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LEAVING NO CHILD BEHIND?

ABIGAIL ALLIANCE, PEDIATRIC PRODUCTS AND OFF-LABEL USE

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I. INTRODUCTION

Biologically, children[1] are not simply smaller–sized adults. Because of biological and cultural differences, the law provides extra protection for children in numerous circumstances. Particularly relevant to FDA law, there are important biological differences between children and adults, and they are not limited to differences in size. Explains one doctor: "There are dynamics of growth and maturation of organs, changes in metabolism throughout infancy and childhood, changes in body proportion, and other developmental changes that affect how drugs are metabolized."[2]

Although children and adults have some similar medical needs, they also have some very different needs and risks. Medications that are helpful and safe to adults do not always provide the same benefits to children.[3] For example, in the 1950s, the antibiotic chloramphenicol was widely used in adults to treat infections resistant to penicillin. However, many newborn babies died after receiving the drug because their immature livers could not break down the antibiotic.[4] A recent warning against giving young children certain over-the-counter cold medicines provides another prominent

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1 Throughout this article, we use the term "children" or "pediatric" to refer to patients under age 18. Except as specifically relevant, we do not distinguish between subgroups within this pediatric population.

2 *See* Michelle Meadows, *Drug Research and Children*, FDA CONSUMER MAG., Jan.–Feb. 2003, *available at* http://www.fda.gov/fdac/features/2003/103_drugs.html.

3 The fact that inadequately tested pediatric products led to injury and death in children has been recognized by the FDA. *See*, *e.g.*, *Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients*, 62 FED. REG. 43,900 (Aug. 15, 1997).

4 *See* Meadows, *supra* note 2.

example.[5] The established risk of suicidal thinking that antidepressants pose to adolescents is still another.[6]

Despite these well-known differences, drugs, devices, and biologics[7] (intended or used to treat, cure, or mitigate disease in children, or to affect the structure and function of children's biological systems)[8] have historically either been developed using systems and regulatory structures identical to those used for adult products, or have been developed and approved as adult products and then simply used for children. Even today, government and medical groups concur that many drugs—perhaps as many as two-thirds—used to treat pediatric patients have not been adequately studied in the relevant pediatric population.[9] This gap and the need for pediatric drug studies have been clearly recognized by the medical community. "Drugs used in children should be studied in accordance with sound ethical and scientific principles to define differences in efficacy, age-dependent changes in pharmacokinetics and/or pharmacodynamics, and to identify unique pediatric events, as well as verify adverse events that are similar to those experienced by adults."[10]

Over the past few years, increasing efforts have been undertaken to address the development and approval of pediatric products. These efforts have not been uniform. When they have occurred, they have approached this issue from different perspectives and methods.

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5 *See* FDA Public Health Advisory, Nonprescription Cough and Cold Medicine Use in Children, http://www.fda.gov/cder/drug/advisory/cough_cold_2008.html.

6 *See* FDA News, FDA Proposes New Warnings About Suicidal Thinking, Behavior in Young Adults Who Take Antidepressant Medication, http://www.fda.gov/bbs/topics/NEWS/2007/NEW01624.html.

7 As discussed in more detail below, these terms are used in the statutory sense as defined in the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 (1938). Specifically, these terms are defined in 21 U.S.C. § 321(g) (drug definition), 21 U.S.C. § 321(h) (device definition), and 42 U.S.C. § 262(j) ("biological definition" definition).

8 Products intended for such purposes (or intended uses) satisfy the statutory definition of a drug or device under the FDCA.

9 *See* United States Government Accountability Office, The Study And Labeling of Drugs For Pediatric Use Under The Best Pharmaceuticals For Children Act (2007), *available at* http://www.gao.gov/new.items/d07898t.pdf; Rosemary Roberts et al., *FDA Incentive Program Improves Study of Medications for Children*, 290 JAMA 905 (2003); Peter P. Budetti, *Ensuring Safe and Effective Medications for Children*, 290 JAMA 950 (2003).

10 Roberts, *supra* note 9, at 911.

This article identifies the four approaches that have been used to provide pediatric populations with access to drugs and devices: increasing the speed and number of pediatric approvals, congressional action to encourage pediatric products, off-label use, and "enhanced" off-label use. It also identifies gaps in these approaches and looks forward to new approaches to this challenge. Finally, it considers whether there is a constitutional right of access to products for pediatric uses.

II. THE CHALLENGE OF PEDIATRIC DRUGS, DEVICES, AND BIOLOGICS: WHY GETTING PRODUCTS FOR CHILDREN IS HARDER THAN FOR ADULTS

There are unique challenges to the development, testing, FDA review, and approval of pediatric medical products.

A. Economic Constraints

Whether one likes it or not, economics play a role in decisions about what products to develop and what uses to investigate. If there is no economic return, private industry—the primary source of new drugs and medical devices—cannot justify supporting limitless research and development of pediatric products.[11] Unfortunately, there can be fewer economic incentives to develop products for children.[12] Childhood diseases and conditions generally affect populations smaller than those with similar adult conditions simply because there are fewer children in the population, and smaller patient populations often cannot provide the necessary economic return on such investments. This is especially true when considering even smaller patient numbers in sub age groups (e.g., neonates or adolescents). Yet the cost to develop, test, and seek FDA approval of a new pediatric product is no less than that for adult products.

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11 The vast majority of products tested by industry for possible pediatric indications have been patented compounds. Specifically, in the 2002-2005 time frame, 173 on-patent pediatric drug studies were conducted by industry. There was only one off-patent pediatric study conducted. NIH funded 7 pediatric studies on off-patent compounds. GAO, PEDIATRIC DRUG RESEARCH: THE STUDY AND LABELING OF DRUGS FOR PEDIATRIC USE UNDER THE BEST PHARMACEUTICALS FOR CHILDREN ACT, (2007).

12 *Id.*

That is not to say that there is no market for pediatric products. Children can have specific medical needs not seen in adults, including childhood diseases, developmental issues, conditions such as lack of human growth hormone, and the need for childhood vaccines. However, because the market for these products is generally limited to children, drug-makers cannot rely on adult use to help absorb the cost or risk of development. The combination of these economic pressures reduces the probability that a product will be developed and tested for pediatric use.

B. Clinical Trial Challenges

It is more difficult to conduct clinical trials on children than adults. First, it can be harder to enroll children in clinical trials due to heightened concern about putting children at risk. Can a parent really be expected to agree to enter a child facing a life-threatening disease in a trial for a new therapy, where the child faces a fifty percent chance of receiving a placebo or an older, less effective therapy?

Furthermore, it is difficult to obtain informed consent for a child. For example, how old must a child be before providing his or her own consent? What if the parent consents, but the child objects?[13] Can a parent ethically accept compensation for providing consent where the consent puts the child at risk? Processes must be in place to ensure that the best interests of the child—and not those of the parents or investigator—are paramount.

Participant involvement and data collection can also be limited when children participate in clinical trials. For example, it can be harder to obtain important subjective information from neonates, infants, and small children. Questions that may result in reliable answers from adults, such as "How much pain do you feel?" may not be usable if posed to children. Additionally, collecting follow-up information from children can be more difficult. Staying in contact and obtaining cooperation from both the child and the parents adds additional challenges to pediatric research.

There are regulatory teeth behind these ethical challenges. Clinical research on children is subject to specific regulatory requirements designed to protect children from inappropriate

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[13] *Id.*

research.[14] Institutional review boards (IRBs) play a significant role in the adequacy of the consents and with assessing the benefit of the research, risks, and alternative approaches to the research. Depending on the circumstances, consent may be required from the child if the child is deemed capable of providing knowing consent.[15]

Regulatory precautions and additional review processes put in place to protect children, such as ethics panels and IRBs, ensure greater oversight and additional protection, but also result in slower approval and increased cost when children are involved in clinical studies.

C. Other Risks

Beyond economic, ethical, and scientific challenges, there are serious public relations risks when children are involved in clinical trials. The potential for strong public reaction to any unnecessary "experimentation" on children, or any unnecessary suffering by children, means those conducting such studies are subject to greater oversight and greater regulatory and media scrutiny.[16] In addition, liability risks can also be greater when dealing with children.

Public outrage over medical harm to children has historically had a powerful and tangible effect on FDA law. After elixir of sulfanilamide killed several hundred, including many children, in 1937, Congress passed the 1938 Food Drug and Cosmetic Act. The discovery that thalidomide caused birth defects in children led directly to the 1962 amendments to the Food Drug and Cosmetic Act. And in the 1980s, Ryan White put a different face on AIDS and prompted accelerated approval processes for AIDS drugs.

D. Special Needs of Children

It can be hard to generalize about the special needs of children in

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14 45 C.F.R. § 46 Subpart D sets forth a number of specific requirements and obligations applicable to pediatric research. Additional provisions specific to neonates are found at 45 C.F.R. § 46 Subpart B (1991).

15 45 C.F.R. § 46.408 (1991).

16 As an illustration, while notorious Nazi doctor Josef Mengele's inhumane experiments on Nazi concentration camp victims repulsed all civilized people, his experiments on children tend to cause the most revulsion and condemnation.

the clinical research context because children of different ages may have distinct needs. This has been recognized in the law with the passage of the Food and Drug Administrative Amendments Act of 2007 (FDAAA)[17] on September 27, 2007. The FDAAA divides non-adults into four distinct pediatric patient categories: neonates, infants, children, and adolescents.[18] The reason is simple. Each of these groups has different medical needs and different levels of ability to participate in therapy decisions.[19]

Additionally, concerns about the long-term safety and efficacy of clinical treatment can be especially important when children are involved. Unfortunately, such effects may also take more time to fully understand. For example, an orthopedic product implanted in a child has to account for several decades of growth and development. The impact of drugs on development of biologic systems (including sexual development) also has to be considered when used on children.

In summary, developing medical products for children involves multiple risks and difficulties that are distinct from similar efforts with adults.[20] Despite these difficulties, a key point must be emphasized—there is a need for more pediatric products. The question is then how best to provide pediatric patients with access to safe and effective medical products.

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17 FOOD AND DRUG ADMIN. AMENDMENTS ACT OF 2007, Pub. L. 110-85, Title I, § 102, 121 Stat. 825.

18 *Id*. at § 303.

19 This difference is also reflected in differing needs to obtain consent from the child based on the child's ability to participate in a meaningful way in the decision. *See* 45 C.F.R. § 46.408.

20 *See*, *e.g.*, GAO, PEDIATRIC DRUG RESEARCH, SUBSTANTIAL INCREASE IN STUDIES OF DRUGS FOR CHILDREN, BUT SOME CHALLENGES REMAIN (2007), *available at* http://www.gao.gov/new.items/d01705t.pdf ("Drug companies indicated that they had little incentive to perform pediatric studies on drugs they intended to market primarily to adults and that these drugs would provide little additional revenue from use in children. Companies also said they were concerned about liability and malpractice issues and the difficulty of attracting enough pediatric patients for studies because of the small number of children with a particular disease.").

III. ROLE OF THE FDA IN CONTROLLING ACCESS TO PEDIATRIC DRUGS AND DEVICES

The FDA plays a critical role in providing access to medical products for pediatric uses. Generally speaking, the FDA regulates the testing, manufacturing, labeling, marketing, and selling of medical products. While this article is not intended to provide a detailed analysis of FDA processes, some basic familiarity is necessary. (Readers already familiar with FDA processes and the Food Drug and Cosmetic Act[21] are welcome to skip this section.)

For our purposes, the FDA regulates three key types of products: drugs, devices, and biologics.[22] Drugs are articles "intended" to diagnose, treat, cure, prevent, or mitigate disease, or to affect the function and structure of the body. Drugs act chemically or metabolically.[23] Medical devices are also "intended" to diagnose, treat, cure, mitigate, or prevent disease, or to affect the structure or function of the body, but they do not act chemically or metabolically.[24] Rather, they act mechanically or physically. Biologics are defined by the source of the product.[25] Examples of biologics are blood products, vaccines, serums, and antitoxins.[26]

A. Drugs

"New drugs"[27] must be shown to be safe and effective when used for the intended purpose.[28] It is critical to understand that the drug itself is not approved. Rather, the specific use or "indication" of

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21 *See generally* 21 U.S.C. § 301.

22 The FDA also regulates food, food additives, color additives, dietary supplements and certain other products not relevant to our discussion. *Id*. at § 343.

23 *Id*. at § 321(g)(i) (2007).

24 *Id*. at § 321(h).

25 42 U.S.C. § 262(i).

26 *Id*. Note that the Public Health Service Act is the statutory source for biologics regulation. The FDA, however, is responsible for the oversight and control of biologic products and the FDCA supplies most specific statutory requirements; *See also id*. at § 262(j).

27 21 U.S.C. § 321(p). "New drugs" are basically post-1938 drugs.

28 "Old drugs" are essentially pre-1938 drugs which are generally considered safe and effective (or GRASE) for the intended use. A drug can be an "old drug" for one use and a "new drug" for a different indication.

the drug is approved.[29] A drug might be approved for one purpose but not for another.[30] In fact, a drug might be highly beneficial for one purpose but deadly for another. The infamous drug thalidomide causes horrific birth defects.[31] However, it is highly beneficial in treating leprosy.[32] Both safety and efficacy are established on an indication-by-indication basis. In order to establish safety and efficacy, the drug must successfully complete various human clinical studies. There are generally three phases to drug clinical trials, all under FDA supervision.[33] These studies are conducted under an FDA-approved Investigational New Drug (IND) application and must include informed consent, periodic reports to the FDA, and adverse event reporting.[34] Products often fail one phase and then do not advance to the next phase.[35]

Specific (and successful) pediatric testing is required before such a drug can be indicated for the pediatric population. Even today, if a pediatric population is not included in the clinical studies, the

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29 *See* 21 U.S.C § 355 (e)–(f).

30 *Id*.

31 *See* Celgene Corporation, Proposed changes to approved thalomid package insert 11, *available at* http://www.fda.gov/cder/foi/label/2006/021430s000,020785s031lbl.pdf and FDA Talk Paper, FDA, FDA Issues Approval Letter to Celgene for Thalomid, (Sept. 22, 1997) *available at* http://www.fda.gov/bbs/topics/ANSWERS/ANS00820.html.

32 *See* FDA Talk Paper, FDA Issues Approval Letter to Celgene for Thalomid, *supra* note 33.

33 For a more detailed overview of this process, *see* The Pharmaceutical Research and Manufacturers of America (PhRMA), *Research and Development–Drug Discovery*, http://www.phrma.org/index.php?option=com_content&task=view&id=382&Itemid=118. For more detailed statutory and regulatory provisions, *see* 21 U.S.C. § 355(i) and 21 C.F.R. § 312.30.

34 *See* 21 C.F.R. §§ 312.34(c) and 312.30(b)(iii).

35 Phase I studies are conducted using a relatively small number of healthy volunteers. Phase I studies assess basic safety, including pharmacology and toxicity questions. If the drug passes Phase I testing, it moves to Phase II studies. These studies often involve several hundred patients and provide the first human data on the use of this drug for the disease or condition in question. Phase II studies gather additional safety data and start the development of efficacy data. Phase III studies are large, often multi-center studies that can easily involve many thousands of subjects with the disease or condition at issue. Assuming successful completion of these studies, all of this data, as well as reams of other information, is then submitted to the FDA as part of a New Drug Application (NDA) seeking FDA approval of the drug for the specific purpose. For more details on the NDA process and submission requirements, see 21 U.S.C. § 355(b) and 21 C.F.R. § 314.

approval generally will be for the adult indication only.[36] For example, a relatively new cancer drug, Velcade, is approved for certain types of adult cancers.[37] However, it is not approved (or "indicated") for pediatric use even in the same cancer type.[38]

Drug labeling includes the indications for use of the drug, as well as contraindications, risks, warnings, pharmacology, and dosage.[39] The manufacturer is permitted to "promote" or market and advertise the product only for approved indications or uses.[40] Thus, if the drug is not indicated for a pediatric use, the manufacturer cannot promote or market that drug for such a pediatric purpose.

B. Biologics

Biologics are tested in the same manner as drugs (under the IND process).[41] The actual approval of the biologic is through a Biologics License Application (or BLA).[42] Otherwise, for our purposes, the processes, restrictions, and issues are the same between biologics and drugs.

C. Devices

Devices have a somewhat more complex statutory structure. While there are no subcategories of "new drugs," new devices are divided into three classes.[43] Very generally speaking, Class I devices (such as tongue depressors and elastic bandages) are low risk devices and do not require clinical studies or prior FDA marketing approval.[44] The company is, however, limited to the labeled

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36 Note that, as discussed in more detail below, recent statutory changes have increased the ability to extrapolate from one population to another.

37 *See* FDA, US PACKAGE INSERT (2003), *available at* http://www.fda.gov/cder/foi/label/2003/021602lbl.pdf.

38 *Id.* at 2.

39 For the definition of "labeling," see 21 U.S.C. § 321(m).

40 42 U.S.C. § 262(a).

41 *Id*. Compare 21 C.F.R. § 312 Subpart B.

42 *Id*.

43 21 C.F.R. § 860.84 (2008).

44 *Id*. at § 860.

indications for promotional purposes[45] (changing the indicated use could change the risk profile of the device and, thus, change its classification).[46]

Class II devices are medium risk devices.[47] While again only an approximation, Class II devices generally receive premarket clearance from the FDA if they are deemed to be "substantially equivalent" to a "predicate" device.[48] This process does not explicitly include a safety and efficacy review, although the agency will address any identified safety issues.

Class III devices such as heart valves, pacemakers, and artificial joints must be approved by the FDA as being safe and effective for the indicated purpose prior to marketing.[49] The review and approval process is roughly analogous to the new drug process. Class III devices usually must go through clinical trials under an Investigational Device Exemption (IDE) process.[50] Other aspects of the regulatory structure for clinical trials such as informed consent and reporting of adverse events are, for our purposes, similar to the drug world. As with drugs, the manufacturer can promote or market the device only for the approved or indicated purposes.

D. Application to Pediatric Products

So why is this regulatory process relevant to the issue of access to pediatric products? In one sense, the current FDA regulatory processes act to limit, to at least some extent, access to FDA-approved pediatric products. The regulatory process limits the labeling, promotion, and marketing of products for pediatric uses to situations in which the product has been approved for pediatric purposes. Even if the product has been approved for one pediatric age group (e.g., adolescents), additional testing and FDA review and approval may

45 *See* 21 U.S.C. § 360c(b)(7).

46 *Id.* § 360c(e).

47 *Id.* § 360c(a)(1)(b).

48 Medtronic v. Lohr, 518 U.S. 470 (1996). *See also* 21 U.S.C. § 360(k) and 21 C.F.R. § 809. Technically, a 510(k) is "cleared," while a PMA is "approved." For our purposes, there is no relevant difference.

49 21 U.S.C. § 360e.

50 21 C.F.R. § 812. The device world does not have the same formal three-phase clinical trial structure found in the drug world.

well be required for an indication for a different, younger population such as infants.[51] These requirements obviously increase the time and expense needed to obtain a pediatric indication and limit the manufacturers' ability to market and promote the product for pediatric uses.

Though manufacturers' ability to label, promote, and market are limited, it is perfectly legal and actually quite common for a health care professional to use a product approved only for adults on a pediatric patient. This is generally referred to as "off-label use."[52] The Supreme Court has explicitly recognized the important role played by off-label use of drugs and devices. In *Buckman v. Plaintiffs Steering Comm.*, the Supreme Court stated that the off-label use of FDA-regulated products, a medical device in this case, is "an accepted and necessary corollary" to the FDA's regulatory scheme.[53] Congress has also supported such uses.[54]

One core reason for this apparent contradiction between restricting off-label promotion of products and permitting off-label use is that neither the FDA nor Congress regulates the practice of medicine.[55] As such, if the drug or device is available for any one purpose, a physician can use it for any other purpose.[56] While doctors may be subject to state malpractice laws in cases of abuse, the FDA will not get involved in these patient-specific medical decisions.

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51 As an illustration, remember the differences in risks and benefits to pediatric age groups posed by certain OTC cold remedies.

52 For the Supreme Court's definition of "off-label use," *see* Buckman v. Plaintiff's Steering Comm., 531 U.S. 341, 350 (2001).

53 *Id*.

54 In the legislative debates over the FDA Modernization Act of 1997 ("FDAMA") in 1997, several members of Congress explicitly recognized the role of off-label uses and the need for information about such off-label uses. *See, e.g.,* 143 Cong. Rec. S8205-02 (daily ed. July 28, 1997) and 143 Cong Rec. S9712 (1997) (Statement of Senator Mack). In Washington Legal Foundation v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998), even the FDA acknowledged the important role of off-label uses of drugs, biologics and devices. For various statements of FDA officials, see *id*. at 55-56. For further examples of government statements in favor of off-label use, *see* Ralph F. Hall & Elizabeth S. Sobotka, *Inconsistent Government Policies: Why FDA Off-label Regulation Cannot Survive First Amendment Review under Greater New Orleans*, 62 Food Drug L.J. 1 (2007).

55 *See* 21 U.S.C. § 396.

56 For further judicial support, *see* Buckman v. Plaintiffs Steering Comm., 531 U.S. 341 (2001) and Washington Legal Foundation, 13 F. Supp. 2d at 55-56.

In summary, the FDA regulatory system generally requires pediatric-specific testing, approval, and label of products for pediatric uses. Outside of a regulated clinical trial, the typical physician or patient cannot get access to a product for which there is no approved use. If, however, the product is physically available in the marketplace (because, for example, it is already approved for some non-pediatric use), the FDA structure does not prevent the off-label use of the product for an unapproved pediatric use.[57]

One obvious disadvantage is that bypassing the FDA testing and approval process limits the information available about the safe and effective use of the product for such a pediatric purpose. Absent labeling for pediatric purposes, physicians must act without important clinical, pharmacological, toxicological, and dosage information. Overall, off-label use that bypasses the FDA testing and approval process decreases the storehouse of medical and clinical knowledge that can weed out unsafe or inefficacious products.

The issues for pediatric medical products are thus:

1) should there be pediatric access to products for which there is no approval for any purpose?;

2) should we encourage FDA-regulated testing and approval of pediatric products?;

3) if so, how should that be done so that safety and efficacy are not compromised?; and

4) does the off-label use of products advance the medical needs of pediatric populations?

All these lead to the core question: Do we have an appropriate system in place for providing safe and efficacious pediatric therapies?

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57 There can be special rules for very specific products such as narcotics and human growth hormone. These few exceptions are not relevant to this issue of pediatric access, and so our discussion deals with the typical drug or device.

IV. APPROACHES TO PEDIATRIC PRODUCTS AND MEDICAL NEEDS OF CHILDREN

A. Increase the Speed and Number of Pediatric Approvals

There are several options for increasing the speed and number of FDA approvals for specific pediatric indications (keeping in mind the need to have appropriate safety and efficacy protections).

First, one could encourage or require the FDA to conduct faster reviews of pediatric applications. The faster applications get processed, the sooner the sponsor will start to recoup the substantial investment required to conduct the clinical trials and prepare the application. Faster approvals should encourage investment, formation of new companies, and venture financing.

Second, one could simply require the sponsor of a drug or device to conduct pediatric testing (unless the FDA concurred that there were legitimate safety or efficacy reasons not to do so). Such a requirement would ensure pediatric consideration, but would add another cost (in both time and money) to the already expensive drug approval process.

Third, one could require the sponsor to describe in the New Drug Application (NDA) or PMA potential pediatric uses, how such uses could be tested, and why the sponsor is not conducting such tests. This pediatric assessment could be made public. This approach combines forced consideration of pediatric uses with the "bully pulpit" offered by the FDA and public opinion. It is less prescriptive than requiring pediatric testing and relies more on the power of knowledge and public opinion.

A fourth approach is to make the clinical testing and application process less burdensome. This approach postulates that equivalent (or at least adequate) safety and efficacy protections can be included in the system while reducing the time, expense, and burden of the clinical trial and application process. One could use surrogate endpoints in clinical trials. Surrogate endpoints use biomarkers or other measurements that can be obtained faster and cheaper than waiting for more traditional clinical trial endpoints such as death, cure, or morbidity. For example, if one is testing a new compound for cancer, one could use death or five-year survival rates as the endpoint (or measurement for trial success or failure). Obviously,

these endpoints require substantial passage of time and the study of large patient populations before one can declare success or failure. However, if one can use a surrogate endpoint—perhaps a sustained decline in a tumor marker—as the measuring stick for study success or failure, one can get results substantially faster. This allows faster adoption of beneficial therapies and faster elimination of unsafe or ineffective products. Provided that medically correct surrogate endpoints are selected, the advantages are obvious.

A fifth approach for limiting the burden of clinical studies for pediatric products is to permit greater extrapolation or use of data from different populations. Such data can be used either in lieu of pediatric studies, as an adjunct in order to decrease the size and time of the study, or to narrow the scope of the study. Here, studies on adults could possibly be used to speed testing and approval for a pediatric population. Likewise, rather than conduct identical, large trials on different age groups, one could use data from one age group to support (or reject) the use of that product in a different age group.

Sixth, one could permit expanded access to unapproved therapies through "treatment" clinical studies, humanitarian use exceptions, or other mechanisms to permit access to products before all testing and review has been completed. If coupled with payment for such uses,[58] there are then both additional medical and economic incentives for developing pediatric products. Again, one must understand the potential trade off between access and risk.

Finally, one can encourage pediatric testing and submissions using basic economic tools. Potential economic incentives could take many forms. If a sponsor can get a higher price for a pediatric product, the incentive for seeking approval increases. The government could pay a premium for pediatric products that have been approved by the FDA in administering public health care programs. Under such a system, an off-label use would either not be reimbursed or would be reimbursed at a lower rate than if the product had an FDA-approved indication for the pediatric use. While

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58 Note that generally there is no payment or reimbursement to the sponsor for drugs used in FDA-regulated clinical trials. *See* 21 C.F.R. § 312. Certain medical devices—so called Category B devices—can be reimbursed when used in clinical trials. Other Category A devices are not reimbursed. The lack of reimbursement obviously increases the cost of the clinical trial. In most drug trials, the subjects are also compensated for participation in the study, which also increases costs.

private insurance programs might or might not follow such an approach, a government decision to adopt this could have a significant impact given the major role played by government payment programs.

Another economic incentive is to use the patent system or the FDA approval system to provide expanded market exclusivity to the company initially obtaining the pediatric indication. This additional market exclusivity could be provided via extending the patent life for the product (at least for pediatric indication) or by prohibiting FDA approval of a competing product for some defined time. Either way, the expanded market exclusivity permits the pioneer company more time to recover costs and obtain a reasonable economic return.

B. Congressional Action to Encourage Pediatric Products

The ideas outlined above are not just theoretical. Congress and the FDA have actually used several of these tools in an effort to increase the number of FDA-approved pediatric products. While some of these efforts go back a number of years,[59] Congress adopted the most comprehensive set of provisions in 2007 when it passed the FDA Administrative Amendments Act of 2007 (commonly referred to as "FDAAA").[60] This legislation directly addressed increasing the testing, review, and approval of products for pediatric use in three key provisions.[61]

1. Pediatric Drugs and the Best Pharmaceuticals for Children Act

FDAAA[62] reauthorized the Best Pharmaceuticals for Children

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59 For example, in 1994 the FDA implemented a certain specific pediatric labeling rule that required sponsors to review possible pediatric uses in NDA submissions. *See* Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in Labeling, 59 Fed. Reg. 64,240 (Dec. 13, 1994) (to be codified at 21 C.F.R. pt. 201). Later efforts included provisions regarding additional pediatric studies. *See*, for example, Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,636 (Dec. 2, 1998) (to be codified at 21 C.F.R. pts. 201, 312, 314, and 601). The subsequent passage of provisions such as BPCA and PREA has added Congressional impetus to these efforts and has added additional incentives and requirements.

60 *See* FDAAA, *supra* note 17.

61 *See id.* at Title III, IV, V.

62 *See id.* at Title V.

Act (BPCA), which had been initially enacted in 2002.[63] BPCA combines several approaches to increase the number of drugs approved. First, BPCA creates financial incentives for pediatric indications for drugs.[64] This is done by providing an additional period of market exclusivity for the first company that conducts the clinical studies and obtains FDA approval for the pediatric indication.[65] Generally, BPCA permits an extra six months of market exclusivity.[66] Although this may not seem like much time, six months can provide substantial economic benefit in the world of pharmaceuticals. Suppose, for example, that the product has U.S. sales of three hundred million dollars a year (not an extraordinary number given that a blockbuster drug will have sales in excess of a billion dollars a year). Six months will result in an extra $150 million in gross revenue to the pioneer. That certainly helps defray the additional time and expense incurred in seeking pediatric approval.

Market exclusivity is available both for new drugs and for drugs that have previously been approved for some other, non-pediatric indication.[67] It is also important to note that this six-month market exclusivity is in addition to other patent term extensions or market exclusivity provisions.[68] Longer periods of market exclusivity also give the pioneer the opportunity to further build brand loyalty and reduce the economic incentives for another company to enter the market. Congress' goal here is simple: to encourage pediatric studies by providing an economic reward through market exclusivity.[69]

BPCA also includes fairly elaborate procedures by which the FDA formally requests that a company conduct specific pediatric studies.[70] Generally, after the FDA makes a formal written request to

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63 Note that certain provisions contained in BPCA of 2002 go back to earlier days. For example, the pediatric exclusivity provisions first appeared in FDAMA in 1997. *See* 21 U.S.C. § 355a. Implementing regulations for earlier pediatric provisions can be found at 63 Fed. Reg. 66,632, supra note 62.

64 21 U.S.C. § 355a(b), (c).

65 *Id*.

66 *Id*.

67 21 U.S.C. § 355a(b), (c).

68 *See, e.g.*, 21 U.S.C. § 355a(b)(1).

69 *See* 21 U.S.C. § 355a.

70 21 U.S.C. § 355a(d).

the sponsor to conduct specific pediatric studies, the company has 180 days to agree or disagree with the request.[71] If the sponsor agrees to conduct the study, the sponsor must follow the designated protocol and comply with applicable regulatory requirements,[72] submit all adverse events, and submit a final report to the FDA.[73] The FDA then reviews and publishes the results.[74] The data is also reviewed by the Office of Pediatric Therapeutics,[75] an internal FDA committee created to oversee these pediatric studies. Proving once again Congress' recognition of the role of off-label use in pediatric health care, the Office of Pediatric Therapeutics is also mandated to make available to the public data on both on-label and off-label uses.[76]

The FDA is also required to treat any application submitted as a result of a pediatric study conducted pursuant to the BPCA as a "priority application."[77] By mandating faster reviews, Congress not only gets approved products to pediatric patients faster, but also provides an economic incentive to the sponsor, because faster reviews can translate into faster revenue streams. Speed is, of course, relative. The manufacturer has 180 days to respond to the request to conduct a pediatric study, and the FDA has 180 days to review the NDA seeking a pediatric indication. These and other timelines contribute to the extended time limit needed to obtain a pediatric indication and frustrate those concerned with the lack of approved pediatric therapies. The FDA also has the authority under the BPCA to require certain labeling changes to address information (both

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71 21 U.S.C. § 355a.

72 21 U.S.C. § 355(i).

73 Detailed analysis of the BPCA and actual numbers of requests, studies, etc. can be found in, among other places, several recent GAO reports. *See* GAO, *Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act,* GAO-07-557 (Washington D.C. March 22, 2007 *(available at* http://www.gao.gov/new.items/d07557.pdf) and GAO, *Pediatric Drug Research: The Study and labeling of Drugs for Pediatric Use Under the Best Pharmaceuticals for Children Act,* GAO-07-898T (Washington D.C. May 22, 2007) (available at http://www.gao.gov /new.items/d07898t.pdf).

74 *See* 21 U.S.C. § 355a(e) for the dissemination provisions, and 21 U.S.C. § 355a(f) for the internal FDA review processes.

75 *See* Office of Pediatric Therapeutics, http://www.fda.gov/oc/opt/default.htm.

76 21 U.S.C. § 355a(f)(6) and (k).

77 21 U.S.C. § 355a(i) and (o).

positive and negative) learned through studies conducted under the BPCA or to take enforcement action if the sponsor does not make the mandated changes to the product labeling.[78]

Of course the sponsor can refuse to conduct the requested pediatric studies. In those cases, the FDA has the option to refer the request to the National Institutes of Health (NIH). The NIH can then decide whether to fund or conduct the proposed study.[79]

Finally, because of its interest in pediatric products, Congress is monitoring these programs to ensure that they are effective. In addition to this routine oversight, Congress has mandated a future study by the Institute of Medicine assessing the effectiveness of these incentives and programs.[80] If Congress determines that its goals are not being met, one can anticipate that it will act again.

2. Pediatric Research Equity Act

When enacting FDAAA, Congress did not stop with the BPCA reauthorization. Congress also included the Pediatric Research Equity Act of 2007[81] (PREA) as part of FDAAA. PREA requires the sponsor of a new drug or biologic to include in the NDA an assessment of "the safety and effectiveness of the drug in all relevant pediatric subpopulations."[82] The hope is that forcing such an assessment will increase sponsors' awareness of pediatric uses and opportunities and consequently make it more likely that the sponsors will seek approval for a pediatric indication. This assessment also gives the FDA information upon which it can request a pediatric study under the BPCA or refer the drug to the NIH for government sponsored studies. The sponsor can seek a waiver of the obligation to submit a pediatric assessment for a number of reasons involving a lack of safety or efficacy (or impracticality) for a pediatric

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78 21 U.S.C. §355a(j) and (i)(2)(C) and (D).

79 There are also some fairly elaborate provisions by which the NIH can propose certain pediatric studies and have labeling changes considered by the FDA. *See* 42 U.S.C. § 284m. To date, these provisions have not been used to any meaningful extent. That can, of course, change with more experience and additional funding.

80 21 U.S.C. § 355a(p). *See also* 42 U.S.C. § 284m for some additional review activities.

81 FDAAA at Title IV. FDAAA reauthorized the original 2002 enactment of PREA.

82 21 U.S.C. § 355c(a)(2)(A)(i).

population.[83] Information regarding such a waiver must be included in the product labeling, presumably so that physicians will know of those issues before using the drug for an off-label pediatric purpose.[84]

PREA also explicitly permits the sponsor and the FDA to extrapolate data from different subpopulations.[85] Such extrapolations can reduce or even eliminate the need for age specific clinical testing. For example, if the clinical trial data shows that the drug or biologic is safe and effective for young children, it may also be safe and effective for teenagers. If such extrapolation was not permitted, the sponsor would have to commit time and resources to a clinical study on teenagers. That additional time and cost could well dissuade a sponsor from seeking such an indication.

Like BPCA, PREA also addresses the extensive off-label use of drugs in pediatric populations.[86] The FDA can require not only the assessment mandated for newly submitted NDAs, but also such an assessment for drugs that have already been approved and for which there is not a pending NDA.[87] The FDA can do so if the product is used in a substantial[88] number of pediatric patients and the safe and efficacious use of the drug would be increased with better labeling or information, or if the drug presents a possible significant improvement in therapies for pediatric patients.[89]

Along the same lines, PREA also requires the FDA to make publicly available the "medical, statistical and clinical pharmacology" information contained in the pediatric assessments.[90] Again, this provides additional information to health care professionals who are considering using a drug for an off-label purpose.

As with the BPCA, in order to assess the effectiveness of these provisions in encouraging pediatric studies and indications,

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83 21 U.S.C. § 355c(a)(4).

84 *Id*.

85 21 U.S.C. § 355c(a)(2)(b).

86 21 U.S.C. § 355c(b)(1).

87 *Id*.

88 "Substantial" is not defined in the statute. *See* 21 U.S.C. § 355c(b)(1).

89 21 U.S.C. § 355c(b).

90 21 U.S.C. § 355c(h).

Congress in PREA has mandated enhanced adverse event reporting and additional studies.[91] To ensure adequate FDA focus on these issues, Congress also mandated the creation of a specific internal FDA committee (currently the Office of Pediatric Therapeutics) that is responsible for the implementation of these programs. Congress even mandated certain membership for this committee.[92]

3. Pediatric Medical Device Safety and Improvement Act

Congress did not forget pediatric needs for medical devices. As part of FDAAA, Congress passed the Pediatric Medical Device Safety and Improvement Act of 2007 (PMDS).[93] In some ways, Congress used similar incentives and approaches to encourage pediatric indications for devices as it did for drugs.

For example, like BPCA, PMDS requires a company submitting a Premarket Approval Application (PMA) or Humanitarian Device Exemption (HDE) to include in the application a description of pediatric uses of the device in question.[94] And again, if the pediatric safety and efficacy issues are similar to those seen in adult populations, a company can avoid additional clinical testing. This also includes the right, when clinically appropriate, to extrapolate between pediatric subpopulations.[95]

The device regulations also include specific pediatric use provisions, which permit the limited use of devices for unapproved purposes for patient populations of less than four thousand individuals.[96] In fact, the relevant statute now includes a specific definition of what constitutes a pediatric patient and has definitions of pediatric subpopulations.[97]

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91 *See, e.g.*, 21 U.S.C. § 355c(i) and (l); *see also* FDAAA § 404.

92 21 U.S.C. § 355d. This is one example of the level of management and oversight used by Congress. Mandating specific internal committees and committee membership may strike some as micromanaging. Congress obviously thought that it was necessary to go to this level of detail in order to ensure adequate implementation of these programs.

93 FDAAA at Title III.

94 FDCA § 515A(a).

95 FDCA § 515A(b).

96 The Humanitarian Device Exemption provisions can be found in 21 U.S.C. § 360j(m) and 21 C.F.R. § 814(H).

97 21 U.S.C. § 360j(m)(6)(E) defines a pediatric patient as someone twenty-one years old or

The Humanitarian Device Exemption (HDE) is intended to provide device-based therapies for small populations in which it is not economically feasible to conduct traditional IDE regulated clinical trials, and then obtain FDA approval of that indication through a PMA submission.[98] Such uses, however, must meet all ethical standards and must be consistent with public health needs. In PMDS, Congress expanded the scope of the HDE provisions such that more devices can be used in pediatric populations. The FDA also set a maximum number of devices that can be used under the HDE provisions to maintain some control over usage.[99] In doing so, Congress has authorized some expanded pediatric uses but has maintained at least some control of this off-label use. In addition to the distribution limitations under the HDE provisions, Congress has also mandated enhanced assessment of adverse events relating to pediatric medical devices.[100] These events are reviewed by the same group that reviews pediatric drug adverse events.

Congress also amended the Public Health Service Act and obligated the FDA, the NIH, and the head of the Agency for Healthcare Research and Quality to submit a plan to Congress for expanding pediatric medical device research.[101] This report is to address federal research issues, the FDA review processes, and gaps in such processes. Congress also mandated that the government provide grants to nonprofit organizations for studying ways to encourage and facilitate pediatric medical device research, testing, and approval.[102]

To assess the effectiveness of these programs in increasing pediatric indications for medical devices, Congress has mandated periodic reports comparing the number of pediatric devices approved with prior years and reports on pediatric subpopulation

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younger at the time of diagnosis or treatment. The statute also sets forth four pediatric subpopulations – neonates, infants, children and adolescents. While of interest, including the fact that someone twenty-one is a pediatric patient, these classifications are not relevant to this discussion.

98 21 U.S.C. § 360j(m)(1).

99 21 U.S.C. § 360j(m)(6)(A)(ii).

100 21 U.S.C. § 360j(m)(7).

101 42 U.S.C. § 282(b)(23); FDAAA § 304(b).

102 *Id*. at § 305.

needs.[103] The HDE exemptions are also subject to annual review and reporting.[104] Interestingly, these reports and assessments include not only medical and clinical issues and approval rates, but also health economic issues, such as insurance coverage, device costs, profit and the impact of permitting profit and usage rates of adults and children.

However, it should be noted that not all of the incentives utilized to promote pediatric drug access have been applied to pediatric devices. A key incentive used in the drug world—granting additional market exclusivity—has not yet been applied to the medical device world.

4. Summary

As can be seen, Congress and the FDA have implemented a number of laws to encourage the development of pediatric indications for medical products. These systems include economic incentives, regulatory obligations, mandated consideration of pediatric uses, and public information disclosures. Historically, such approaches have had a positive impact on the number of pediatric approvals.[105] Other factors such as improved research tools and a desire to address new markets and populations may have also played a part in this increase. Though available data does not permit a definitive answer as to the influence of each approach, most experts have concluded that these changes have had a positive impact on approval numbers. Thus, the Congressional purpose has been advanced.

It is also of interest to note that there are certain ways to encourage pediatric studies, submissions, and approvals that have not been used. As noted above, market exclusivity is used in the drug world but not in the device world to encourage such studies. Extrapolation rules also vary.[106]

Some approaches have been uniformly rejected. No one has

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103 FDCA § 515A(a)(3).

104 21 U.S.C. § 360j(m)(8); FDCA § 515A(b).

105 Rosemary Roberts et al., *Pediatric Drug Labeling: Improving the Safety and Efficiency of Pediatric Therapies*, 290 JAMA 905 (2003).

106 Compare 21 U.S.C. § 355c(a)(2)(B) with FDAAA § 302(b).

expressly suggested a reduced safety or efficacy requirement. No one has suggested automatically including a pediatric indication with every approved adult indication. No one has suggested eliminating approval requirements. Rather, Congress, the FDA, and other stakeholders have been seeking that elusive balance between two inconsistent objectives: safety—which requires time, resources and analysis—and speed.

C. Off-Label Use

It is clear, and Congress has acknowledged, that not every pediatric need can be met by an FDA-approved product. If health care providers are limited to only FDA-approved therapies, then significant pediatric medical needs will go unmet. One long-standing answer to this problem is the use of products for unapproved (or "off–label") uses. Once the product is approved for any purpose—perhaps for the adult iteration of a disease or condition that also affects pediatric patients—the physician may use the product for an off-label pediatric purpose.[107]

In many cases the physician simply adjusts the adult dose in proportion to the smaller size of the pediatric patient.[108] In doing so, the physician is making both the decision to use the product and in what amount without the benefit of the information contained in the FDA-supervised clinical trials or in the FDA-approved labeling for the indicated or approved uses.[109] Without such studies, the physician has to assume that the contraindications, warnings, adverse events, and risks included in the FDA-approved labeling for

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107 As noted above, this off-label use is common and perfectly legal. *See Buckman*, 351 U.S. at 350; *see also* David C. Radley et al., *Off-label Prescribing Among Office Based Physicians*, 166 ARCH. INTERN. MED. 1021 (2006). There are some special rules for a limited number of products such as human growth hormone. For our purposes, these exceptions are not relevant.

108 Determining proper dosages is both a safety and an efficacy issue. Too much of a drug is often toxic. Too little of a drug is inefficacious. The physician is seeking the middle ground of enough to work but not enough to harm. In some cases there may be age specific dosing studies for this off-label use that might address upper or lower limits. The physician is free to use this data, if he or she is aware of it, in making dosing decisions. These studies are generally not FDA reviewed.

109 Remember that the drug clinical trials specifically study dosing ranges and the product labeling including specific dosing recommendations based on these studies and related information. 21 C.F.R. §§ 312, 812 (2008).

adults are similar or proportional for pediatric patients. (It is not possible for manufacturers to offer guidance to physicians in their labeling: inclusion of usage, contraindications, warnings, and dosage information for an unapproved use in the product labeling or promotional material would be illegal promotion of an unapproved use. As such, the product would be considered misbranded).[110]

If two important facts are assumed to be true, this approach is logical. The first assumption is that any dosage adjustment to account for the smaller size of the pediatric patient is accurate enough to assure both a safe and effective dose. The validity of this assumption is undoubtedly variable depending on the disease, drug, and other available information. It is clear that this is already being done thousands of times each day. While not optimal, the medical community (and the Supreme Court in *Buckman*) has accepted this practice.

The second, and perhaps more critical assumption, is that adults and children experience similar biological effects.[111] This second assumption is, however, clearly not always true. As noted above, OTC cold remedies, which are safe and effective for adults and older children,[112] are unsafe for infants under age two. The potentially deadly effects of chloramphenicol in children are another example. Because these two critical assumptions are not always correct, FDA-supervised clinical testing and approval may seem best for overall public health protection.

However, before placing too much criticism on the medical community for using off-label products for pediatric patients, several points must be considered. First, in many cases such off-label use is the established standard of care.[113] In the vast majority of cases, the

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110 21 U.S.C. § 352 (2008) sets forth detailed misbranding provisions.

111 The dosage issue assumes generally the same biologic activity or effects. This issue revolves around the different biologic effects the same drug might have on two different age group populations.

112 *See* Public Health Advisory: Nonprescription Cough and Cold Medicine Use in Children, U.S. Food and Drug Administration, http://www.fda.gov/cder/drug/advisory/cough_cold_2008.htm.

113 Studies have indicated that slightly more than twenty percent of all prescriptions are for off-label purpose. If one is given a prescription for a cardiac medication at the physician's office, there is almost a fifty percent chance that it is off-label. Cancer patients, particularly those with advanced cancer, have a sixty to eighty percent chance of receiving an off-label

off-label use can be justified because it works and is the best medical option. Second, the FDA and the manufacturer are by no means the only source of information about the safe and effective use of off-label therapies. There are literally hundreds of medical journals and thousands of Continuing Medical Education (CME) events that can provide the practicing physician with current and accurate scientific and clinical information about off-label uses. Government websites such as the NCI website and www.clinicaltrials.gov also include information on off-label clinical studies. Notably, in some cases Congress has actually mandated that federal health care programs cover certain off-label uses.[114] Likewise, physicians can utilize their own experience and medical education or that of fellow practitioners for information on the safe and effective use of off-label products. In almost all cases, the off-label use of a product is the result of careful medical thought.

Importantly, there may well be no approved or "on-label" alternatives. What is the physician to do when faced with a sick pediatric patient's medical condition for which there is no FDA-approved pediatric therapy? Should the physician completely ignore approved therapies for the same condition in an adult and medical literature supporting off-label use in this situation? These are real patients with real medical needs. Particularly in terminal cases, the risks of off-label use seem more than offset by the potential benefits. Sometimes there is simply no option other than off-label use.

From medical, legal, and policy perspectives, off-label prescribing is well accepted. The AMA has publicly advocated not putting limitations or restrictions on off-label prescribing.[115] The

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therapy as part of the overall treatment plan. *Off-label Drugs, Reimbursement Policies Constrain Physicians in their Choice of Cancer Therapies*, GAO/PEMD-91-14 at 5 (Sept. 1991), *Off-label Use Associated with Prescribing of the Most Frequently Used Drug Products in the United States*, cited at Washington Legal Foundation, 13 F. Supp. 2d. at 56.

114 42 U.S.C. § 1395x(t)(2)(B)(ii); *see also* NCD 110.17: Anti-Cancer Chemotherapy for Colorectal Cancer (Jan. 28, 2005) for an example of coverage of specified off-label uses via government coverage decisions (*available at* http://www.cms.hhs.gov/mcd/m_ncd.asp?id=110.17 &ver=1).

115 *See American Medical Association House of Delegates*, at http://www.ama-assn.org/ama1/pub/upload/mm/469/i07918.doc, resolving the:

> American Medical Association advance and foster regulatory and legislative initiatives to permit and protect the off-label use and reimbursement of US Food and Drug Administration-approved drugs and medical devices off-label whose

Supreme Court in *Buckman* has recognized the important role of off-label uses.[116] Congress has likewise recognized off-label uses, as has the FDA. For example, in 2007 Congress mandated the posting of information about off-label clinical trials and uses in FDAAA.[117]

Given that it is essentially impossible for all pediatric uses to go through the FDA clinical trial and approval process, off-label use will continue to be a significant path for getting therapies to pediatric populations. Policy-makers cannot simply ignore the significant medical value of off-label products.

D. "Enhanced" Off-Label Use Offers Benefits

Given that off-label use will continue to be an important aspect of pediatric therapies, are there ways to make it safer? In an attempt to do so, Congress has encouraged increased information flow to the treating physician. In theory, this "enhanced" off-label process will allow the physician to make better medical decisions.

One key way to do this is to make detailed information about ongoing clinical trials—such as the nature of the trial, therapy being researched, enrollment status, and contact information—publicly available.[118] This generally works by requiring information from corporate or government-sponsored clinical trials to be promptly posted on publicly available websites. Often, these sites also include information about the results of the clinical trials, including interim results. Some of these sites were pioneered by industry and industry trade associations.[119] Others are government-mandated. Key medical journals such as JAMA, Lancet, and NEJM now require posting of clinical trial information before they will publish articles about such trials. These efforts have been led by the International Committee of

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use should be considered to have demonstrated to be reasonable and necessary medical care (New HOD Policy).

Such use is also acknowledged in Budetti, *supra* note 9.

116 *Buckman*, 351 U.S. at 350.

117 *See* Hall and Sobotka, *supra* note 57, for a more detailed discussion of government policies encouraging or permitting off-label uses.

118 *See* FDAAA at Title VIII.

119 *See* Clinical Study Results, http://www.clinicalstudyresults.org; *see* Eli Lily and Company Trial Registry, http://www.lillytrials.com (examples of both governmental and non-government clinical trial registries and information sources).

Medical Journal Editors (ICMJE).[120]

Recently, Congress passed legislation mandating more public posting of clinical trial information on a large variety of studies.[121] These postings, available at www.clinicaltrials.gov, include information about the trial and its purpose and can contain actual clinical trial results.

In addition to legislative requirements[122] and voluntary industry initiatives, several enforcement actions have mandated public posting of clinical trial results for unapproved products. The most famous of these is the action brought by the New York Attorney General Eliot Spitzer against Glaxo for allegedly hiding negative clinical trial results involving the pediatric use of the antidepressant Paxil.[123] At that time, Paxil was not indicated for pediatric uses.[124] In a negotiated resolution to this action, Glaxo agreed to post the results of clinical trials on pediatric uses of Paxil on a publicly-available website.[125]

These public sites serve two core purposes. First, they allow physicians and patients (or parents) to more readily learn about clinical trials. For example, if a child is suffering from some cancer that has not responded to standard therapies, these systems provide information about ongoing clinical trials that might offer hope for such patients.

The second, and for our purposes more relevant, use of these sites is to provide the treating physician with more complete and timely clinical information. With this additional information, the

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120 *See* Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, http://www.icmje.org/#clin_trials.

121 42 U.S.C. § 282(j).

122 We note that a number of states have been considering similar legislation and Maine has enacted such a law. *See* 22 ME. REV. STAT. ANN. tit. 22, § 2700–A (2006). The recent federal legislation includes the eventual preemption of such states laws. *See* FDAAA § 801(d). As such, it appears that state legislative involvement will be largely irrelevant once the clinical trial reporting provisions of FDAAA are fully implemented.

123 People v. GlaxoSmithKline, PLC No. 04401707 (N.Y. Sup. Ct.) filed Jun. 2, 2004, *available at* http://www.oaq.state.ny.us/press/2004/jun/jun2b_04_attch1.pdf and the Consent Decree resolving this case. People v. GlaxoSmithKline consent order and judgment (Aug. 26, 2004) 2004 WL 1932763.

124 *Id.*

125 *Id.*

health care provider theoretically should be in a better position to decide when and how to use a drug or device for an off-label pediatric purpose. These systems are an effort to reduce the information gap (real or imagined) that exists when a product is not FDA-approved.[126]

These sites are also intended to increase the timeliness of access to information. Clinical trial results may not be published promptly, if ever. One of the allegations in the recent Vytorin/Zetia controversy was that drug makers attempted to conceal negative clinical trial results by not making them available to the public in a timely fashion.[127] Arguably, this information could have and should have been made publicly available when the data first became available.[128]

There is an interesting apparent contradiction between the current regulatory limitations on off-label promotion and sites such as clinicaltrials.gov that provide the public with additional information on off-label uses. The FDA requires that there be no off-label promotion or marketing. Thus, a company generally cannot provide or mail unsolicited scientific information to physicians about an off-label use. However, making that information available on a website has the identical effect of providing information on unapproved uses, precisely what the FDA prohibits a manufacturer

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126 By law the label cannot promote or provide information for unapproved uses including dosages, adverse events, contraindications, etc. to physicians or patients. There are some exceptions to this general rule including the provision involving peer reviewed medical journal articles. *See* 21 C.F.R. pt. 99 (2008).

127 For an example of an article relating to such allegations, *see* Forbes.com, What's Next for Vytorin?, at http://www.forbes.com/home/healthcare/2008/01/14/enhance-merck-schering-biz-healthcare-cx_mh_0115bizenhance.html. Public advocacy groups such as Public Citizen have expressed concern over the perceived delay in reporting clinical trial results. *See* http://www.citizen.org/pressroom/release.cfm?ID=2586.

128 *Id.* One can debate when clinical data is sufficiently clear or meaningful such that publication is appropriate. It often takes some analysis and assessment before data can be transitioned into meaningful information. The current Vytorin controversy epitomizes differing views of the timeliness of the reporting of clinical study results. The manufacturers, citing data volume, analytic challenges, and data quality issues assert that they were timely in reporting the results of the Encourage study. *See* Merck.com, http://www.merck.com/newsroom/ press_releases/product/2008_0125.html. Conversely, certain groups, particularly industry critics or watchdogs such as Public Citizen, have roundly criticized the companies for not reporting results for more than eighteen months after the last data collection. *See* http://www.citizen.org/pressroom/release.cfm?ID=2586.

from doing.[129] Whether this apparent inconsistency will affect this trend towards "enhanced" off-label uses is an open question.

If, as is highly probable, off-label use continues to be a significant source of pediatric products, increasing the information flow can help improve medical decision making.

V. IS THERE A CONSTITUTIONAL RIGHT OF ACCESS TO PRODUCTS FOR PEDIATRIC USES?

A. Background on the Constitutional Debate over Access to Experimental Therapies

Restrictions on pediatric access to medical therapies can be practical, economic, triggered by liability fears, or based on regulatory restrictions. It has long been recognized that the FDA regulatory structure operates as a substantial control mechanism on pediatric access to such products.[130] As explained above, one approach to increasing pediatric access to medical products is to modify the regulatory burdens on the development, testing and approval of such pediatric products. These efforts can approach the issue with pediatric product approvals from two directions. First, the statutory structure can seek to create incentives for pediatric products. Second, the regulatory structure can seek to reduce the time and financial burden on pediatric products created by the regulatory processes.

There is, however, another more radical approach to the challenge posed by the regulatory system: eliminate the role of the FDA as the gatekeeper for access to pediatric products. One theoretical, but undoubtedly unlikely, approach is for Congress to repeal the approval requirements or to exempt pediatric products from FDA oversight. Such an approach would clearly pose safety and

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[129] Companies are permitted to provide scientific information such as journal articles to physicians regarding off-label uses in response to a specific, unsolicited request. Wholesale posting by a company of information about off-label uses falls outside of this exception to the off-label promotion rules. For example, a company cannot post on its website a medical article relating to a clinical trial on an off-label use. Posting the results of such a study would, absent some explicit or implicit exception, seem to implicate the same issues.

[130] *See* Pediatric Drug Research, GAO-07-898T (March 22, 2007) for a description of how provisions such as BPCA and PREA have removed some of these barriers.

efficacy risks and return the drug regulatory process to the pre–1938 structure. Neither the FDA nor Congress has proposed such an approach. Powerful advocacy groups would also protest mightily. While predicting the future is always dangerous, no one should anticipate Congress exempting pediatric products from FDA oversight.

An alternative approach is to challenge the FDA's constitutional power over pediatric products. On several occasions, certain stakeholders—generally patients or patient advocacy groups—have advanced constitutional arguments seeking to limit FDA control over access to unapproved drugs. These challenges have generally been brought on behalf of mentally competent adult patients.[131] Early constitutional challenges focused on the FDA's refusal to approve Laetrile, a controversial cancer treatment from the 1970s. Cancer patients (or their supporters) sought access through the courts to Laetrile outside the FDA approval process. These groups asserted constitutional limitations on the FDA's controls over access to unapproved products, particularly for the terminally ill. These efforts were ultimately unsuccessful following the Supreme Court's decision in *Rutherford v. U.S.*[132] At the end of the day, the Court upheld the FDA's right to refuse to approve Laetrile. Unless one wanted to go outside the U.S., one could not get Laetrile even for terminal cancers.[133]

Perhaps because the cancers at issue in the Laetrile controversy were essentially adult cancers, the series of Laetrile-related cases leading up to and following *Rutherford* did not specifically address the issue of children's rights to Laetrile. One can speculate that, for tactical or strategic reasons, the litigants in the Laetrile battles wanted to avoid the potential confounding factors caused by injecting the question of children's rights. In fact, the applicability of the plaintiffs' arguments in the *Rutherford* series of cases was generally bypassed by all litigants.

Shortly after *Rutherford* was decided, the Supreme Court began further defining the scope and elements of constitutional rights under

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131 *See* United States v. Rutherford, 442 U.S. 544 (1979).

132 *Id*.

133 For additional information on the Laetrile dispute, *see Rutherford*, *supra* note 100, and earlier cases such as Rutherford v. United States, 438 F. Supp. 1287 (W.D. Okla. 1977).

the Substantive Due Process Clause of the Fifth Amendment for rights not specifically enumerated in the Constitution. Many of these cases arose in the context of privacy and reproductive rights, culminating in *Washington v. Glucksberg*.[134] *Glucksberg* provided two approaches to establish some non-specific constitutional right under the Substantive Due Process Clause. The first is that, absent some compelling government interest, the Substantive Due Process Clause protects rights that are fundamental to personal dignity and autonomy.[135] The second approach protects rights deeply rooted in the nation's history and legal traditions. The asserted right must be "implicit in the concept of ordered liberty, such that neither liberty nor justice would exist" if this right were abridged.[136]

Courts have routinely reminded litigants (and lower courts) that such rights asserted under a *Glucksberg* test should not be easily or routinely found. Judicial restraint is mandated before any court "finds" some new right.[137]

One key aspect of *Glucksberg* is that the proposed or asserted right must be defined specifically and narrowly. In part, this is a reflection of the judicial restraint mandated by the Supreme Court. It ensures that the courts can fully understand and define the asserted right and understand the scope or dimension of the claimed right. This requirement forces clarity and specificity.[138] If such a right is found to exist, the burden switches to the government to establish that any encroachment on that right is "narrowly tailored to serve a compelling [governmental] interest."[139] Recently, litigants have sought to use *Glucksberg* to establish a right of access to unapproved drugs.

B. Abigail Alliance

The constitutional front remained relatively quiet after *Rutherford*

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134 Washington v. Glucksberg, 521 U.S. 702 (1997).

135 Planned Parenthood of Southeastern Pa. v. Casey, 505 U.S. 833, 861 (1992). These cases often involve reproductive rights.

136 *Glucksberg*, 521 U.S. at 720-21.

137 *Id.* at 721.

138 *Id.*

139 *Id.*

until the *Abigail Alliance* case was filed in 2004. This case arose from a human tragedy. Abigail Burroughs was nineteen years old when diagnosed with a serious head and neck cancer. Standard therapies failed and so she, her family, and her physicians sought access to then ongoing clinical trials involving Ebutrex, an anti-tumor drug. Preliminary, but inconclusive, data indicated that this drug might be effective against tumors of her type. She was unable to gain access to these clinical studies because she did not meet the entry criteria. Lacking any effective treatment, she died in 2001.[140] Following her death, her family and supporters formed the Abigail Alliance for Better Access to Developmental Drugs.[141] The Abigail Alliance eventually challenged the right of the FDA to restrict access to certain unapproved products.

The origins of the Abigail Alliance litigation date to a Citizens Petition filed by the Abigail Alliance with the FDA in 2003.[142] After the FDA failed to respond within the statutory deadline, Abigail Alliance filed suit in the U.S. District Court for the District of Columbia seeking a declaration that the FDA could not constitutionally restrict access to unapproved drugs for patients suffering from a terminal illness.[143] Such drugs, according to Abigail Alliance's position, had to be prescribed by a physician, had to have successfully passed Phase I studies, and had to be for adult patients.[144] The District Court did not find any such constitutional right.[145]

Upon appeal, a three-judge panel of the D.C. Court of Appeals reversed the District Court. In doing so, this panel, in a 2–1 decision, found that the right asserted by Abigail Alliance was protected by the

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140 For a general overview of the tragic death of Abigail Burroughs and the factual background of the Abigail Alliance case, *see* Abigail-alliance.org and the complaint in the case Abigail Alliance for Better Access to Developmental Drugs v. McClellan, No. 03-1601, 2004 WL 3777340 (D.D.C. Aug. 30, 2004) *available at* http://www.wlf.org/upload/Abigail%20Alliance%20complaint.pdf.

141 For more information on the mission and organization of the Abigail Alliance for Better Access to Developmental Drugs, *see* http://www.abigail-alliance.org.

142 *See* 21 CFR § 10.25 for a description of the Citizens Petition process.

143 Abigail Alliance for Better Access to Developmental Drugs, 2004 WL 3777340.

144 *Id.*

145 *See* Abigail Alliance v. Von Eschenbach, 445 F.3d 436, 474 (C.A.D.C. 2006).

Due Process Clause under a *Glucksberg* analysis.[146] In essence, the two-judge majority found that FDA control over access to unapproved drugs was of recent origins (going back no further than 1962 when Congress passed the Kefauver Harris Act[147] requiring that new drugs must be found to be safe and efficacious before receiving FDA approval). The Court further found that there had been a long tradition of personal choice and autonomy for medical decisions dating back to at least colonial times. As such, the right to control one's medical decisions, including what drugs to take, was viewed by the two-judge majority as a right of long-standing tradition, and that interference with that right would have a substantial negative effect on the long-standing traditions of freedom and liberty. The Supreme Court also analogized to the "right to die" cases such as *Cruzan v. Director, Missouri Department of Health*.[148] If one has the right to refuse therapy, the argument goes, one has the right to risk therapy.

Specifically, the appellate court found that mentally competent *adults* who were suffering from a terminal condition who had exhausted standard therapies had a right, under physician supervision, of access to post-Phase I drugs.[149] While a manufacturer has no legal obligation to sell or provide the drug, the court held that the FDA could not impose obstacles to such access.

The court remanded the case to the District Court to build a factual record upon which it could determine whether the government's interest in restricting this right was so substantial as to override the substantive due process right. Note that the explicit right asserted by Abigail Alliance and analyzed by the court referenced adults, not pediatric patients. One can speculate as to the reason for this limitation. Perhaps Abigail Alliance had tactical reasons for limiting the initial right being asserted to adults. It seems ironic that had Abigail Burroughs been seventeen instead of nineteen when the cancer was diagnosed, the right being asserted by the foundation named for her would not have included her. Perhaps subsequent

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146 *Id.* at 470.

147 *See* 21 U.S.C. § 355 and 21 C.F.R. §§ 312 and 314 for certain key statutory and regulatory provisions implementing this act.

148 *Abigail Alliance,* 445 F.3d at 472 (citing Cruzan v. Director, Missouri Dep't of Health, 497 U.S. 261 (1990)).

149 *Id.* at 486.

litigation would have sought to expand the right from adults to children.

As one would expect, this decision created quite a stir. The FDA sought reconsideration by the original three-judge panel and a rehearing en banc by the entire D.C. Court of Appeals. In doing so, the FDA described the decision of the three-judge panel as "the biggest attack on the FDA in a generation."[150] On November 21, 2006, the original three-judge panel denied the motion for reconsideration and upheld its initial decision.[151] On the same day, the D.C. Circuit Court of Appeals granted the petition for rehearing en banc.[152]

The briefing on the rehearing en banc focused on whether there was a long tradition of individual control and access to medical therapies such that it is a right protected under the substantive due process clause and *Glucksberg*. The litigants on both sides argued the history of drug regulation from modern times back to the colonial regulation (or lack thereof) of pharmacy activities and the practice of medicine. This debate included an assessment of eighteenth and early nineteenth century regulatory systems in, among other places, Virginia, Louisiana, and England.[153] The concept of "medical self defense"[154] was also raised as a justification for allowing individuals to have access to these unapproved but post-Phase I drugs.[155] The

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150 *See* Appellee's Petition for Rehearing and for Rehearing en banc at Abigail Alliance v. Von Eschenbach, 445 F.3d 470, No. 04-5350 (June 16, 2006).

151 Abigail Alliance v. Von Eschenbach, 469 F.3d 129, 138 (D.C. Cir. 2006).

152 Abigail Alliance, 2006 U.S. App. Lexis 28974.

153 *See, e.g.*, Brief of Defendant-Appellee at 31, Abigail Alliance v. Von Eschenbach, No. 04-5350 (Rule 10.83).

154 Eugene Volokh, *Medical Self-Defense, Prohibited Experimental Therapies, and Payment for Organs*, 120 HARV. L. REV. 1813, 1815 (2007). As articulated in Volokh, Medical Self-Defense, Prohibited Experimental Therapies, and Payment for Organs, an individual, in an effort to save his or her life when faced with a terminal illness, had a right to self-help that overrode the government's interest in regulating access to drugs not yet shown to be safe and effective. Abigail Alliance argued that this right of self-help or self-defense had a long tradition in Anglo-American jurisprudence.

155 *See* Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 2007 WL 415084 (C.A.D.C. 2007). An assessment of the logic and support for this medical self defense argument is beyond the scope of this article. A critical assessment of that line of argument might well be interesting. One can only speculate on the general implications of the concept and whether the concept could withstand a critical assessment. Clearly the Court of Appeals did not find that argument persuasive. That argument was also insufficient to persuade the Supreme Court to hear the case.

litigants also took the opportunity, near and dear to at least a few law students, to actually argue about and cite to Blackstone's Commentaries from over four hundred years ago.[156] This historical review was an effort by each side to demonstrate that Anglo-American legal tradition supported their position. Whoever won the history battle would prevail under the *Glucksberg* test.[157]

On August 7, 2007, the en banc D.C. Circuit Court of Appeals reversed the original three-judge panel and found no substantive due process right of access to post-Phase I drugs.[158] The en banc court found a substantial history of government regulation of access to drugs. The FDA won the battle of historical interpretation. At its core, the en banc decision views the historical record of government regulation of drugs, pharmacies, and medicine diametrically differently than the original appellate panel. The en banc decision found substantial FDA regulation of access to drugs going back to least 1938 with the passage of the first drug premarket approval requirements.[159] The en banc decision also found support for government regulation of access to drugs in colonial and early American legal pronouncements[160] and rejected the medical self-defense position. In the end, the Court soundly rejected Abigail Alliance's asserted right of access to post-Phase I drugs. The only findings in favor of Abigail Alliance in the en banc decision came from two judges in the original panel.

Following this decision, Abigail Alliance filed a Petition for a Writ of Certiorari with the United States Supreme Court.[161] This petition for certiorari was denied on January 14, 2008.[162] As such,

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156 *See* Petition for Writ of Certiorari, Abigail Alliance, 128 S. Ct. 1069 (No. 07-444), 2007 WL 2846053. It is a rare case indeed, in which Blackstone's Commentaries are more than an historical footnote.

157 There was little debate over whether G*lucksberg's* "long standing historical tradition" test was the relevant legal standard. Neither side particularly argued the "personal dignity" approach also found in *Glucksberg*.

158 495 F.3d 695 (C.A.D.C. 2007). In essence, the en banc court upheld the result from the original District Court decision.

159 *Id.* at 705.

160 *Id.* at 703-04.

161 Petition for Writ of Certiorari, Abigail Alliance, 128 S. Ct. 1069 (No. 07-444), 2007 WL 2846053.

162 Abigail Alliance v. von Eschenbach, 128 S. Ct. 1069, 2008 WL 114305.

absent some new argument, it appears that the efforts to convince a court that there is a constitutional right to access of unapproved drugs without government interference have failed for the time being.

C. The Implications of Abigail Alliance for Pediatric Products

The case, as filed and litigated, has two interesting aspects to those interested in products for pediatric uses.

The first is whether, contrary to the en banc decision of the D.C. Court of Appeals, the constitutional arguments do support a right of access to unapproved therapies. Assuming that the courts continue to utilize the current Supreme Court test in *Glucksberg* for the identification of substantive due process rights, the debate centers on whether there is a history of pediatric access to unapproved therapies and whether restrictions on such rights would be contrary to long standing notions of liberty and personal rights. One can certainly argue that the Court of Appeals decision, followed by the denial of the petition for a writ of certiorari, has answered this constitutional question for the near future. It took over twenty years for another constitutional challenge to be launched after the Supreme Court rejected a constitutional argument in *Rutherford* that the FDA could not interfere with access to Laetrile; perhaps, it will be another twenty years before this issue is re-raised. Of course, another court could view the historical record differently.[163]

If one assumes that the en banc court is correct, that there is no constitutional right of access for mentally competent *adults*, there appears to be no better argument for such a constitutional right for children. The historical record cited by *Abigail Alliance* does not provide special rules or privileges for children. The concept of medical self defense is likewise not age dependent. Finally, the interface between access to unapproved products and concepts of ordered liberty (as described in *Glucksberg*) does not provide more protection to children than adults. If anything, children historically have often been the recipients of greater levels of government protection, or less liberty, than adults.

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163 Had the Supreme Court issued a substantive decision in *Abigail Alliance*, we might have a conclusive answer to this question.

A litigant could, of course, develop a new substantive or factual approach to this question. One potential argument is that the current expansive use of off-label products[164] and government policies, actually encouraging off-label uses, reflects not only a historical tradition or policy favoring access to unapproved drugs, but also reflects current policies advancing access to unapproved products. Such an argument was not specifically advanced in the *Abigail Alliance* case and was only mentioned in passing in the various court decisions.[165] We have detailed above some examples of this pervasive use of off-label drugs and Congressional and FDA acceptance of such uses. We have also noted that the Supreme Court has explicitly recognized the critical and important role of off-label products[166] by ensuring that physicians and patients have information about such uses. These legislative policies could well support an argument under *Glucksberg* that there is both a tradition and a well-accepted practice of using products without FDA approval, and that our nation's concepts of liberty and freedom drive us toward expanded access.[167]

The second matter of interest involves how *Abigail Alliance* framed its asserted constitutional rights. (Remember that *Glucksberg* requires a specific description of the asserted right and that, in part, the courts in the *Abigail Alliance* series of cases debated whether *Abigail Alliance* had met the requirement of a detailed and specific description of the asserted right.[168]) *Abigail Alliance* claimed a right of

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164 Remember, using a product for an off-label purpose is providing access to an unapproved product. Products such as new drugs are approved for specific purposes or "indications" and are not approved for any use desired by the manufacturer.

165 The dissent to the en banc decision mentions off-label use in just several lines near the end of the dissent's analysis. *Abigail Alliance*, 495 F.3d at 726.

166 *Buckman*, 531 U.S at 350.

167 For a more detailed discussion of government policies encouraging or allowing off-label uses, *see* Hall and Sobotka, *supra* note 57. Whether inconsistent government policies can support the constitutional right being asserted by Abigail Alliance is an open question. To date, the briefing in the various *Abigail Alliance* cases have not focused on this line of argument.

168 *See, e.g., Abigail Alliance*, 495 F.3d at 702, 703 ("We nonetheless have serious doubt about whether the Alliance's description of its proposed constitutional right could ever pass constitutional muster."). The en banc court seemed skeptical that Abigail Alliance had met this requirement but did not decide the case on those grounds. Had it relied on this specificity requirement, Abigail Alliance would have been free to recast its claimed right and restart this litigation in the District Court.

access to post-Phase I drugs for mentally competent *adults* facing a terminal illness who were under a physician's care.[169]

Does limiting this asserted right to adults make legal or medical sense?[170] In this context, do children have fewer rights than adults? If there is a right of access for adults facing a terminal illness, there seems to be no logical, medical, or legal reason not to extend it to a pediatric population.[171] Of course, one can argue that a mentally competent adult is able to make an informed decision whether, when faced with a terminal illness, to take the risk of using an unapproved therapy. A child, on the other hand, may not be capable of making such an informed decision. Yet, we face this same issue whenever

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169 One can question the logic and legal basis for drawing the line at post-Phase I studies. While speculative, it would seem that this limitation was advanced by Abigail Alliance to limit the history of government control over access to unapproved drugs to the post-1962 period. Prior to 1962, a drug could be approved if it was deemed to be safe. The sponsor did not have to demonstrate efficacy. That changed in 1962 when both safety and efficacy had to be demonstrated. Phase I studies are the initial safety determination, and so Abigail Alliance could argue that limiting the asserted right to post-Phase I drugs was consistent with the longer history of government approval of drugs for safety. Another reason for this limitation might have been to distinguish this case from the earlier *Rutherford* series of cases. Laetrile, the drug in question in *Rutherford*, never passed any safety testing.

170 We recognize that there well may be important litigation strategies and tactics surrounding the decision of Abigail Alliance to assert the constitutional right of access for adults. Certainly Abigail Alliance has not, to our knowledge, taken an explicit position that there is no right of pediatric access. They just have not claimed such a right. Perhaps a claim for a pediatric right is to follow if the initial litigation is successful. Perhaps Abigail Alliance wants to avoid making the case more complex or emotional by including pediatric patients and their rights. Perhaps Abigail Alliance does not want to add issues surrounding protection of children to this already complicated litigation. We can only speculate as to the reason. However, the reality is that the claimed right is for adults and on its face does not apply to children.

171 In addition to the age limitation under discussion, one can also question what a "terminal" disease is. The Supreme Court in *Rutherford,* 442 U.S. 544, 556 (1979), stated that it was unable to state with certainty whether a disease is terminal. There are always examples, however rare, of a spontaneous remission or cure. In addition, if there is the right to control one's medical decisions and therapies, why should that be limited to a terminal disease? If one has a debilitating condition such as Alzheimer's or multiple sclerosis, one might logically decide that the potential benefit of the therapy outweighed the risks, given the impact of the disease or condition on one's enjoyment of life. The courts in cases such as *Cruzan,* 497 U.S. 261 (1990), have upheld one's right to refuse therapy or even nutrition when faced with a permanent disability such as being in a permanent vegetative state. While outside the scope of this article, one can easily question some of the limitations Abigail Alliance proposed for this asserted constitutional right. Whether this arguable inconsistency affected the court is unknown.

informed consent is needed for medical therapy. Parents or guardians are empowered to make such decisions for the child. In unusual cases, one can even employ the guardian ad litem process to ensure that the best interests of the child are protected.[172]

This process already is in place and is working. If the parent or guardian can consent to the participation of the child in an FDA-regulated clinical trial of an unapproved drug, there is no reason why that same consent should not be adequate for using an unapproved therapy outside of a clinical trial.

If an adult has a right to try an experimental therapy as a last resort, why can't a child? There appears to be no logical reason to limit the asserted constitutional right to adults. Abigail Burroughs had just as strong an interest in living whether she was nineteen or seventeen. If there is ever a constitutional right of access to unapproved products, we see no reason or argument to limit that right to adults. The converse is also true. The constitutional right of access for pediatric patients rises and falls with the existence of such a right for adults.

VI. CONCLUSION

There is an ongoing need for safe and effective therapies for pediatric patients. Congress has explicitly recognized and addressed this need just recently by passing the Best Pharmaceuticals for Children Act of 2007 (BPCA), the Pediatric Research Equity Act of 2007 (PREA), and the Pediatric Medical Device Safety and Improvement Act of 2007 (PMDS). But for any number of reasons, including cost, time, priorities, legal liability, public perception, changing medical needs, and scientific challenges, this need has not been and cannot be completely filled by FDA-approved products. Other mechanisms, primarily off-label use, exist to fill some of this void. Yet challenges remain even with these avenues of access.

We have identified four current approaches to providing medical

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172 There is a potential disconnect between at least one definition of a pediatric patient as being twenty-one or younger (*see* 21 U.S.C. § 360j(m)(6)(E)(2007)) and general concepts defining adults as being eighteen or older. It would seem that the pediatric product definition is due to biological differences. As such, for consent purposes it would seem that eighteen is the dividing line.

therapies to pediatric patients:

1) Faster and more effective FDA-regulated testing and approvals;
2) Congressional efforts to encourage pediatric products;
3) Off-label uses; and
4) "Enhanced" off-label uses.

The various strategies advanced by Congress and the FDA to improve the testing, review, and approval of new medical therapies must continue to balance the benefit of improved and faster access to drugs and devices with the risks inherent in any accelerated testing and approval. These programs have made a difference in the past[173] and should continue to make a difference going forward. Experience to date with earlier enactments, particularly the Best Pharmaceuticals for Children Act, indicates that these programs will have a positive impact. According to the major pharmaceutical trade association, BPCA led to pediatric labeling in 120 new or approved drugs during the 1997–2006 time period compared with only 11 such pediatric indications in the 1990–1997 time frame.[174] A Department of Health and Human Services report likewise concludes that these incentives have substantially increased the number of pediatric studies and indications.[175] Though FDA testing, review, and approval process clearly does add value by developing data necessary to the risk/benefit ratio for the product, no one expects that all pediatric medical needs will now be addressed by FDA-approved products.

As such, off-label uses will continue to play an important role. The trend toward what we have called enhanced off-label use will continue. If, as predicted, off-label use continues, it is best done with the most possible information. Here, programs such as clinicaltrials.gov and the posting of information from pediatric product assessments under PREA or PMDS provide the health care

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173 *See Roberts*, *supra* note 9, at 20.

174 Phrma Statement on Pediatric Medicine, http://www.phrma.org/news_room/press_releases/phrma_statement_on_pediatric_medicines/.

175 Department of Health and Human Services Federal Drug Administration (2001), *The Pediatric Exclusivity Provision Status Report to Congress*, http://www.fda.gov/Cder/pediatric/ reportcong01.pdf.

provider with more information upon which better prescribing decisions can be made.[176] We would anticipate additional public and private efforts to make more off-label information public.[177]

There is, however, a fundamental gap in the total coverage of pediatric medical needs provided by the combination of FDA approval of new therapies and the off-label (including enhanced off–label) use of products. This gap is epitomized by the tragic story of Abigail Burroughs. In order for the physician or patient to have access to an off-label product, the product has to be approved for some (often unrelated) on-label use. Stated differently, if the drug is approved for adult use, the physician can prescribe it for a pediatric purpose (whether similar or not to the adult indication) and the patient can simply get that prescription filled. However, if the drug is not approved for any purpose, then there is no access to that product for the desired off-label purpose.

Assume that an individual such as Abigail Burroughs has cancer, and there is no FDA-approved drug for that cancer. The physician wants to prescribe an off-label drug for that cancer. If that drug is not approved for some other purpose, absent enrollment in an FDA-regulated clinical trial (which is often not possible), she cannot get that drug in the U.S. In essence, her access to the off-label drug depended upon the serendipity of whether it is approved for some totally different purpose such as hair loss. Abigail Burroughs and her physician wanted access to Ebutrex. That drug had no approved use. She did not qualify for the then-existing clinical trials. She could not get the prescription filled. She died from her cancer.

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176 We note that such information is off-label. Historically, manufacturers are prohibited from disseminating most off-label information. There is an obvious tension between programs designed to provide better information on off-label uses and the FDA's prohibition on off-label promotion. This can lead to interesting enforcement and First Amendment issues. These issues are beyond the scope of this article.

177 Many people tend to think of the health care professional as the audience or recipient of this off-label information. Yet we cannot forget the patient. More and more patients and family members of patients are playing an active role in personal medical decisions. Information sources, such as clinicaltrials.gov, are equally available to patients and are often intended for patient access. For example, information on off-label clinical trials now being posted on the internet as required by PHS, 42 U.S.C. § 282(j)k (2007), helps patients learn of treatment options, treatment benefits, and treatment risks. There is no other logical reason to post such information. These information sources are powerful tools to enable personal medical decision making.

This gap in access to therapy led to the efforts of Abigail Alliance to obtain judicial recognition of a constitutional right of access even to post-Phase I drugs not approved for any purpose. To date, that effort has been unsuccessful. This gap will continue to be the lightning rod. Parents will continue to face the heartache of not having access to the only product that might save their child's life. There is no easy answer to this problem. In the meantime, the new statutory and regulatory provisions making pediatric testing, review, and approval easier, and off-label use of otherwise approved products will be the mainstay of pediatric therapies and should serve to narrow this gap.