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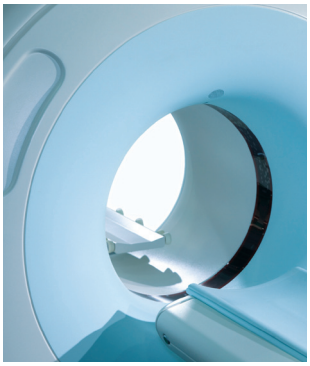

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Do Incentives Drive Pediatric Research?

Economic and Societal Impact: the Hard Numbers

To increase the number of children in clinical trials, the United States embarked on a regulatory and health strategy that culminated in the extension of a drug's overall market exclusivity if pediatric trials were included. McKinsey analyzed the results of that strategy and the benefits gained from it by society and industry. We also looked at the strategy's implications for the next frontier in drug development in general, and for children in particular: biologics.

In the past, clinical trials have rarely included children. As a result, they are an underserved market. A number of factors drive their absence. Treatments are generally developed for adults and clinical trials logically focus on adults. Pediatric subjects are also difficult to identify: they are a highly fragmented population with many more segments than are found in adult populations. Few pharmaceutical companies databases include children. Children are also a dynamic population and can change over the course of a single study, complicating design and interpretation. Additionally there are ethical concerns with gaining consent: often both parents and subjects must agree to participate.

To stimulate greater involvement of children in clinical trials, the United States developed a regulatory and health strategy that centers on extending a drug's overall market exclusivity when pediatric clinical trials are included. To move the discussion of pediatric research forward, McKinsey analyzed the results of this strategy. We probed how widely it has been used and what benefits it has given to society and industry. With those results in hand, we looked at implications for future regulatory policies.

How the strategy came to be

The history of drug development is largely a story of adults. Because of adults' purchase and decision making authority and the ethical issues with pediatric trials, pharmaceutical companies have focused almost exclusively on adult indications. For a wide range of diseases, however, there is a need to develop treatments and garner knowledge about how children respond to them. For example, safety and efficacy in children are more difficult to predict than they are with adults.[1]

1 US Congressional Research Service. FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective (RL33986, May 1, 2007), by

Drug dosages don't scale with patient weight. As a result, some diseases can be more difficult to treat in children.

In 1979, the U.S. Food and Drug Administration (FDA) started to address the issue and close the gap between children and adult clinical trials. It established a pediatric use subsection on drug labels.[2] However, sponsors had few incentives to enroll pediatric patients. Even if the trial were successful, label revisions offered little upside, since the market would be small for most indications. If safety issues did emerge, that discovery carried the distinct danger that the adult market would decline because of the subsequent label warning.

To address this rock-and-hard-place scenario, the FDA expanded pediatric labeling provisions in 1994. The new provisions allowed pharmaceutical companies to extrapolate adult data for pediatric labeling. But there was no mandate to conduct clinical trials.[3] As a result, most pharmaceutical companies continued to pursue adult markets. Treatments prescribed for children were usually given off label based on adult experience: many products simply included a statement cautioning that "safety and efficacy below age 18 have not been established."

Three years later, the U.S. Congress stepped in and passed the Food and Drug Administration Modernization Act of 1997.[4] A section of the act, Better Pharmaceuticals for Children Act (BPCA), granted manufacturers an additional six months of market exclusivity if they would conduct pediatric trials in line with an FDA request. At the same time, the FDA required that pediatric testing data be provided with all new drug applications (NDA)[5] going forward: the FDA strategy combined the "carrot" of additional market exclusivity with the "stick" of mandatory pediatric data to increase knowledge about drug usage in pediatric populations.

Before 1997, sponsors that received a new indication for children would see only a slight increase in sales because off-label use already accounted for most pediatric patient revenue. After 1997, however, pharmaceutical companies that performed clinical trials with children could receive six months of additional market exclusivity—including the adult population. In order to qualify for an adult indication, companies had to address the pediatric population unless the FDA made an exception. The revenue increase from label extensions was still modest. But the market exclusivity drove billions in incremental revenue for some blockbuster drugs. It did so by delaying the impact of generic challengers.

Although the FDA rule mandating pediatric trials was overturned by the courts in 2002, it was set into law through the 2003 Pediatric Research Equity Act (PREA).[6] BPCA was renewed in 2002.[7] Both BPCA and PREA were made permanent laws by the U.S. Congress in 2012.[8]

Susan Thaul. Accessed 10/2/2012 at http://assets.opencrs.com/rpts/RL33986_20070501.pdf

2 FDA, "Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs; Final rule," Federal Register, vol. 44, no. 124, June 26, 1979, pp. 37434-37467.

3 FDA, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection In the Labeling; Final rule," Federal Register, vol. 59, no. 238, December 13, 1994, pp.64240-64250.

4 FDAMA (P.L. 105-115), BPCA sec 505A(21 U.S.C. 355a)

5 FDA, "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final rule," Federal Register, vol. 63, no. 231, December 2, 1998, pp. 66632-66672.

6 FFDCA Section 505B (21 U.S.C. 355c) (2003)

7 FFDCA Section 505A (21 U.S.C. 355a) (2002)

8 Food and Drug Administration Safety and Innovation Act of 2012, 112 U.S.C. (2012)

The strategy's results

Economic Impact

The BPCA and PREA together have had significant impact on the pharmaceutical industry. Pediatric clinical trial activity, for example, continues to be strong—69 trials were reported at ClinicalTrials.gov in the first seven months of 2012 alone.[9]

The financial rewards to pharmaceutical companies have been dramatic. Since 1997, the additional six months of exclusivity has driven $71 billion in incremental revenue. Exhibit 1a details the drugs receiving the greatest impact.[10]

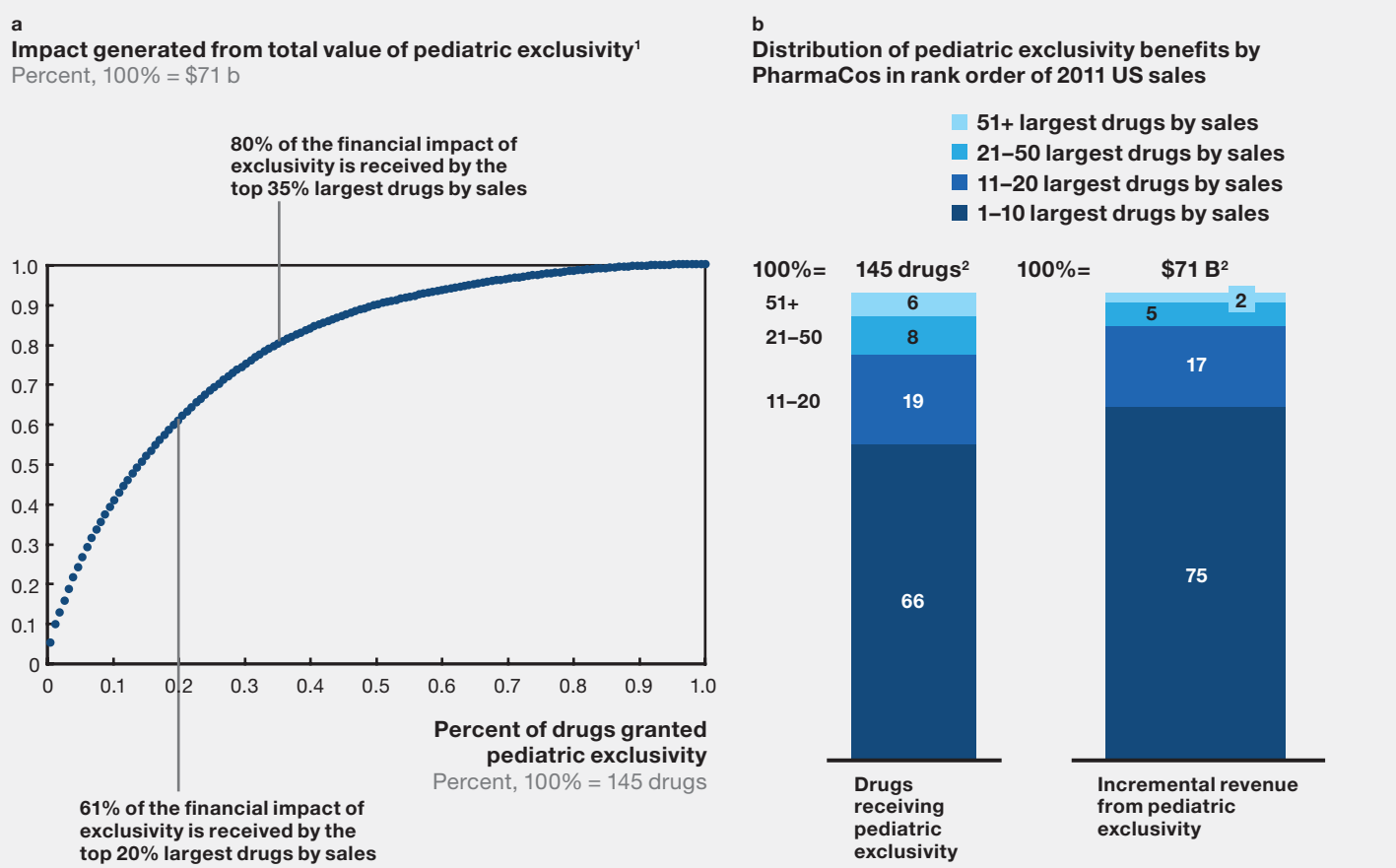
The benefits, however, skew heavily toward blockbuster treatments and large pharmaceutical companies.[11] (See exhibit 1b.) The top ten drugs, for

9 ClinicalTrials.gov, August 10, 2012

10 FDA; EvaluatePharma, August 2012

11 FDA; EvaluatePharma, August 2012

Exhibit 1 | Incremental revenue from pediatric exclusivity



1 Impact estimated as the peak six months of sales during the 1995–2006 period in U.S. Full year 2012 and 2013–2016 sales from analysts' estimates.
2 Includes only drugs for which EvaluatePharma had financial data (out of a total of 192 drugs approved in the period). Impact estimated as six months of 1995-2016 peak sales in U.S. For full year 2012 and 2013-2016, sales figures are from analyst's estimates.
SOURCE: Sources: FDA; Evaluatepharma, as of August 2012

example, garnered 31 percent of the total. The top ten companies accounted for 75 percent.

For drugs with blockbuster revenue (more than $1 billion annually), there is a clear benefit to conducting dedicated pediatric trials to gain market exclusivity. With trials costing up to $25 million and average industry profit margins of 23 percent, blockbuster manufacturers have significant incentives—$300 million in value per drug against $25 million in trial costs. However, for drugs with annual sales below $100 million, the incentives seem to be less alluring given the complexities and risks of conducting pediatric trials. Arguably, this is a gap that should be addressed, since it may be the result of scale advantages that large companies have in conducting trials along with the greater profitability of their products.

Societal Benefits

The societal benefits of the BPCA and PREA have been substantial as well—made clear by the FDA's success in generating pediatric trials for targeted pharmaceuticals. We started by identifying how many drugs had been granted FDA exclusivity. Between 1997 (passage of the FDA Modernization Act) and 2011, 185 drugs were granted pediatric exclusivity.[12] (See exhibit 3.)

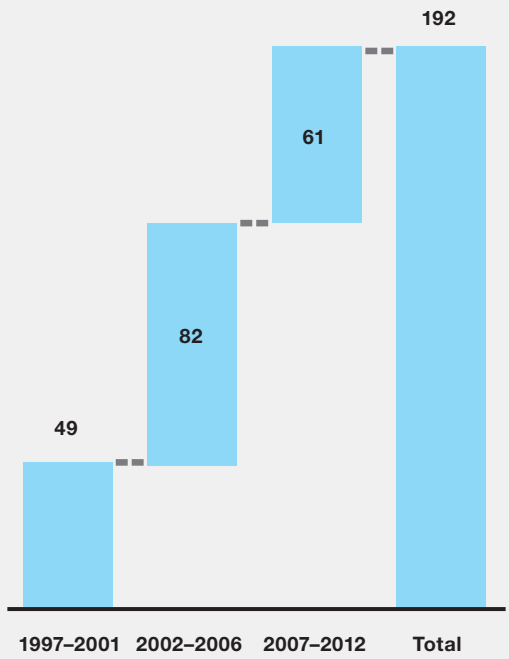
The number of total drugs approved in a given year is another gauge of the significant societal impact of pediatric exclusivity. McKinsey analyzed NDAs approved in 2001. This allows sufficient time for most drugs to lose their market exclusivity, after which the exclusivity provision would have no benefit. Using 2001 as an example, we found 69 approved NDAs. Of these, 11 were granted pediatric exclusivity between 2001 and 2006 and ten between 2007 and 2011. Forty-eight, or 70 percent, have not received pediatric exclusivity.[12] (See exhibit 4).

Although analysis of the recent past shows a consistent number of pediatric trials, the future benefits are less clear. Between 2005 and 2011, the average annual number of pediatric trials was 140. During the same period, the average annual number of exclusivity grants was 11.[13] (See exhibit 5.) The number of pediatric exclusivity extensions does not correlate closely to the total number of ongoing pediatric clinical trials. There is also an emerging trend of decreased exclusivity extensions after 2009. If this trend continues, it will be important to understand if pediatric clinical trials are still being conducted without resulting in pediatric exclusivity or if the pediatric exclusivity strategy has become less potent.

12 FDA, ClinicalTrials.gov, August 10, 2012

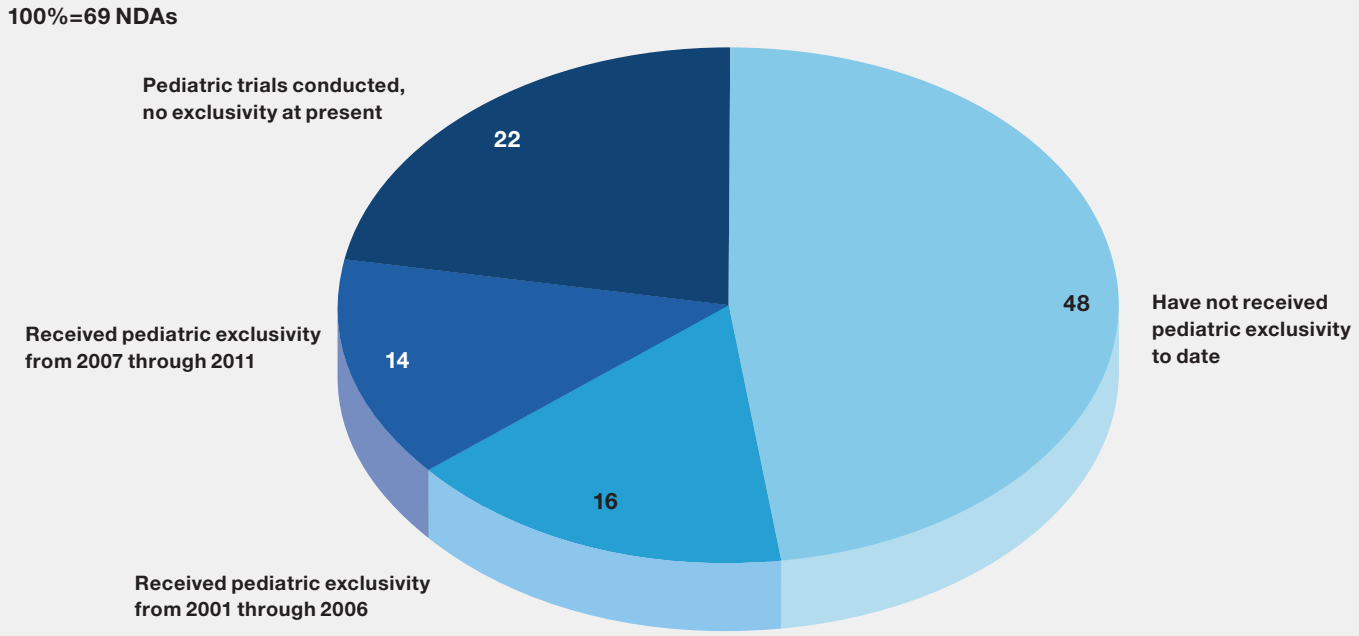
13 FDA, ClinicalTrials.gov, August 10, 2012

Exhibit 3 | Drugs granted pediatric exclusivity between 1997 and July 2012



SOURCES: FDA; Evaluatepharma, as of August 2012

Exhibit 4 | Pediatric exclusivity for NDAs approved in 2001



The number of pediatric label changes is also a clear indication of the strategy's impact. The BPCA drove 152 and PREA, 192. The BPCA and PREA combined account for 59. Before it was overturned by the courts, the FDA's 1997 Pediatric Rule created an additional 48 label changes.[14] (See exhibit 6.) Thus, for the 185 drugs granted pediatric exclusivity through the BPCA, there have been 211 associated label changes. This indicates that the program achieved widespread adoption.

Methodology

McKinsey analyzed pediatric extensions that were granted after 1997 with the passage of the FDA Modernization Act. Using publically available information from the U.S. FDA website, we determined which drugs received a pediatric exclusivity extension[15] and also compiled data on label changes.[16]

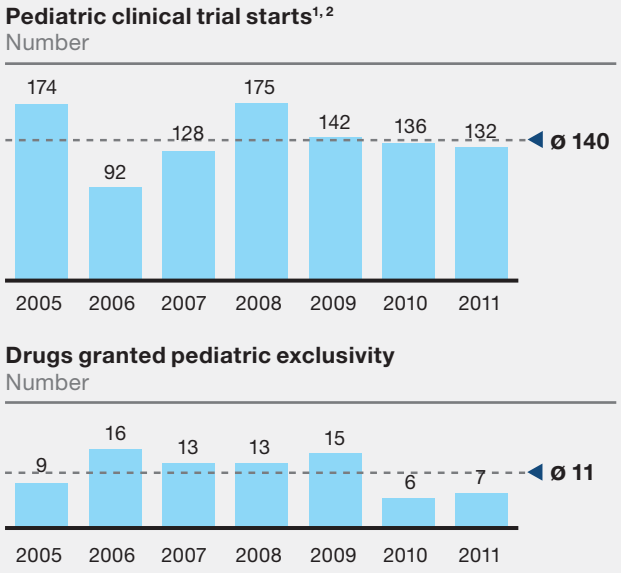
For drugs granted exclusivity, we estimated the incremental value to a pharmaceutical company as six months of additional peak level sales. We assumed peak sales were the largest annual monies received from 1999 to 2016. Future sales were drawn from analyst estimates based on company filings. We used EvaluatePharma (2012) to estimate peak sales for each drug in the analysis.

14 FDA Report, July 24, 2012

15 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM223058.pdf Accessed 8/2012

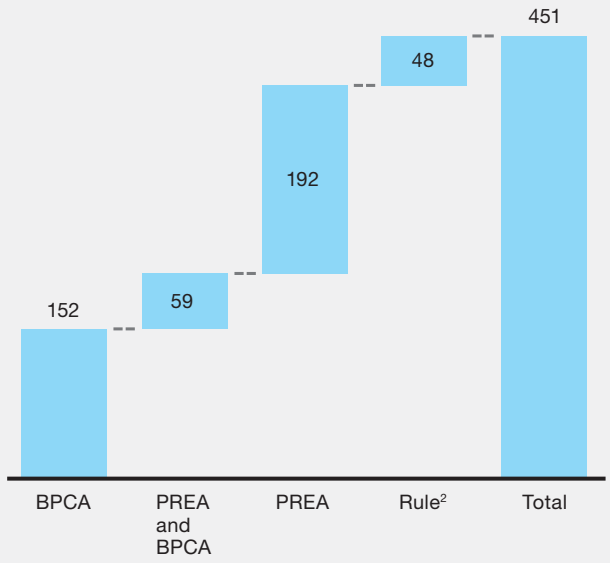
16 http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase Accessed 8/2012

Exhibit 5 | Comparison of pediatric trial starts to exclusivity grants by year



1 All trials including listed age group of "child"
2 Clinical trial data before 2005 is less complete and so was excluded

Exhibit 6 | Mechanism for label change with new clinical trials



1 41 label changes occurred without new clinical trials
2 Label change motivated by Pediatric Rule established in 1997; precursor to PREA

Looking ahead

Prior to 1997 the pharmaceutical industry had little incentive to test its products in children. This lack led to a pronounced gap in society's ability to fully benefit from advances in drug development. Through a combination of regulatory and legislative actions, the FDA has successfully increased the number of pediatric clinical trials undertaken. It has closed the knowledge gap.

The next frontier in drug development in general, and for children in particular, is biologics. As regulations and laws for biologic drugs are defined and clarified over the next few years, it is likely that a strategy similar to the BPCA and PREA will achieve similar societal and industry impact.

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