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Kid Tested, FDA Approved: Examining Pediatric Drug Testing

ALLAN M. JOSEPH*

ABSTRACT

Hoping to increase the number of drugs tested in children, Congress and FDA have placed a set of incentives for and requirements on drug manufacturers, notably through sections 505A and 505B of the Food, Drug, and Cosmetic Act. Using publicly-available data, I demonstrate that many drugs still lack pediatric study, and that many pediatric studies provide only weak evidence. I also show that requirements have been more important than incentives in encouraging these trials. Finally, I recommend steps Congress and FDA can take to improve the evidence available to pediatric prescribers to ensure drugs are used safely and effectively in children.

INTRODUCTION

"Children are not little adults," cautions the common refrain of pediatric medical educators, and for good reason—making the mistake of treating children as if they were simply smaller adults can have devastating clinical consequences. Medical trainees ignore this dictum at their peril, and more importantly, at the peril of patients. Understanding this difference is particularly important when it comes to choosing, dosing, and monitoring a course of treatment. Not only does pediatric physiology often differ from that of adults,[1] but importantly, drug pharmacokinetics (i.e., how a drug is metabolized by the body) and pharmacodynamics (i.e., how a drug works to produce

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I originally wrote this paper to fulfill a course requirement of Harvard Law School's Winter 2017 "Food and Drug Law" course while completing a Masters in Public Health at the Harvard T.H. Chan School of Public Health in Boston, Massachusetts. I am currently a medical student in my final year of training at the Warren Alpert Medical School of Brown University, in Providence, Rhode Island.

[1] *See generally* Doreen Soliman et al., *The Pediatric Patient*, *in* ANESTHESIA & UNCOMMON DISEASES 586 (Lee A. Fleisher ed., 6th ed. 2012).

an effect) can be very different in children than in adults.[2,3,4] Though the general principles underlying drug actions in children resemble those in adults,[5] those principles are often *not* the same for any given drug. Even after adjusting for weight, children may require lower[6] or higher[7] doses to produce the same drug effect as in adults; meanwhile, a drug like aspirin—commonly used in adults[8]—may be so dangerous in children[9] as to have only limited acceptable uses,[10] with controversy even over those uses.[11] As every parent knows all too well, a drug's formulation is critical to whether it can be given to a child. Though most adolescents and adults can take simple tablets and capsules, younger children generally cannot or will not. Given that the choice of formulation may affect a drug's actions, pediatric formulations of the same drug may differ in important ways from the adult versions.[12]

Physicians rely on the results of clinical trials and scientific investigation to prescribe safe and effective medications. In the United States, they are assisted in this task by the Food and Drug Administration (FDA), which approves drugs for sale only if manufacturers can sufficiently prove safety and efficacy with such trials. Pediatricians are no different from other physicians in relying on studies to help them choose drugs. Yet because of the differences between adults and children, pediatricians aiming to appropriately prescribe medications to pediatric patients[13] would like to rely on clinical trials *performed in pediatric patients*. This is no trivial task, as the ethics of conducting drug trials in protected groups such as children can be challenging. Exposing children to the risks of clinical trials carries significant ethical issues, while avoiding clinical trials in these patients carries a different but no less weighty set of concerns.

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[2] *See generally* Ryan S. Funk et al., *Pediatric Pharmacokinetics: Human Development & Drug Disposition*, 59 PEDIATRIC CLINICS N. AM. 1001 (2012).

[3] *See generally* Hannah K. Batchelor & John F. Marriott, *Paediatric Pharmacokinetics: Key Considerations*, 79 BRIT. J. CLINICAL PHARMACOLOGY 395 (2013).

[4] *See generally* Brian J. Anderson, *Pharmacokinetics and Pharmacodynamics in the Pediatric Population*, *in* PEDIATRIC SEDATION OUTSIDE OF THE OPERATING ROOM 173 (Keira P. Mason ed., 2d ed. 2015).

[5] *See generally* Terence Stephenson, *How Children's Responses to Drugs Differ from Adults*, 59 BRIT. J. CLINICAL PHARMACOLOGY 670 (2005).

[6] *See generally* Harumi Takahashi, *Developmental Changes in Pharmacokinetics and Pharmacodynamics of Warfarin Enantiomers in Japanese Children*, 68 CLINICAL PHARMACOLOGY THERAPEUTICS 541 (2000).

[7] *See generally* James D. Marshall & Gregory L. Kearns, *Developmental Pharmacodynamics of Cyclosporine*, 66 CLINICAL PHARMACOLOGY THERAPEUTICS 66 (1999).

[8] *See generally* Yingjun Zhou et al., *Trends in the Use of Aspirin & Nonsteroidal Anti-Inflammatory Drugs in the General U.S. Population*, 23 PHARMACOEPIDEMIOLOGY DRUG SAFETY 43 (2014).

[9] *See generally* J. F. T. Glasgow & B. Middleton, *Reye Syndrome—Insights on Causation and Prognosis*, 85 ARCHIVES DISEASE CHILD 351 (2001).

[10] *See generally* Adnan S. Dajani et al., *Diagnosis and Therapy of Kawasaki Disease in Children*, 87 CIRCULATION 1776 (1993).

[11] *See generally* Kai-Sheng Hsieh et al., *Treatment of Acute Kawasaki Disease: Aspirin's Role in the Febrile Stage Revisited*, 114 PEDIATRICS e689 (2004).

[12] *See generally* Verica Ivanovska et al., *Pediatric Drug Formulations: A Review of Challenges and Progress*, 134 PEDIATRICS 361 (2014).

[13] Pediatric patients are defined for purposes of this article as those under eighteen years of age.

This paper explores the landscape of pediatric drug testing in the United States. Part I reviews the relevant legal developments over the course of the 20th and 21st centuries. Part II contains an analysis of publicly-available data to further understand the current state of pediatric drug testing. Implications of this data analysis are drawn out in Part III, which suggests the current policy landscape is insufficient to reach the goals implicit in the approach to pediatric drug testing. Part IV outlines policy recommendations that might help attain the goal of safe and effective medicines for children.

I. RELEVANT STATUTES AND REGULATIONS

A. Historical Background

The Federal Food, Drug, and Cosmetics Act (FDCA), passed in 1938, was the foundation of the regulatory regime governing drugs. This Act made no specific mention of testing drugs in children, as it did not require any testing of drugs before they were sold. However, § 502(f) of the FDCA did provide that:

> A drug or device shall be deemed to be misbranded . . . Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health . . . in such manner and form, as are necessary for the protection of users . . . [14]

The rules promulgated pursuant to this section provided no detail as to how the executive branch (at the time, the Secretary of Agriculture enforced the FDCA) would determine if use of a drug "may be dangerous to health" when used in children. Rather, they mentioned only that "directions for use may be inadequate by reason (among other reasons) of omission, in whole or in part, or incorrect specification of . . . quantity of dose (including quantities for persons of different ages and different physical conditions)."[15]

Little has been clarified since the initial enactment of § 502(f). The 1941 updates of the relevant regulations provided no more information on the topic.[16] Experts who interpreted the law for physician audiences suggested only that "it may be assumed that the physician will provide his patient with warnings which will be more specific and comprehensive than anything which can be given in a general way on the labeling of drugs."[17] Though many countless FDA actions have been taken regarding § 502(f)(1), the only case relying upon § 502(f)(2)—that is, the subsection relating to children—was not brought to court until 2007, and even then focused on the general presence or absence of labeling.[18] In general, the mention of children in the original FDCA seems to have largely been forgotten.

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[14] FDCA, Pub. L. No. 75-717, § 502(f), 52 Stat. 1040, 105051 (1938) (codified as amended at 21 U.S.C. §§ 301–99(h) (2016)).

[15] Promulgation of Regulations Under the FDCA, 3 Fed. Reg. 3161, 3167 (Dec. 28, 1938).

[16] *See* Regulations for the Enforcement of the FDCA, 6 Fed. Reg. 1920, 1920–21 (Apr. 15, 1941).

[17] Theodore G. Klumpp, *The Federal Food, Drug and Cosmetic Act: As it Applies to Drugs Dispensed by Physicians or on Physicians' Prescriptions*, 116 JAMA 830, 831 (1941).

[18] *See* United States v. Schraud, No. 4:07 CR 411 CDP DDN, 2007 WL 4289660, at *4 (E.D. Mo. Dec. 4, 2007).

In the early 1960s, the emerging thalidomide crisis[19] led Congress to pass the Kefauver-Harris Drug Amendments (the 1962 Amendments).[20] These amendments created the modern structure of premarket approval of new drugs, including the requirement of clinical-trial data to support FDA approval. Despite being prompted by a crisis whose visible victims were children, the 1962 Amendments again made no specific mention of testing drugs in pediatric patients. The regulations promulgated under these amendments only mention that preclinical testing should be relevant to the drug's intended conditions of use, including whether the drug is intended for use in children.[21]

FDA's first formal action regarding pediatric drug testing took the form of a regulation finalized in 1979 under the FDCA.[22] This rule required that prescription-drug labels either include a specific pediatric indication (if supported) or an explicit statement that "safety and effectiveness in children have not been established."[23] The inadequacies of this regulation quickly became clear, as an informal study performed by the American Academy of Pediatrics showed that 80 percent of drugs approved between 1984 and 1989 carried no labeling for a pediatric indication.[24] Yet the issue languished for years, garnering little attention from policymakers.

In 1994, FDA revisited the 1979 regulation to clarify that data supporting pediatric labeling did not need to be of the same kind or quality as that supporting approval for general marketing. In this updated rule, FDA allowed that:

> products may be labeled for pediatric use based on adequate and well-controlled studies in adults together with other information supporting pediatric use (e.g., pharmacokinetic data, safety data, pharmacodynamic data) . . . provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients.[25]

This rule effectively lowered the bar for pediatric labeling by allowing applicants to argue that data from adult study subjects could be extrapolated to pediatric populations. FDA could still, of course, respond that such extrapolation was inappropriate, but the implications of this precedent would return in future policies.

B. The Current Regime

The 1979 rule and its 1994 update elicited a meager response from the pharmaceutical industry. Observers ascribed this to two major factors: an initial lack of agreement on the ethics of pediatric drug testing, as well as a lack of economic

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[19] *See* Jeremy A. Greene & Scott H. Podolsky, *Reform, Regulation, and Pharmaceuticals—The Kefauver-Harris Amendments at 50*, 367 NEW ENG. J. MED 1481, 1481 (2012).

[20] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended at 21 U.S.C. §§ 301–399(h) (2016)).

[21] Regulations for the Enforcement of the FDCA, 28 Fed. Reg. 6375, 6378 (June 20, 1963).

[22] *See generally*, Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434 (June 26, 1979).

[23] *Id.* at 37,465.

[24] Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 Fed. Reg. 64,240, 64,240 (Dec. 13, 1994).

[25] *Id.* at 64,241.

incentive.[26] An ethical consensus did develop in the last decades of the 20th century, with pediatricians broadly agreeing that enrolling children in ethically-conducted studies was preferable to drug use in children without justification from trials.[27] However, the economic challenges remained. After all, pediatricians, like all physicians, could (and did) still prescribe these drugs off-label; the only advantage for firms to obtain a pediatric label was in order to promote the drug to pediatricians. Given the small size of the pediatric market for most drugs, this clearly was not a sufficient incentive for firms to invest the significant resources required to conduct pediatric trials.

To overcome this deficiency, the FDA Modernization Act (FDAMA) of 1997 added § 505A to the FDCA, constituting the first statutory language regarding pediatric trials.[28] This section grants six additional months of market exclusivity to drugs for which pediatric testing was conducted at FDA's request, providing a powerful new economic incentive for firms to conduct pediatric testing. Two points regarding this grant of exclusivity are important to note. First, "the granting of pediatric exclusivity does not depend on finding that the drug is safe and effective for pediatric use"[29]—only on the *performance* of such trials. Second, FDA has interpreted § 505A to mean that "pediatric exclusivity will attach to exclusivity and patent protection listed in the *Orange Book* for any drug product containing the same active moiety as the drug studied and for which the party submitting the studies holds the approved new drug application."[30] This is particularly important for drugs with multiple formulations, as it means that a manufacturer may test a pediatric-specific formulation (such as a syrup) in pediatric patients, but then receive additional exclusivity for *all formulations* of that drug, including those meant for adults, thereby increasing the potential value of additional exclusivity.

In its 2001 status report to Congress on this provision, FDA reported that "the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date."[31] Due to its apparent success, the exclusivity provision (which was originally due to sunset every five years) was renewed in 2002 as part of the Best Pharmaceuticals for Children Act (BPCA),[32] again in the FDA Amendments

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[26] PETER BARTON HUTT ET AL., FOOD AND DRUG LAW: CASES AND MATERIALS 697 (Robert C. Clark et al. eds., 4th ed. 2014).

[27] *See generally*, Am. Acad. of Pediatrics Comm. on Drugs, *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*, 60 PEDIATRICS 91 (1977); Norman Fost, *Ethical Dilemmas in Medical Innovation and Research: Distinguishing Experimentation from Practice*, 22 SEMINARS PERINATOLOGY 223 (1998).

[28] Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 111, 111 Stat. 2296, 2305 (1997) (codified as amended at 21 U.S.C. §§ 301–399(h) (2016)).

[29] U.S. GOV'T ACCOUNTABILITY OFF., GAO-07-557, PEDIATRIC DRUG RESEARCH: STUDIES CONDUCTED UNDER BEST PHARMACEUTICALS FOR CHILDREN ACT 10 (2007).

[30] FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: QUALIFYING FOR PEDIATRIC EXCLUSIVITY UNDER SECTION 505A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 13 (1999).

[31] FOOD & DRUG ADMIN., THE PEDIATRIC EXCLUSIVITY PROVISION: JANUARY 2001 STATUS REPORT TO CONGRESS 12, at ii (2001).

[32] Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, § 8, 115 Stat. 1408, (codified as amended in scattered sections of 18 U.S.C, 21 U.S.C., and 42 U.S.C.).

Act (FDAMA) of 2007,[33] and made permanent in the FDA Safety and Innovation Act (FDASIA) in 2012.[34]

Yet § 505A was no panacea. Manufacturers are often reluctant to perform additional trials of any sort after approval because such trials "pose a risk of exposing previously unrecognized toxicities, thereby reducing rather than expanding product demand."[35] Additional exclusivity was also a hollow incentive to the makers of drugs whose exclusivity and patent protection had already expired. Thus, many drugs commonly used in children did not undergo additional testing, helping prompt passage of BPCA in 2002.

In addition to reauthorizing § 505A, BPCA provided mechanisms for FDA to initiate research on specific drugs for pediatric approval, described here in brief. This process begins when FDA formally determines that a drug may provide health benefits to children and issues a written request to the drug sponsor to conduct pediatric drug studies. If the sponsor of an on-patent drug accepts the request and submits relevant data, its drug is eligible for additional exclusivity under § 505A as previously described. If the sponsor declines, however, FDA may refer the drug to the Foundation for the National Institutes of Health (FNIH), which may fund studies. BPCA also provided a short period of funding to the National Institutes of Health (NIH) to conduct pediatric studies on off-patent drugs. Though FDA has the authority to grant six months of exclusivity to off-patent drugs if sponsors fulfill the study requirements, it generally does not do so, and sponsors generally do not seek it.[36]

While § 505A represented a "carrot" to increasing pediatric drug testing (i.e., providing rewards for conducting such testing), Congress added a "stick" in 2003 with the passage of the Pediatric Research Equity Act (PREA)[37] which added § 505B to the FDCA. FDA first tried a "stick" approach around the time Congress passed FDAMA by proposing in 1997 and finalizing in 1998 what became known as the Pediatric Rule.[38] In this regulation, FDA asserted its authority to require manufacturers of certain new drugs to conduct pediatric studies applicable to the claimed indications. Though this rule became effective at the beginning of 1999 and a number of studies were conducted under its auspices, it was struck down in federal district court in 2002 for overstepping FDA's statutory authority.[39] FDA chose not to appeal the ruling, in part due to PREA's impending passage.

Section 505B has two major provisions. First, it imposes new requirements on all New Drug Applications (NDAs) and Biologic License Applications (BLAs) regarding pediatric testing. In general, § 505B requires that NDAs/BLAs include data used "to assess the safety and effectiveness of the drug or the biological product for the claimed

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[33] FDA Amendments Act of 2007, Pub. L. No. 110-85, § 106, 121 Stat. 823, (codified as amended in scattered sections of 5 U.S.C., 18 U.S.C., 21 U.S.C., and 42 U.S.C.).

[34] FDA Safety and Innovation Act of 2012, Pub. L. No. 112-144, § 501(a), 126 Stat. 993, (codified as amended in scattered sections of 5 U.S.C., 18 U.S.C., 19 U.S.C., 21 U.S.C., 28 U.S.C., 31 U.S.C., 42 U.S.C., and 44 U.S.C.).

[35] Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 720 (2005).

[36] *See*, U.S. GOV'T ACCOUNTABILITY OFF., *supra* note 29, at 8.

[37] Pediatric Research Equity Act of 2003, Pub. L. No. 108–155, §§ 2, 117 Stat. 1936 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

[38] *See*, FOOD & DRUG ADMIN., *Rules and Regulations*, 63 FED. REG. 66,632 (1998).

[39] Ass'n of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204, 222 (D.D.C. 2002).

indications in all relevant pediatric subpopulations; and to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective."[40] Unless a drug has been granted orphan designation, manufacturers must submit an initial Pediatric Study Plan (iPSP) to FDA, generally around the end of Phase II testing.[41]

Firms have three options for an iPSP. First, they can outline a plan to study the drug's safety and effectiveness in pediatric populations, including (in an echo of FDA's 1994 regulation) an assessment of whether extrapolation from adult studies may be appropriate and/or sufficient.[42] Second, firms can request a *deferral* of the requirement to study the drug in pediatric patients. FDA may grant such a request if it agrees that: "(1) the drug or biological product is ready for approval for use in adults before pediatric studies are complete; (2) pediatric studies should be delayed until additional safety or effectiveness data have been collected; or (3) there is another appropriate reason."[43] Finally, firms can request a full waiver of § 505B requirements; FDA can grant such a waiver if it finds that:

> (1) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed); (2) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or (3) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.[44]

FDA may also grant partial waivers for specific pediatric subgroups. Thus, despite the nominal "equity" in the law's title, firms clearly have multiple pathways to minimize their commitment to pediatric drug testing. Given the broad statutory language establishing these pathways, FDA has significant discretion over how these pathways operate in practice, including how easy it is for firms to use them.

In addition to making § 505A permanent in 2012, FDASIA also made § 505B permanent. In other words, after nearly a decade of experience with § 505B (the stick approach), and fifteen years of experience with § 505A (the carrot approach), Congress felt such a two-pronged system was working reasonably well and ought to become the landscape for the foreseeable future. Congress' intentions on this front were confirmed in late 2016 with the passage of the 21st Century Cures Act, a broad-ranging pharmaceutical-reform bill which renewed the priority-review voucher program for rare pediatric diseases,[45] but left § 505A and § 505B of the FDCA untouched. These statutory provisions, along with their associated regulations, form the backbone of today's policy approach to testing drugs in pediatric patients.

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[40] FDCA, 21 U.S.C. §§ 355(c), 2(A)(i)–(ii) (1938).

[41] FOOD & DRUG ADMIN., PEDIATRIC STUDY PLANS: CONTENT OF AND PROCESS FOR SUBMITTING INITIAL PEDIATRIC STUDY PLANS AND AMENDED INITIAL PEDIATRIC STUDY PLANS: DRAFT GUIDANCE FOR INDUSTRY 4 (2016).

[42] *Id.* at 8.

[43] *Id.* at 11.

[44] *Id.* at 9.

[45] 21st Century Cures Act, Pub. L. No. 114–255, § 3013, 130 Stat. 1033, 1093 (2016).

II. DATA ANALYSIS

While lawmakers seem to believe the current policy approach is working well, it is important to bring data to bear on this question. Accordingly, a three-part data analysis was performed, the methods and results of which are reported here, and the implications of which are discussed in Part III. The analysis first assessed which drugs have gained FDA-approved labeling for pediatric uses and which policies prompted these labeling changes. Second, it evaluated the specific characteristics of studies in pediatric populations. Finally, it analyzed the statistical power of pediatric drug trials. Though other groups have studied time-limited subsets of the data analyzed here,[46] this analysis appears to be the most comprehensive review of data publicly available from FDA.

A. Labeling Changes

FDA maintains a publicly-available database of all pediatric-related changes to drug labeling (including those enacted as part of an NDA) between 1998 and 2016; this database is publicly available on its website.[47] These changes vary dramatically in their scope and impact, from new approved pediatric indications, to changes in the approved age ranges, to subpopulation-level warnings and technical changes. In this 18-year period, there were 657 such changes to the labels of 539 unique drug brand names representing 448 distinct active moieties. (For context, 2,617 unique active moieties appear in FDA's comprehensive database of approved drug products.[48]) In this database, FDA assigns each label change to the relevant statute or regulation under which the change fell; Table 1 describes the distribution of labeling changes by relevant policy.

Table 1. Number of pediatric labeling changes made between 1998 and 2016 under the auspices of various statutes and regulations, as assigned by FDA.

	Pediatric Rule (1998–2002)	**BPCA only (2002–pres.)**	**PREA only (2003–pres.)**	**BPCA & PREA**	**Other**
Changes between 1998–2016 (total = 657)	49 (7.5%)	174 (26.5%)	340 (51.8%)	86 (13.1%)	8 (1.2%)

These labeling changes occurred in over 100 "therapeutic categories," as classified in the FDA database. Each change is assigned to one category, but the categories may have some clinical overlap, such as "antiallergy" and "antihistamine," which are listed as separate categories in the database, but have a class-subclass

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[46] *See generally,* Marilyn J. Field et al., SAFE AND EFFECTIVE MEDICINES FOR CHILDREN: PEDIATRIC STUDIES CONDUCTED UNDER THE BEST PHARMACEUTICALS FOR CHILDREN ACT AND THE PEDIATRIC RESEARCH EQUITY ACT ch. 7 (2012).

[47] FOOD & DRUG ADMIN., *New Pediatric Labeling Information Database,* https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase (last visited Jan. 18, 2017).

[48] *Drugs@FDA: FDA Approved Drug Products*, FOOD & DRUG ADMIN., http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (last visited Feb 23, 2017).

relationship. Table 2 (below) lists the most common therapeutic categories in the labeling-change database and compares them to the most common categories in the study-characteristics database. The vast majority (*n*=606, 92.2 percent) of these labeling changes occurred in response to a pediatric study not previously submitted to FDA.

B. Study Characteristics

FDA also maintains a publicly-available database of pediatric studies that led to changes in drug labeling pursuant to BPCA and PREA.[49] This database covers a much shorter time period than the study-characteristics database (entries only cover approvals from 2007 to 2012), but is in many ways much richer; it includes details on each study, including the number of patients in the study, information on the study design, and the features under study (e.g., safety, efficacy, pharmacokinetics, etc.). There are 397 studies contained in this database, covering 139 unique brand names and 130 unique chemical entities in approximately 50 therapeutic categories. As in the labeling-changes database, though each study is only given one category, these categories are not mutually exclusive. Table 2 lists the most common categories of drugs studied in the database.

Table 2. Most common therapeutic categories in FDA's pediatric labeling-changes database and pediatric study-characteristics database. Percentages are calculated as the percentage within the database.

Label Changes 1998–2016 (*n* = 657)	**Study Characteristics 2007–2012 (*n* = 397)**
Antiviral (*n*=76, 12.0%)	Vaccine (*n*=46, 11.6%)
Vaccine (*n*=34, 5.4%)	Antiviral (*n*=32, 8.1%)
Antiasthmatic (*n*=32, 5.1%)	Antihistamine (*n*=30, 7.6%)
Antibiotic (*n*=27, 4.3%)	Antiasthmatic (*n*=28, 7.1%)
Topical anti-inflammatory (*n*=25, 4.0%)	Antipsychotic (*n*=19, 4.8%)
Anticonvulsant (*n*=25, 4.0%)	Antiulcerative (*n*=18, 4.5%)

Table 3 lists the characteristics of various studies in the database for various groups and subgroups of the database.

[49] *Pediatric Studies Characteristics,* FOOD & DRUG ADMIN., http://www.accessdata.fda.gov/scripts/SDA/sdNavigation.cfm?sd=fdaaadescriptorssortablewebdatabase.

Table 3. Characteristics of study groups contained in FDA's database of pediatric study characteristics, covering studies filed with FDA between 2007 and 2012. Control groups may be designated as active control, placebo control, or in other forms.

Study group	Number of studies	Unique drugs		Number of patients				Control Groups			Relevant Statute		
		Unique brand names	Unique chemical entities	Mean	25th percentile	Median	75th percentile	Any control group	Active control group	Placebo control group	BPCA	PREA	Both
All studies	397	139	130	455	32	107	285	224 (56.4%)	33 (8.3%)	151 (38.0%)	69 (17.4%)	249 (62.7%)	76 (19.1%)
Studied efficacy	233	110	104	530	43	115	290	176 (74.3%)	25 (10.6%)	131 (55.3%)	42 (17.7%)	162 (68.4%)	31 (13.1%)
Studied safety	346	133	125	510	47	129	305	212 (61.3%)	31 (9.0%)	144 (41.2%)	53 (15.3%)	224 (64.7%)	66 (19.1%)
Studied efficacy and safety	217	106	100	562	51	141	298	166 (75.1%)	23 (10.4%)	125 (56.6%)	40 (18.1%)	150 (67.9%)	29 (13.1%)
Non-vaccine study	347	125	118	165	30	86	220	191 (54.4%)	30 (8.6%)	143 (40.7%)	69 (19.7%)	203 (57.8%)	76 (21.7%)
Vaccine study	41	14	12	2915	400	1,257	2,276	33 (71.7%)	3 (6.5%)	8 (17.4%)	0	46 (100.0%)	0

C. Power Analysis

To understand whether a sample size is sufficient to discern an effect of interest, it is necessary to use a power calculation. These calculations are designed to answer a deceptively simple question: *Is this study big enough to detect a real effect?* The answer to this question depends on multiple factors, including the size of the effect the researcher is seeking (e.g., a smaller study is needed to detect a 100-fold difference than a 10-fold difference), the level of statistical significance used, the certainty with which the baseline level is known, and whether the effect of interest is two-sided (i.e., different in either direction) or one-sided (i.e., only higher or only lower). Based on these parameters, a researcher can estimate how many subjects she will need to recruit to successfully run a trial; or, having recruited a cohort of subjects, can estimate the "power" of that sample size—that is, the chances of detecting a theorized effect size given the size of the sample.

This analysis examined both purposes of power calculations, focusing specifically on the question of safety. The focus on safety is for the sake of convenience, as studies are more easily compared on the basis of side-effect incidence (where the "goal" rate is zero in all cases) rather than the basis of differences in outcome measures (where the goal rate may differ by drug and condition). The power of median sample sizes to detect various effect sizes (regarding side effects) was calculated and reported in Table 4.[50] That is, Table 4 demonstrates the chance that the median study in each category would detect a doubling, quintupling, or one-order-of-magnitude increase in the incidence of a side effect that occurs just one percent of the time in a control group.

Table 4. Power of various median study sizes to detect increases in the incidence of a side effect with a baseline incidence of 1 percent and a 95 percent significance level.

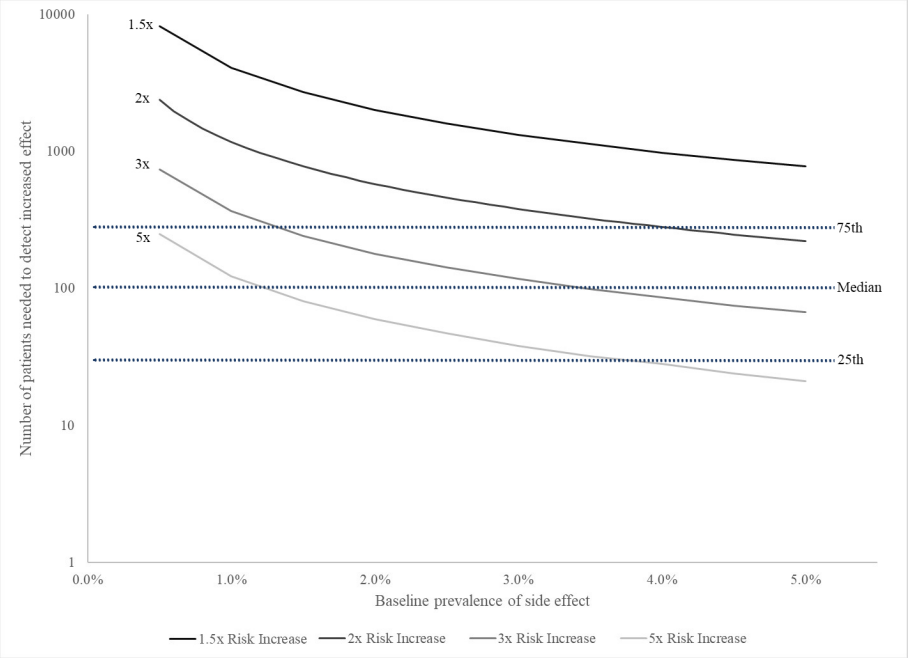
Study group	**Median study size**	**Power**		
		2x increase	**5x increase**	**10x increase**
All studies	107	11.1 %	33.0 %	65.4 %
Studied efficacy	115	11.4 %	34.6 %	68.2 %
Studied safety	129	11.9 %	37.4 %	72.6 %
Studied efficacy and safety	141	12.3 %	39.8 %	75.9 %
Non-vaccine study	86	10.3 %	28.7 %	57.5 %
Vaccine study	1,257	42.6 %	99.4 %	99.9 %

It is also informative to determine the sample size required to detect various effect sizes for side effects of various baseline prevalence. Building on a format previously

[50] For readers interested in the technical details of my calculations: I used the -power- command in Stata version 14 to perform a power calculation for a one-sided two-proportion test with groups of equal size given a five hundredths level of significance.

used in health policy literature,[51] Figure 1 graphically displays the results of this calculation, as well as the 25th, 50th, and 75th percentiles of current pediatric drug studies.[52] The solid lines graph the required sample size to detect a given effect by the baseline prevalence of the side effect; as the effect becomes more common or as the size of the effect increases, the required sample decreases. Dashed lines represent the quartile cutoffs of sample sizes in the study-characteristics database. Therefore, where a dashed line is *above* a given solid line, any study of that size or larger can detect the given effect. For example, the median study in the database is sufficiently powered to detect a 5-fold increase in the rate of any side effect with a baseline prevalence of greater than approximately 1.25 percent.

Figure 1. Power thresholds. Solid lines represent the sample size threshold at which has 90 percent power to detect the specified risk increase at a 95 percent confidence level, according to the baseline prevalence. Dashed lines represent the 25th, 50th, and 75th percentiles of all studies in the study-characteristics database (see also: Table 3). Note logarithmic *y*-axis.



[51] *See* Justin B. Dimick et al., *Surgical Mortality as an Indicator of Hospital Quality: The Problem With Small Sample Size*, 292 JAMA 847, 847–48 (2004).

[52] Technical details: this displays the results of series of calculations using the -power- function in Stata version 14 to calculate sample sizes necessary for detecting the effect size in question using a one-sided two-proportion test with a five hundredths level of significance and 90 percent power.

III. IMPLICATIONS OF DATA ANALYSIS

A. Drugs Studied

The first question to answer is simply whether, under current policy, there is enough drug testing in children. Since the data in the pediatric-labeling database goes back to 1998 (just months after § 505A was added to the FDCA), it captures the vast majority of drugs that have been labeled for pediatric use—after all, FDA and Congress took policy action in the late 1990s in order to address the paucity of pediatric labeling. The 448 active moieties in this database represent just 17.1 percent of the 2,617 active moieties in FDA's database.[53] Admittedly, this is likely an *underestimate* of the proportion of true interest; not all drugs in the database are in regular use for children, and some drugs had pediatric labeling prior to 1998. Nevertheless, even if this estimate is too low by half, the vast majority of drugs in current use lack pediatric labeling of any sort. As demonstrated below, FDA's standards for studies used to justify labeling are not particularly high either, suggesting the lack of labeling is in fact due to a simple lack of study. In turn, this suggests the current incentives and requirements for pediatric trials are insufficient.

Some may argue that this overstates the problem by not weighting by the number of prescriptions for each drug—that perhaps the most commonly-prescribed drugs for children are in fact labeled, and that the rarely-used drugs are disproportionately represented among the un-labeled. Though such an analysis is beyond the scope of this paper, there are two rejoinders to note. First, the available evidence does not support this argument. In the early 2000s, approximately 62 percent of pediatric prescriptions in American outpatient settings were for off-label uses.[54] Data in an American pediatric intensive care unit[55] as well as international data in various clinical settings also suggest a large proportion of off-label use.[56] For some context, in 2001 approximately 20 percent of all prescriptions in the American outpatient setting were for off-label purposes,[57] while in the late 2000s approximately 10 percent of all prescriptions in Quebec primary care were off-label.[58] Second, even if the available evidence is out of date or wrong, the argument is mistaken on a more fundamental level. It may not be that rarely-used drugs are not studied *because of their rare use*, but rather that some drugs are rarely used *because of the lack of study.* This too implies significant weaknesses in the current policy approach to pediatric testing.

Table 2 can also inform whether the "right" drugs are being studied. On this, the evidence is mixed, though mostly positive. Vaccines, antihistamines, antiasthmatics, and antibiotics are all commonly-used medications in children, and their presence as

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53 FOOD & DRUG ADMIN., *supra* note 48.

54 Alicia T.F. Bazzano et al., *Off-Label Prescribing to Children in the United States Outpatient Setting*, 9 ACAD. PEDIATRICS 81, 83 (2009).

55 *See e.g.*, Angela S. Czaja et al., *Patterns of Off-Label Prescribing in the Pediatric Intensive Care Unit and Prioritizing Future Research*, 20 J. PEDIATRICS PHARMACOL. THER. 186, 188 (2015).

56 *See e.g.*, Elin Kimland & Viveca Odlind, *Off-Label Drug Use in Pediatric Patients*, 91 CLIN. PHARMACOL. THER. 796, 796–97 (2012).

57 David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1021, 1023 (2006).

58 Tewodros Eguale et al., *Drug, Patient, and Physician Characteristics Associated with Off-label Prescribing in Primary Care*, 172 ARCHIVES INTERNAL MED. 781, 781, 783 (2012).

frequently-studied medications is encouraging. Anticonvulsants and antipsychotics are not particularly commonly used, but when used, they are used to treat diseases with significant burdens such as epilepsy, bipolar disease, and schizophrenia. Some of the antivirals studied target HIV, another rare but high-burden disease. Since these drugs also generally carry significant side effects, their presence on this list is also heartening.

Topical anti-inflammatory drugs are often used for children with atopic dermatitis, more commonly known as eczema. Though this is a common use, atopic dermatitis is usually a relatively low-impact condition, and topical therapies generally pose lower risk than systemic ones. Many of the antivirals, of course, are neither particularly common or high-impact. Both topical anti-inflammatories and antivirals have potentially large adult markets, and their presence on this list is likely related to the fact that pediatric studies may help their manufacturers attain additional exclusivity for adult formulations as well.

B. Statutes Used

Next, the information in Tables 1 and 3 sheds light on which parts of the current policy regime seem to be having the largest effect. PREA appears to have been the dominant force in producing pediatric studies. Over half of the labeling changes were attributed to PREA alone, and nearly two-thirds relied in some way on PREA; an even greater proportion of the studies in the smaller study-characteristics database relied on PREA. Clearly § 505B (the "stick" approach) has been the most important policy for spurring pediatric drug trials.

Unfortunately, the database is unclear whether attribution to BPCA includes all drugs that added labeling due to § 505A (though that is the most likely explanation). Regardless, BPCA's relative weakness may be surprising, as six additional months of market exclusivity can be extremely valuable. Data from the mid-2000s suggests six months of additional exclusivity under § 505A is worth a median of $134 million, compared to a median drug-trial cost of $12 million;[59] more recent data on the similar orphan-drug designation suggests slightly smaller, but still substantial, returns.[60] It is unclear why § 505A has not been as effective as hoped, but risk aversion may play a role. One reason may be that the return on trials can be quite variable and difficult to predict,[61] and firms may be risk-averse in these investments. Another reason, as mentioned in Part I**,** is that additional trials run the risk of uncovering new side effects and harming the drug's business case. In addition to its relatively modest effect, there have been significant criticisms of the § 505A approach, summarized well by Kesselheim[62] (footnote numbering changed from original):

> Pediatric trials have been conducted on a number of products with marginal public health importance for children, and the drugs most frequently used by children have been underrepresented; instead,

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[59] Jennifer S. Li et al., *Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program*, 297 J. AM. MED. ASS'N 480, 483–84 (2007).

[60] Aaron S. Kesselheim et al., Six-Month Market Exclusivity Extensions To Promote Research Offer Substantial Returns For Many Drug Makers, 36 HEALTH AFFS. 1, 5 (Feb. 2017).

[61] Li et al., *supra* note 60, at 487.

[62] Aaron S. Kesselheim, *Using Market-Exclusivity Incentives to Promote Pharmaceutical Innovation*, 363 NEW ENG. J. MED. 1855, 1859 (2010).

> pediatric exclusivity studies have tended to involve drugs that were both popular and profitable in the market for adults.[63] In addition, some pediatric studies were of subpar quality[64] or were not subject to peer review and publication in the medical literature.[65] In these cases, the manufacturers' goal may have been to obtain the pediatric exclusivity bonus rather than to conduct clinically meaningful tests of their products in pediatric patients or to have the widest possible influence on public health. Finally, some manufacturers have delayed pediatric trials until late in the period of their product's market exclusivity, thereby increasing their return and minimizing the public health benefit.[66]

Kesselheim's summary contains an important implication for policymakers. As discussed in Part I, § 505A was implemented in a way that created the largest incentive possible by allowing additional exclusivity to attach to *all* forms of a drug. This approach encourages companies to focus their pediatric trials on drugs that are popular in the much more lucrative adult market rather than drugs primarily used for children, as the additional exclusivity is much more valuable for these drugs. This is borne out by research indicating that drugs for conditions with a high disease burden in children (relative to adults) are less likely to be studied in children, particularly by pharmaceutical firms themselves.[67] It seems, then, that despite FDA's initial excitement over the exclusivity provision,[68] it has become less important and its flaws more apparent since the addition of § 505B.

C. Study Adequacy: Power and Rigor

Though § 505A and § 505B do have their weaknesses, they have also spurred the performance of more pediatric drug trials than ever before—but not all trials are created equal. Properly assessing the success of these provisions requires assessing the quality of the studies that result. The FDA database on study characteristics only offers a partial window into study quality, but with nearly 400 studies in the database, the view is clear enough—and it shows that the studies are all too often of poor quality. Two key aspects of study quality are specifically examined: *power* (as defined in Part II), and *rigor*, the use of appropriate design (e.g., the use of control groups).

As Table 4 and Figure 1 demonstrate, most pediatric drug studies are underpowered to detect even large increases in the risk of rare side effects. Figure 1 is particularly striking, as effect sizes of 2-fold, 5-fold, or 10-fold are much larger than many effects of interest; thus, the figure represents a conservative analysis. Vaccine studies are a notable (and happy) exception to the finding of low power; they appear to generally

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[63] Isabelle Boots et al., *Stimulation Programs for Pediatric Drug Research--Do Children Really Benefit?*, 166 EUR. J. PEDIATRICS 849, 852 (2007).

[64] Daniel K. Benjamin et al., *Pediatric Antihypertensive Trial Failures: Analysis of End Points and Dose Range*, 51 HYPERTENSION 834, 839 (2008).

[65] Daniel K. Benjamin et al., *Peer-Reviewed Publication of Clinical Trials Completed for Pediatric Exclusivity*, 296 J. AM. MED. ASS'N 1266, 1269 (2006).

[66] Joseph Deveaugh-Geiss et al., *Child and Adolescent Psychopharmacology in the New Millennium: A Workshop for Academia, Industry, and Government*, 45 J. AM. ACAD. CHILD ADOLESCENT PSYCHIATRY 261, 263–65 (2006).

[67] Florence T. Bourgeois et al., *Pediatric Versus Adult Drug Trials for Conditions With High Pediatric Disease Burden*, 130 PEDIATRICS 285, 285 (2012).

[68] FOOD AND DRUG ADMIN., *supra* note 31, at ii.

undergo studies comparable to Phase III studies in size and power. Given that vaccines are administered to millions of children, rare side effects are certain to manifest in real-world use; thus, informing parents and physicians of these side effects in advance is critical. Since vaccines are given to healthy children, the burden of proof for safety is also heavier. Intuitively, the acceptable risk level increases as the patient's sickness increases. (Of course, vaccines are also subject to additional regulation under section 351(g) of the Public Health Service Act,[69] but this is beyond the scope of this paper.)

Meanwhile, Table 3 demonstrates that rigor is often lacking as well—over 40 percent of these trials do not include a control group. Efficacy studies are more likely to be controlled, but even then, one in four of these studies does not have a control group of any sort. Of course, the presence of control/comparator groups is a keystone principle in statistics; without such groups, drawing actionable lessons from trials is extraordinarily difficult, if not impossible. This sizable minority of uncontrolled studies casts further doubt on FDA's current standards for pediatric drug testing.

In response to these findings, some may point out that the current policy regime has not resulted in any safety crises, based on the premise that if FDA's criteria for pediatric drug trials were indeed underpowered or if controls were critically important, a crisis would have emerged by now. This is a worthwhile consideration, but there are two responses: one specific and one more general. The specific point is that the analysis above relies on side effects for the sake of convenience. Efficacy is even more difficult to discern than are side effects, and underpowered, uncontrolled studies will pose larger problems here even though they are more difficult to demonstrate in a single analysis. More generally, such an objection does risk falling into the pattern that has defined American drug regulation through its history—that of waiting for crises to prompt a change, rather than heading off issues in advance. (This is a defensible approach, but many may disagree.)

IV. RECOMMENDATIONS

The central difficulty in a policy approach to pediatric drug testing is balancing the ethical tradeoff between organized drug-testing on children and "flying blind" in the clinic. It may be that subjecting minors to clinical trials with potentially serious risks is unacceptable, accepting that this means pediatricians will not have strong data to use in the clinic and turning each prescription into an "*n* of one" trial. Alternatively, it may be unethical to have pediatricians make ad hoc judgments for individual patients, and it may be that properly-conducted clinical trials are the only reliable way to generate systematic knowledge that benefits children as a class. Despite policymakers' best intentions, current policies have taken an unsatisfying third way: accepting the ethical challenges attendant to conducting pediatric clinical trials, but in a disturbing fraction of cases, these trials are not generating findings of sufficient quality to genuinely inform pediatric prescribers.

Moreover, the practice of labeling drugs for pediatric use on the basis of weak studies is particularly concerning. The public has tasked FDA with the complicated task of assessing study quality as part of its mandate to ensure drug safety and quality

[69] Public Health Service Act, Pub. L. No. 78-410, § 351(g), (1994), (codified as amended at 42 U.S.C. 6A).

and has long had high levels of trust in FDA.[70] FDA-approved labeling, then, is likely to be interpreted as a trustworthy marker of a drug's safety and efficacy. Yet, as shown above, labeling for a pediatric use appears to rely on *inferior* studies than that for a drug's initial indication, which tends to be based on multiple studies of many hundreds of patients, almost all of which are double-blinded trials with control groups.[71] This is a fine distinction all but certain to be lost on parents whose primary concern is their sick child. Given that physicians generally tend to overestimate the minimum level of evidence required of new drugs,[72] it is not clear that pediatricians may be any more informed than parents on this score. The implication of the results in this analysis, then, is that those caring for children are likely operating with a false sense of security regarding the demonstrated safety and efficacy of their therapeutic armamentarium. If this sense of security is ever punctured, FDA risks losing public trust on a much broader scale. Some observers already suspect the modern drug-approval process is tilted too far in favor of drug companies and against patients;[73] if the public feels that lucrative exclusivity extensions (which undoubtedly raise prices for consumers by extending market monopolies[74]) are regularly given out in exchange for studies of little use, such sentiments will only grow.

Policymakers can address these problems in a variety of ways. FDA can take a set of *regulatory* actions without Congress to improve the quantity and quality of pediatric drug studies. Approximately half of small-molecule and biologic approvals receive some sort of exemptions from pediatric study requirements in PREA;[75] though some are undoubtedly appropriate, FDA should review and tighten its criteria for granting full or partial waivers from PREA requirements. Given that deferrals of pediatric study are also quite common,[76] FDA could do the same for its criteria for granting deferrals, especially repeat deferrals for the same drug. Since PREA's "stick" approach appears to be a stronger incentive than BPCA's "carrot" approach, these are likely to be the highest-impact actions FDA can take of its own accord to improve the quantity of studies.

Of course, when it comes to the quality of studies, FDA has the authority to issue guidance (or rules) strengthening its own criteria for evaluating pediatric studies, as PREA sets forth no statutory criteria for when research is sufficient to support safety and efficacy in pediatric populations. FDA should reassess its own criteria for appropriate study size and study design, particularly with an eye towards increasing trial power and increasing the use of control groups. A National Academy of Medicine

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[70] PEW RESEARCH CTR., TRUST IN GOVERNMENT NEARS RECORD LOW, BUT MOST FEDERAL AGENCIES ARE VIEWED FAVORABLY (2013).

[71] *See* Nicholas S. Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005–2012*, 311 J. AM. MED. ASS'N 368, 372–73 (2014).

[72] Aaron S. Kesselheim et al., *Physicians' Knowledge About FDA Approval Standards and Perceptions of the "Breakthrough Therapy" Designation*, 315 J. AM. MED. ASS'N 1516, 1517 (2016).

[73] *See, e.g.,* Alexandra Sifferlin, *Is the FDA Too Cozy With Drug Companies?* TIME (Sept. 28, 2016), http://time.com/4510025/fda-drug-companies-pharmaceutical-industry-medical-reviewers (last visited Oct. 9, 2017).

[74] *See generally* Ernst R. Berndt et al., *A Primer on the Economics of Prescription Pharmaceutical Pricing in Health Insurance Markets*, 14 FORUM HEALTH ECON. POL'Y (2011).

[75] *See* Florence T. Bourgeois & Thomas J. Hwang, *The Pediatric Research Equity Act Moves Into Adolescence*, 317 J. AM. MED. ASS'N 259, 259 (2017).

[76] *Id.*

committee has also recommended that FDA reconsider and more fully justify its acceptance of data extrapolated from adult populations to pediatric drug labeling.[77]

Congress, of course, has more options than has FDA alone. For example, Bourgeois and Hwang have suggested that legislators could amend PREA to include pediatric orphan drugs (an approach already taken by European regulators), as well as modify BPCA to require companies who are repeatedly noncompliant with pediatric testing requirements to provide funds to NIH to conduct studies instead.[78] Other "stick"-style approaches could include imposing additional post-marketing requirements on drugs without pediatric study, or even granting FDA the authority to remove products from the market if they do not have pediatric studies performed by some deadline. Some may suggest Congress make the "carrot" approach more attractive by increasing the length of additional exclusivity granted to drugs with pediatric studies. The apparent weaknesses of § 505A make this an approach with significant drawbacks, and policymakers would do better to avoid it.

The simplest approach Congress could take, however, is the one I most strongly recommend: appropriating significant additional funds for NIH with the explicit purpose of conducting pediatric drug trials using extant mechanisms. Under BPCA, NIH already maintains a yearly Priority List of the drugs most in need of pediatric testing;[79] additional funding would allow NIH to fund more studies of these drugs—a particularly important step for off-patent drugs. Funds could be raised from increases in FDA user fees, from a small (e.g., 25-cent) surcharge on each pediatric prescription, or from many other sources such as general revenues.

It is true that none of these recommendations will result in a perfect world where all drugs used in children are rigorously tested in large trials. There are some practical concerns to consider. First, certain diseases (e.g., orphan diseases) and subgroups (e.g., neonates) are too small to support large drug trials—there are simply not enough patients. It would be unreasonable to expect large trials in these situations. Congress, however, has recently encouraged the performance of smaller trials in these rare diseases with the rare-pediatric-disease priority voucher program. Though this program is relatively small and has received some criticism,[80] it does suggest an appetite for improving data quality even in rare diseases in small populations.

Second, infants in particular pose a challenging set of ethical considerations regarding drug testing.[81] However, it is worth noting that international consortia have recently been formed to guide trials in neonates, with FDA support,[82] and that these consortia have recently released guidelines for drug trials in infants.[83] This does not

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[77] SAFE AND EFFECTIVE MEDICINES FOR CHILDREN, *supra* note 47, at 13.

[78] Bourgeois & Hwang, *supra* note 76, at 259–60.

[79] NAT'L INST. OF HEALTH, BEST PHARMACEUTICALS FOR CHILDREN ACT (BPCA) PRIORITY LIST OF NEEDS IN PEDIATRIC THERAPEUTICS 1 (2017), https://bpca.nichd.nih.gov/prioritization/status/Documents/2017_Priority_List.pdf.

[80] S*ee generally* Aaron S. Kesselheim et al., *Experience With the Priority Review Voucher Program for Drug Development*, 314 J. AM. MED. ASS'N 1687 (2015).

[81] Sanjiv Amin et al., *Clinical Trials of Drugs Used Off-Label in Neonates: Ethical Issues and Alternative Study Designs*, 15 ACCOUNTABILITY RES. 168, 170 (2008).

[82] Megan Scudellari, *Newborns Often Get Unapproved Drugs. Now, a Push for Data.* STAT 2 (2017), https://www.statnews.com/2017/01/03/neonatal-drugs-unapproved (last visited Oct. 9, 2017).

[83] *See generally* Robert M. Ward et al., *Safety, Dosing, and Pharmaceutical Quality for Studies that Evaluate Medicinal Products (Including Biological Products) in Neonates*, PEDIATRIC. RES. (2016).

mean all challenges have been suitably resolved—there is still significant room for improvement.

Third, there are significant operational barriers to successfully conducting randomized trials of any kind in pediatric populations. Recent data from Germany, Switzerland, and Canada suggests that 40 percent of pediatric trials are prematurely discontinued, primarily for reasons of slower-than-expected recruitment, and this is a much higher risk than in adult trials.[84] This difficulty, however, should not be an excuse to avoid funding pediatric trials. Rather, it reminds policymakers that additional funding is necessary but not sufficient. Other forms of support, such as research consortia and coordinated patient-recruitment efforts, are needed as well.

Finally, there is a resource-allocation consideration. If FDA/NIH have sufficient funds for large trials on existing drugs, those funds might be better used towards developing new therapeutics—or if additional trial requirements are imposed on drug firms, the flow of new drugs might be inadvertently stanched. These are real concerns, but they require two separate responses. Governmental funding is a potential solution for off-patent drugs for which no private-sector incentive for drug trials could conceivably exist;[85] such funding streams will not divert monies that otherwise would have gone towards the development of new drugs. The threat of reducing the flow of new therapeutics is real, as clinical trials add to the cost of development, thereby reducing the expected rate of return on capital and plausibly reducing investment.[86] This is a real cost of imposing additional requirements for new patented drugs, and it explains why policymakers might prefer "carrot" approaches (increasing the rate of return to offset the cost of new trials) to "stick" approaches. Since the current six-month exclusivity period generates quite large returns,[87] a sensible first step might be tightening criteria for deeming research sufficient to trigger § 505A. If this is insufficient, further requirements with real costs may be justified. This will open a debate of values around this tradeoff, keeping in mind that children are a vulnerable group and require special attention to ensure the safety of the medications prescribed to them.

CONCLUSION

Setting policy for drug trials is an inherently challenging task, which are all the greater in pediatric populations. However, the importance of performing high-quality drug trials in children cannot be minimized. Simply relying on adult data for pediatric patients would be a mistake—it would be assuming children are simply "little adults." Congress and FDA have made significant strides in improving pediatric drug testing in the 75-plus years since the touchstone FDCA of 1938, but there is still considerable distance to go to reach the goal of a pediatric pharmacopoeia stocked with drugs *proven* to be safe and effective in children. Congress has a number of options to help move in that direction, most notably by appropriating additional funding for studying these drugs. FDA can do its part by tightening its exemption criteria and requiring

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[84] Stefan Schandelmaier et al., *Premature Discontinuation of Pediatric Randomized Controlled Trials: A Retrospective Cohort Study*, 184 J. PEDIATRICS 209, 2011 (2017).

[85] *See generally* Eisenberg, *supra* note 35.

[86] Robert Kocher & Bryan Roberts, *The Calculus of Cures*, 370 NEW ENG. J. MED. 1473, 1474 (2014).

[87] Li et al., *supra* note 60.

stronger studies of the drugs submitted for its approval. Without such changes, Americans run the risk of continuing to treat children like "little adults."