
> 1,000,000,000	5/9 (55.6%)	13/59 (22%)
200,000,000–1,000,000,000	3/9 (33%)	28/59 (47%)
<200,000,000	1/9 (11%)	18/59 (31%)

Table 2

Program description

Drug	Year Submitted	Summary of Label Change	Trial	Indication	Study Type	Lower Age (years)	Upper Age (years)
1	2002	Efficacy not demonstrated; “black-box” warning for suicidality; not approved for used in children; adverse effects on weight and growth	1	Depression & Generalized Anxiety Disorder	Efficacy	6	17
			2		Efficacy		17
			3		Single-dose PK	6	17
			4		Efficacy	6	17
			5		Efficacy	6	17
			6		Efficacy	7	17
			7		Efficacy	6	17
			8		Multi-dose PK	6	17
2	2002	New dosing/PK data; new dosing for children >50kg	1	Hypertension	Single-dose PK	1 month	16
			2		Efficacy	6	16
3	2003	No growth concerns	1	Asthma and allergy	Efficacy	2	4
			2		Efficacy	6 months	2
4	2003	Not indicated; no change in pain/fractures	1	Osteogenesis imperfecta	Efficacy	4	18
			2		Single-dose PK	4	16
5	2004	Approved down to 3 mos; not recommended for meningitis	1	Bacterial infection	Multi-dose PK	4 months	17
			2		Single-dose PK	4 months	17
			3		Efficacy	4 months	17
			4		Efficacy	4 months	17
6	2004	Approved from 1–17 yrs of age	1	Gastroesophageal reflux	Single-dose PK		
			2		Multi-dose PK		
			3		Efficacy	12	17
7	2004	Data insufficient to recommend use	1	Type 2 Diabetes	Efficacy	8	17
8	2004	Older children have a lower clearance than younger children thus dosing >20mg/day did not confer additional benefit	1	ADHD	Multi-dose PK	13	17
			2		Safety	13	18
			3		Efficacy	13	18
			4		Single-dose PK	13	17
9	2004	Not effective in children	1	Refractory tumors	Efficacy	1	21

Table 3

Trial description

Drug	Trial	Duration of Study (months)	Number of Sites	Number of United States Sites	Number of Patients	Total Number Case Report Forms	Number of Unique Case Report Forms	Number of Tables Listings and Figures for Final Study Report
1	1	43.0	3	3	25	155	24	47
	2	45.9	16	16	165	187	30	129
	3	21.0	35	35	158	184	44	149
	4	22.0	31	31	97	187	30	111
	5	22.0	31	31	97	187	30	111
	6	18.0	37	37	201	140	41	124
	7	18.0	39	39	165	217	57	145
	8	6.1	1	1	18	43	29	28
2	1	28.0	6	5	43	36	20	25
	2	29.0	78	62	253	72	29	153
3	1	33.9	80	80	332	63	24	35
	2	29.0	71	67	211	63	24	34
4	1	63.9	16	15	130	168	42	129
	2	12.0	1	1	24	66	39	18
5	1	38.9	8	6	84	61	26	51
	2	27.9	5	1	13	73	34	2
	3	28.0	50	23	404	93	52	166
	4	28.0	15	12	113	164	49	129
6	1	14.9	10	10	63	35	23	32
	2	18.0	11	11	66	57	23	92
	3		20	20	87	73	25	49
7	1	41.9	59	34	195	57	20	55
8	1	35.0	14	14	407	244	36	95
	2	18.0	118	118	1088	33	21	75
	3	10.9	15	15	220	63	21	295
	4	6.0	2	2	26	14	14	76
9	1	15.0	56	17	151	76	48	72

Table 4

Financial costs

Drug	Trial	Coordinating Center Costs--Low	Coordinating Center Costs-- High	Sponsor Management Costs	Site Payments Low	Site Payments High	Central Lab Payments	Total Costs Low	Total Costs High	Annual Sales Estimate (× 1,000)
1	1	$ 402,600	$ 902,970	$ 767,285	$ 501,550	$ 1,087,275	$ 13,036	$ 1,684,471	$ 1,770,566	$ 2,737,971
	2	$ 1,610,934	$ 3,522,359	$ 1,184,791	$ 2,394,975	$ 2,713,260	$ 139,772	$ 5,330,472	$ 7,560,182	$ 2,737,971
	3	$ 1,785,030	$ 3,953,164	$ 1,045,185	$ 1,577,472	$ 1,957,488	$ 158,383	$ 4,566,070	$ 7,114,220	$ 2,737,971
	4	$ 1,348,831	$ 3,103,933	$ 791,530	$ 972,231	$ 1,204,740	$ 105,050	$ 3,217,642	$ 5,205,253	$ 2,737,971
	5	$ 1,348,831	$ 3,103,933	$ 791,530	$ 972,231	$ 1,204,740	$ 105,051	$ 3,217,643	$ 5,205,254	$ 2,737,971
	6	$ 1,652,980	$ 3,628,700	$ 945,198	$ 2,605,428	$ 2,893,548	$ 132,539	$ 5,336,145	$ 7,599,985	$ 2,737,971
	7	$ 2,009,007	$ 4,379,511	$ 1,106,104	$ 1,653,795	$ 2,049,300	$ 118,788	$ 4,887,694	$ 7,653,703	$ 2,737,971
	8	$ 162,614	$ 341,240	$ 158,784	$ 88,758	$ 132,390	$ 23,415	$ 433,571	$ 655,829	$ 2,737,971
2	1	$ 283,226	$ 659,036	$ 444,827	$ 110,166	$ 127,323	$ 15,045	$ 853,264	$ 1,246,231	$ 291,796
	2	$ 3,455,444	$ 8,520,504	$ 1,759,668	$ 1,454,497	$ 2,294,963	$ 373,190	$ 7,042,799	$ 12,948,325	$ 291,796
3	1				$ 836,784	$ 1,422,096	$ 353,251	$ 5,825,482	$ 11,056,967	$ 1,682,551
	2	$ 2,304,563	$ 5,853,942	$ 1,288,465	$ 412,716	$ 627,725	$ 238,443	$ 4,244,187	$ 8,008,575	$ 1,682,551
4	1	$ 1,795,059	$ 4,159,294	$ 1,479,653	$ 1,929,042	$ 2,512,842	$ 1,687,443	$ 6,891,197	$ 9,839,232	$ 1,990,158
	2	$ 185,078	$ 372,287	$ 237,900	$ 39,936	$ 44,952	$ -	$ 464,546	$ 655,139	$ 1,990,158
5	1	$ 566,340	$ 1,310,789	$ 66,051	$ 209,496	$ 287,784	$ 38,146	$ 1,534,321	$ 2,297,250	$ 44,970
	2	$ 215,640	$ 519,036	$ 345,300	$ 23,311	$ 29,042	$ 1,563	$ 588,178	$ 894,941	$ 44,970
	3	$ 3,026,117	$ 6,929,406	$ 1,835,405	$ 739,320	$ 1,012,828	$ 541	$ 5,674,103	$ 9,778,180	$ 44,970
	4	$ 1,445,489	$ 2,996,314	$ 1,047,217	$ 341,825	$ 405,218	$ -	$ 2,848,656	$ 4,448,749	$ 44,970
6	1	$ 363,532	$ 839,118	$ 407,178	$ 345,429	$ 523,656	$ 101,837	$ 1,286,772	$ 1,871,789	$ 3,984,656
	2	$ 491,577	$ 1,106,579	$ 767,406	$ 703,626	$ 1,066,494	$ 178,516	$ 2,280,385	$ 3,118,995	$ 3,984,656
	3	$ 710,199	$ 1,563,596	$ 498,352	$ 661,931	$ 695,319	$ 487,863	$ 2,358,613	$ 3,245,130	$ 3,984,656
7	1	$ 2,280,335	$ 6,121,190	$ 1,422,589	$ 422,175	$ 567,255	$ 254,373	$ 4,432,122	$ 8,365,407	$ 1,863,283
8	1	$ 7,903,925	$ 14,905,215	$ 1,127,604	$ 4,024,416	$ 4,934,468	$ -	$ 13,482,481	$ 20,967,287	$ 751,033
	2	$ 3,288,887	$ 7,904,527	$ 1,359,939	$ 2,437,120	$ 2,923,456	$ -	$ 7,372,178	$ 12,186,922	$ 751,033
	3	$ 1,110,565	$ 2,448,654	$ 599,678	$ 1,789,480	$ 2,273,040	$ 48,288	$ 3,663,291	$ 5,369,660	$ 751,033
	4	$ 199,120	$ 409,242	$ 166,988	$ 88,192	$ 121,290	$ -	$ 472,058	$ 697,520	$ 751,033
9	1	$ 1,657,935	$ 3,775,276	$ 867,740	$ 310,003	$ 487,881	$ -	$ 2,916,765	$ 5,130,897	$ 775,045

Table 5

Economic return estimates based on assumptions of 6 and 3 months of exclusivity

Drug	Adjusted sales (disc/returns) (000$)	After taxes (000$)	Cash flow (000$)	Years to exclusivity end	Discounted value	Cost of trials	After tax cost of trials	6 month benefit	3 month benefit	6 Month Benefit/Cost Ratio
1	2,146,937	1,502,856	751,428	3.95	554,305,254	49,641,232	34,748,863	242,403,765	103,827,451	6.98
2	302,384	211,669	105,834	0.40	102,604,403	14,802,945	10,362,062	40,940,140	15,289,039	3.95
3	1,631,151	1,141,806	570,903	5.12	384,958,919	20,466,708	14,326,696	178,152,764	81,913,034	12.44
4	1,755,584	1,228,909	614,455	4.61	431,079,479	11,055,492	7,738,845	207,800,895	100,031,025	26.85
5	28,310	9,817	9,909	1.89	8,568,726	18,900,565	13,230,396	(8,946,033)	(11,088,214)	−0.68
6	3,811,086	2,667,760	1,333,880	3.36	1,029,594,956	9,854,434	6,898,104	507,899,374	250,500,635	73.63
7	1,453,255	1,017,278	508,639	7.72	280,894,489	8,831,127	6,181,789	134,265,456	64,041,833	21.72
8	601,738	421,217	210,608	0.71	199,415,407	43,062,613	30,143,829	69,563,874	19,710,022	2.31
9	717,671	502,370	251,185	0.29	245,684,923	5,278,408	3,694,886	119,147,576	57,726,345	32.25

Table 6

Ratios of net return to cost for 6, and 3 month periods of exclusivity

Drug	Exclusivity	Capital	Investment	Net	Ratio
1	6	277,152,627	34,748,863	242,403,765	6.98
	3	138,576,314	34,748,863	103,827,451	2.99
2	6	51,302,202	10,362,062	40,940,140	3.95
	3	25,651,101	10,362,062	15,289,039	1.48
3	6	192,479,459	14,326,696	178,152,764	12.44
	3	96,239,730	14,326,696	81,913,034	5.72
4	6	215,539,740	7,738,845	207,800,895	26.85
	3	107,769,870	7,738,845	100,031,025	12.93
5	6	4,284,363	13,230,396	(8,946,033)	−0.68
	3	2,142,181	13,230,396	(11,088,214)	−0.84
6	6	514,797,478	6,898,104	507,899,374	73.63
	3	257,398,739	6,898,104	250,500,635	36.31
7	6	140,447,244	6,181,789	134,265,456	21.72
	3	70,223,622	6,181,789	64,041,833	10.36
8	6	99,707,703	30,143,829	69,563,874	2.31
	3	49,853,852	30,143,829	19,710,022	0.65
9	6	122,842,461	3,694,886	119,147,576	32.25
	3	61,421,231	3,694,886	57,726,345	15.62