

Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program

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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 US Food and Drug Administration Modernization Act.⁵ Section 505A of this act, 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 with the very lim-

Context In 1997, Congress authorized the US 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 and 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 expire in 2007.

Objective To quantify the economic return to industry for completing pediatric exclusivity trials.

Design and Setting A cohort study of programs conducted for pediatric exclusivity. Nine drugs that were granted pediatric exclusivity were selected. From the final study reports submitted to the FDA (2002-2004), key elements of the clinical trial design and study operations were obtained, and the cost of performing each study was estimated and converted into estimates of after-tax cash outflows. Three-year market sales were obtained and converted into estimates of after-tax cash inflows based on 6 months of additional market protection. Net economic return (cash inflows minus outflows) and net return-to-costs ratio (net economic return divided by cash outflows) for each product were then calculated.

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

Results The indications studied reflect a broad representation of the program: asthma, tumors, attention-deficit/hyperactivity disorder, hypertension, depression/generalized anxiety disorder, diabetes mellitus, gastroesophageal reflux, bacterial infection, and bone mineralization. The distribution of net economic return for 6 months of exclusivity varied substantially among products (net economic return ranged from -\$8.9 million to \$507.9 million and net return-to-cost ratio ranged from -0.68 to 73.63).

Conclusions The economic return for pediatric exclusivity is variable. As an incentive to complete much-needed clinical trials in children, pediatric exclusivity can generate lucrative returns or produce more modest returns on investment.

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ited amount of such research before pediatric exclusivity. To date, the program has generated more than 300 pediatric studies and more than 115 products have undergone labeling changes for pediatric use. Despite this increase in pediatric drug studies, critics of the Pediatric Exclusivity Program contend that it has provided a "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

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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 has estimated higher study costs ranging from \$5 million to more than \$35 million.³ In a 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 of 2002 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

Clinical trials performed for pediatric exclusivity though the written request were identified. 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 the 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 the FDA. We selected the products to study using the following algorithm. We subdivided the program into the following areas: allergy/immunology (n=6 products), cancer (n=9), central nervous system (n=8), cardiovascular

(n=9), psychiatry (n=5), endocrine (n=6), gastrointestinal (n=4), infectious disease (n=10), and other (eg, osteogenesis imperfecta and kidney transplantation; n=2). We selected 1 product from each area, using the most recent application for which data were most complete in the electronic document room of the 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. The following definitions were used: *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 to their present values as of June 30, 2005, using a discount factor comparable with 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 2 organizations to assist in our estimates, Fast Track Systems Inc (Conshohocken, Pa) and Covance Central Laboratory Services (Indianapolis, Ind).

Fast Track Systems provided access to 3 separate global cost and procedure benchmarking databases drawn from more than 240 000 negotiated investigator agreements, 25 000 finalized protocols in 800 indications, and 3000 contract research organization contracts.¹⁰ Investigative site, coordinating center, and internal pharmaceutical costs were estimated based on input of trial param-

eters, including trial phase, indication, trial locations, number of sites, screen failure percentage, number of enrolled patients, study procedures, overhead costs, document preparation, prestudy 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 Services¹¹ 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 included.

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 varied between 25% and 35% in sensitivity analyses.

Yearly sales data for each drug product were obtained from IMS Health Inc (Fairfield, Conn) from pharmaceutical sales data audits.¹³ Data were obtained from either 2002-2004, or the last 3 years before patent exclusivity expired.

We used contribution margin (sales revenue minus variable costs),¹⁴ 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 (eg, a 45% contribution margin means that to sell an additional \$1.00

Table 1. Annual US Sales for the Selected Cohort and for All Drugs Submitted 2002-2004

	No. (%) of Drugs With Annual Sales Estimate		
	<\$200 Million	\$200 Million-\$1 Billion	>\$1 Billion
Selected cohort (n = 9)	1 (11.1)	3 (33.3)	5 (55.6)
2002-2004 cohort (n = 59)	18 (30.5)	28 (47.5)	13 (22.0)

worth of product, it costs the company an additional 55¢ in variable costs).

To estimate net cash inflows from average annual IMS Health sales, we assumed a 10% sales discount rate, a 50% contribution margin, and a 30% tax rate. The IMS Health reports gross sales and does not include discounts to managed care; we therefore adjusted the IMS Health 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 life cycles 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 of 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 the FDA final submissions for all products would occur on June 30, 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 2002-2004 period because of lower interest rates on debt capital and lower returns on equity capital than were prevalent in the 1990s.¹² As cash out-

flows 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. STATA version 8.2 (StataCorp LP, College Station, Tex) was used for statistical analysis and $P < .05$ was considered statistically significant.

RESULTS

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 and 22 991 children were enrolled in these trials. The largest trial enrolled 795 children and the smallest enrolled 10 children, with median trial enrollment of 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. The median annual sales of the 59 products submitted in the 2002-2004 cohort was \$181 254 000. A total of 13 products (22%) studied between 2002-2004 were considered in the blockbuster category of more than \$1 billion in annual sales (TABLE 1).

Selected Cohort

For our analysis, we obtained the final study reports from 9 drugs in a broad range of therapeutic areas under the algorithm described (TABLE 2). Eight 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 multidose pharmacokinetic, 6 were single-dose pharmacokinetic, and 1 was a safety study.

The median number of patients enrolled was 140 (range, 13-1088), the median number of US 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 2 years to complete. Most of the trials collected detailed data: the median number of case report forms for a trial was 73 (interquartile range, 59-166 pages collected), and the median number of tables, listings (a compilation of a collection of variables), and figures for the final study report was 81.

The estimated costs of conducting each trial with coordinating center costs, sponsor management costs, site payments, central laboratory 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.¹⁵⁻¹⁸ Using this estimate, the median cost per written request was \$12.34 million (range, \$5.13-\$43.80 million). The median cost for a single-dose pharmacokinetic study was \$894 941 (range, \$655 139-\$7 114 220), median multidose pharmacokinetic study cost was \$2 297 250

(range, \$655 829-\$20 967 287), and median efficacy study cost was \$6 464 921 (range, \$1 770 566-\$12 948 325). Five of the 9 products in this cohort would be considered blockbuster drugs with yearly US sales exceeding \$1 billion (Table 1). This is substantially higher than the 2002-2004 cohort for which 22% (13/59) of the products were blockbuster drugs ($P=.03$). 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 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-\$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-\$34 748 863). Assuming 6-months exclusivity, the median net economic benefit was \$134 265 456

Table 2. Program Descriptions

Drug	Year Submitted	Indication	Summary of Label Change	Trial	Study Type	Lower Age	Upper Age, y
1	2002	Depression and generalized anxiety disorder	Efficacy not demonstrated; black box warning for suicidality; not approved for use in children; adverse effects on weight and growth	1	Efficacy	6 y	17
				2	Efficacy	6 y	17
				3	Single-dose pharmacokinetic	6 y	17
				4	Efficacy	6 y	17
				5	Efficacy	6 y	17
				6	Efficacy	7 y	17
				7	Efficacy	6 y	17
				8	Multidose pharmacokinetic	6 y	17
2	2002	Hypertension	New dosing/pharmacokinetic data; new dosing for children >50 kg	1	Single-dose pharmacokinetic	1 mo	16
				2	Efficacy	6 y	16
3	2003	Asthma and allergy	No growth concerns	1	Efficacy	2 y	4
				2	Efficacy	6 mo	2
4	2003	Osteogenesis imperfecta	Not indicated; no change in pain/fractures	1	Efficacy	4 y	18
				2	Single-dose pharmacokinetic	4 y	16
5	2004	Bacterial infection	Approved for ≥ 3 mo; not recommended for meningitis	1	Multidose pharmacokinetic	4 mo	17
				2	Single-dose pharmacokinetic	4 mo	17
				3	Efficacy	4 mo	17
				4	Efficacy	4 mo	17
6	2004	Gastroesophageal reflux	Approved for 1-17 y	1	Single-dose pharmacokinetic	12 y	17
				2	Multidose pharmacokinetic	12 y	17
				3	Efficacy	12 y	17
7	2004	Type 2 diabetes mellitus	Data insufficient to recommend use	1	Efficacy	8 y	17
8	2004	Attention-deficit/hyperactivity disorder	Older children have a lower clearance than younger children, thus dosing >20 mg/d did not confer additional benefit	1	Multidose pharmacokinetic	13 y	17
				2	Safety	13 y	18
				3	Efficacy	13 y	18
				4	Single-dose pharmacokinetic	13 y	17
9	2004	Refractory tumors	Retained "Safety and effectiveness in pediatric patients have not been established."	1	Efficacy	1 y	21

(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 net return-to-cost ratios (TABLE 6).

FIGURE 1 and FIGURE 2 show the change in net return-to-cost ratios associated with variations in contribution margin and discount rates. Products with larger cash inflows (eg, drug 6) were more sensitive to variation in contribution margin, whereas products with lower cash inflows (eg, 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 (eg, drugs 6 and 7), while those with short-time lags were less sensitive (eg, drug 9).

COMMENT

The development of therapeutics is based on ownership of pharmaceutical discoveries by for-profit businesses.¹⁹ Drug development is 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.²⁰

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 the FDA. Outside 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 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 also found that a very high rate of return is realized by blockbusters with annual sales of more than \$1 billion; 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

Table 3. Trial Descriptions

Drug	Trial	Duration of Study, mo	No. of Sites	No. of US Sites	No. of Patients	Total No. of Case Report Forms	No. of Unique Case Report Forms	No. 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	17.0	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

cohort may have been close to breaking even with respect to financial return on investment. In fact, 1 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 less than \$200 million.³ Another study demonstrated that most medicines awarded pediatric exclusivity are not among the 200 top-selling drugs.²¹ The median annual sales of the 59 products submitted in the 2002-

2004 cohort was \$181 254 000 and 23 of 59 products had annual sales of less than \$150 million.

Limitations

These data have several limitations, most of which underestimate the cost

Table 4. Financial Costs

		US \$								Annual Sales Estimate, in Thousands
Drug	Trial	Coordinating Center Costs—Low	Coordinating Center Costs—High	Sponsor Management Costs	Site Payments—Low	Site Payments—High	Central Laboratory Payments	Total Costs—Low	Total Costs—High	
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	
	3	1 785 030	3 953 164	1 045 185	1 577 472	1 957 488	158 383	4 566 070	7 114 220	
	4	1 348 831	3 103 933	791 530	972 231	1 204 740	105 050	3 217 642	5 205 253	
	5	1 348 831	3 103 933	791 530	972 231	1 204 740	105 051	3 217 643	5 205 254	
	6	1 652 980	3 628 700	945 198	2 605 428	2 893 548	132 539	5 336 145	7 599 985	
	7	2 009 007	4 379 511	1 106 104	1 653 795	2 049 300	118 788	4 887 694	7 653 703	
	8	162 614	341 240	158 784	88 758	132 390	23 415	433 571	655 829	
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	
3	1	3 045 991	7 692 164	1 589 456	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	
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	NA	464 546	655 139	
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	1563	588 178	894 941	
	3	3 026 117	6 929 406	1 835 405	739 320	1 012 828	541	5 674 103	9 778 180	
	4	1 445 489	2 996 314	1 047 217	341 825	405 218	NA	2 848 656	4 448 749	
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	710 199	1 563 596	498 352	661 931	695 319	487 863	2 358 613	3 245 130	
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	NA	13 482 481	20 967 287	751 033
	2	3 288 887	7 904 527	1 359 939	2 437 120	2 923 456	NA	7 372 178	12 186 922	
	3	1 110 565	2 448 654	599 678	1 789 480	2 273 040	48 288	3 663 291	5 369 660	
	4	199 120	409 242	166 988	88 192	121 290	NA	472 058	697 520	
9	1	1 657 935	3 775 276	867 740	310 003	487 881	NA	2 916 765	5 130 897	775 045

Abbreviation: NA, not applicable.

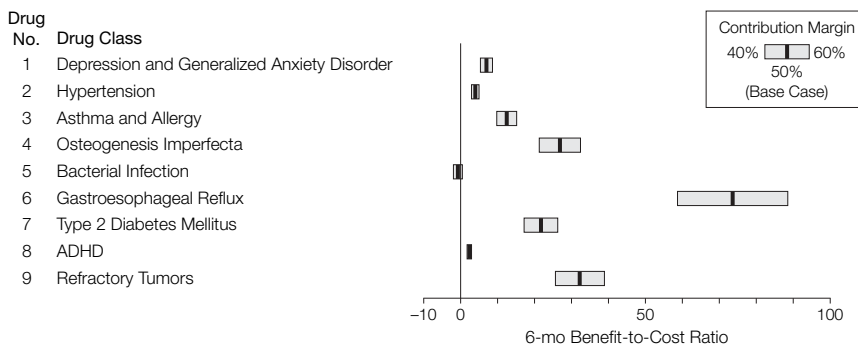
Table 5. Economic Return Estimates Based on Assumptions of 6 and 3 Months of Exclusivity

Drug	US \$, in Thousands			Years to Exclusivity End	Discounted Value, \$	Cost of Trials, \$	After-Tax Cost of Trials, \$	6-mo Benefit, \$	3-mo Benefit, \$	6-mo Benefit/Cost Ratio
	Adjusted Sales (Discount>Returns)	After Taxes	Cash Inflow							
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	19 817	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. Net Return-to-Cost Ratios for 6- and 3-Month Periods of Exclusivity

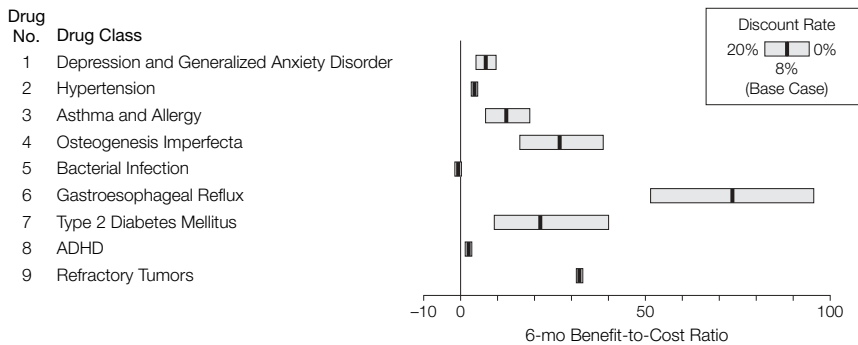
Drug	Exclusivity Duration, mo	US \$			Net Return-to-Cost Ratio
		Capital	Investment	Net	
1	6	277 152 627	34 748 863	242 403 765	6.98
	3	138 576 314	34 748 863	103 827 451	2.99
2	6	51 302 202	10 362 062	40 940 140	3.95
	3	25 651 101	10 362 062	15 289 039	1.48
3	6	192 479 459	14 326 696	178 152 764	12.44
	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

Figure 1. Impact of Contribution Margin on 6-Month Benefit-to-Cost Ratio



The change in net return-to-cost ratio associated with variations in contribution margin for each evaluated drug is shown. ADHD indicates attention-deficit/hyperactivity disorder.

Figure 2. Impact of Discount Rate on 6-Month Benefit-to-Cost Ratio



The change in net return-to-cost ratio associated with variations in discount rate for each evaluated drug is shown. ADHD indicates attention-deficit/hyperactivity disorder.

of submitting the data to the 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 (eg, chewable tablets or liquid preparations) and the costs of required bioequivalence and stability testing. Our sample included an overrepresentation of products with high annual sales (5 of 9 products had annual sales of >\$1 billion).

The software used to estimate the costs of conducting trials is used most frequently in adult trials, and pediatric trials are usually more expensive. The Duke Clinical Research Institute is the data coordinating center for both adult and pediatric trials conducted under FDA guidance,¹⁵⁻¹⁸ 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 and 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. Improved treatment and reduced adverse events resulting from better labeling were not evaluated. 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.²²⁻²⁴ Finally, we did not measure the clinical benefits to children, their families, and society from having pharmaceutical agents 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. Since the start of the program in 1997, more than 115 products have had a labeling change. Approximately one third of these labeling changes showed an important difference in the pediatric dosing, safety, or efficacy compared with 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.

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 that 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 ex-

clusivity. 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 of 59 products had 1 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.²⁵ Of the 9 drugs evaluated in this study, 8 underwent 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 59 drugs, 34% (20 of 59) of the time that physicians prescribed the drugs from this cohort before 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 work, and at an appropriate dosage, is critical to public health. An analysis of the costs and benefits of this program to society, although important, was beyond the scope of this study and would involve projection of the long-term clinical and economic outcomes associated with preventative measures that 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 are necessary to ascertain what constitutes adequate economic return to manufacturers in return for their risk.

Clearly, however, the greatest return of the exclusivity program is the benefits derived in obtaining new information relevant and applicable toward the care of children, and this benefit should not be compromised.

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Study concept and design: Li, Eisenstein, Grabowski, Murphy, Califf, Benjamin.

Acquisition of data: Li, Reid, Mangum, Goldsmith, Murphy, Benjamin.

Analysis and interpretation of data: Li, Eisenstein, Mangum, Schulman, Califf, Benjamin.

Drafting of the manuscript: Li, Eisenstein, Grabowski, Benjamin.

Critical revision of the manuscript for important intellectual content: Li, Eisenstein, Reid, Mangum, Schulman, Goldsmith, Murphy, Califf, Benjamin.

Statistical analysis: Li, Eisenstein, Grabowski, Benjamin.

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What one reads becomes part of what one sees and feels.

—Ralph Ellison (1914-1994)