

## **A Practical Approach for Resolving the Pediatric Oncology Drug Labeling Crisis**

by: Edward John Allera, Barbara Binzak Blumenfeld, Alexandre Gapihan

### **The Problem**

An undisputed crisis exists due to the absence of adequate labeling for pediatric oncology drug products. Almost all drugs used to treat pediatric oncology patients were approved over decades ago, and knowledge of pediatric cancer has increased logarithmically since their initial approvals. Further, the drugs were never tested in pediatric patients prior to New Drug Application (“NDA”) approval by the Food and Drug Administration (“FDA”). The drugs were tested in adult patients who suffered from the same basic disease under 1960’s and 1970’s standards. At that time, the risks associated with testing in children were considered too high to ethically permit. Children absorb, distribute, metabolize, and excrete these highly toxic drugs differently than adults. Almost all are parenterally administered. Most were approved before the enactment of the Waxman-Hatch Act in 1984<sup>1</sup>, which formalized the generic drug approval process. With its focus on new targets for generic drugs, the formalization of the genericization process inadvertently created a practical, but not legal, impediment to private sector pediatric oncology research for these older chemotherapeutic agents. As a result, their labeling is deficient, by contemporary standards, for pediatric patients. These agents remain valuable for treating this vulnerable patient population.

Their archaic labeling, however, creates an information deficit for patients, physicians, and payors. This deficit occurs at a time of limited resources for most health care providers, and optimal value therapy is essential. This article sets forth an administrative procedure for FDA to update the labeling of these oncology drugs for pediatric use. This administrative process follows the long line of such administrative processes created by FDA to ensure that drug labeling remains up to date in terms of safety and effectiveness.

### **History of Reference Product Labeling**

#### **I. Administrative ANDAs**

Many applications for oncology drugs were approved in the so-called Drug Efficacy Study Implementation (“DESI”) era, which encompasses approved NDAs from the enactment of the Federal Food, Drug, and Cosmetic Act (“FFDCA” or the “Act”) of 1938 through the mid to late 1970’s. The language of the labeling indications for these drugs, which were reviewed for safety, was broad and is now considered dated. Literature and other clinical studies about these drugs that were not submitted by the sponsor for inclusion in the approved labeling of the NDA were often used by FDA in the DESI Review process to refine the labeling, as the drugs were reviewed on an active ingredient, or Active Pharmaceutical Ingredient (“API”) in today’s parlance, basis. This approach was designed to ensure that the labeling of the drug products was accurate and revealed all material facts about their safety as well as effectiveness.

The DESI Review was a multistep process to assess the effectiveness for drugs approved between the 1938 enactment of the FFDCA and the imposition of the effectiveness requirement for all drugs mandated by the Kefauver-Harris Amendments of 1962. The Agency conducted the review of all active ingredients marketed between 1938 and 1962 under a contract with the National Academy of

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<sup>1</sup> Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. §355 and 35 U.S.C. §§ 156, 271 and 282).

Sciences/National Research Council (“NAS/NRC”). FDA issued a Federal Register notice for each API and asked sponsors of NDAs and sponsors of Identical, Related, or Similar (“IRS”) drugs to submit all evidence supporting the effectiveness of the API. The NAS/NRC panels, in essence among the first FDA advisory committees, then reviewed the data and made recommendations to the Agency about the effectiveness of the claims on the label, ranking each as effective, probably effective, possibly effective, ineffective or ineffective as a fixed combination.<sup>2</sup> FDA adopted these findings and published them in the Federal Register. Companies then had the opportunity to accept the effectiveness conclusions and market the drug. Or they could request a formal evidentiary hearing and provide additional evidence to demonstrate effectiveness for the less than effective claims, while continuing to market the drug product until the issues were resolved. Sponsors of IRS drug products were permitted to submit labeling and Chemistry, Manufacturing, and Controls (“CMC”) information and market their products if they appropriately requested a hearing. These products were the first Abbreviated New Drug Applications (“ANDAs”), and were a purely administrative creation. The labeling for drug products on the market would vary from those that had only the effectiveness claims to those that contained labeling for all claims, including the less than effective claims. The DESI findings, as adopted by FDA, were the first reference standards for generic products.

## II. Paper NDAs

The number of available targets for generics declined in the late 1970’s and ‘80’s, as FDA came toward the completion of the DESI review process. The value of generic drugs and their public health benefits became well recognized. FDA announced a willingness to consider published reports of safety and effectiveness studies as the equivalent of the submission of full reports of those studies otherwise required for a full NDA, at least where the application was for a generic copy of a drug previously approved by FDA.<sup>3</sup> Accordingly, FDA created another administrative mechanism to provide generic versions of drugs that were approved after 1962 on the grounds of safety and effectiveness and thus were not subject to the DESI Review- the “Paper NDA”. The procedure was created on the basis of a memorandum by Dr. Marion Finkel, the Director of FDA’s Office of New Drugs. FDA concluded that APIs that were supported by literature reports of safety and effectiveness and that were bioequivalent to the original drug product, could be approved as NDAs. Duplicative testing in humans was unnecessary when the literature was legally in the hands of FDA and submitted by applicants based on the on-paper showing of safety and effectiveness. This Paper NDA procedure was created unilaterally by FDA, without legislative input. The pioneer products and their labeling were the reference standards for bioequivalent generics. FDA and the sponsors revised the labeling periodically. This procedure was challenged in court by a number of pioneer manufacturers, and the Agency prevailed.<sup>4</sup>

## III. OTC Review

During this period, FDA also developed the Over-the-Counter (“OTC”) drug review process, to clarify the labeling for hundreds of thousands of drug products that were marketed OTC without any FDA approvals. Rather than act on a product by product basis, the agency evaluated products on APIs basis. FDA created advisory committees to review, in a multistep public process, the literature, submitted studies, expert opinion, and other information on the APIs to determine the indications for which the drugs were generally recognized as safe and effective and not misbranded- the so- called OTC Review

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<sup>2</sup> See 21C.F.R. 201.200.

<sup>3</sup> See 47 Fed. Reg. 1765 (Jan. 13, 1982).

<sup>4</sup> See, e.g., *Upjohn Mfg. Co. v. Schweiker*, 681 F.2d 480 (6<sup>th</sup> Cir. 1982); *Burroughs-Wellcome Co. v. Schweiker*, 649 F.2d 221 (4<sup>th</sup> Cir. 1981).

process which mimicked the DESI Review process. The multistep administrative process created labeling that was generally recognized by qualified experts as safe and effective. As with the Paper NDA, this procedure was created without specific statutory basis and upheld by the courts.<sup>5</sup>

#### IV. Waxman Hatch Act Applications

With the growth of the generic drug industry, the political momentum favored lowering drug prices. The pioneer industry sought a political solution to obtain some comparable benefit for new chemical entities. This confluence of events led to enactment of the Generic Drug and Patent Term Restoration Act of 1984, the Waxman-Hatch Act.<sup>6</sup> The number of potential paper NDA targets was limited because there was literature on the safety of fewer APIs (approximately 1/3 of API applications approved), and the paper NDA system was an absolute counter incentive to publishing safety data or other studies about APIs' effectiveness, which is recognized as a reliable vetting process by the medical and scientific communities. Fearing another administrative expansion of the generic market, the pioneer industry opted for patent term restoration as a counter balance to the onslaught of genericization. The now historic compromise led to the creation and formalization, of a statutory route for the genericization of APIs in return for market exclusivity and extended patent life for the APIs. Not only has each of these segments of the industry burgeoned, but the compromise also created a vibrant 3<sup>rd</sup> segment, the specialty pharma industry. This industry segment started with new dosage forms and routes of administration for API.

Each industry segment uses the labeling of previously approved drug products as its reference standards. That labeling evolves over time as more information on safety becomes available and applicable. The process is iterative and continuous.

##### A. ANDAs

The formalization of the generic drug approval process led to explosive growth in the generic industry. Over 85% of the drug units sold in the U.S are generics.<sup>7</sup> The Congressional objective of facilitating generic approvals to reduce drug costs has been an overwhelming success for drugs coming off patent. This formalization has led to a singular focus on new drugs coming off of patent. To facilitate the new generic process, the statute set forth criteria that must be included in an ANDA. One criterion is an identical copy of the labeling of the marketed pioneer product that the generic seeks to duplicate, known as the Reference Listed Drug ("RLD"). Labeling changes for the RLD are a normal occurrence until generic competition is introduced. Thus, depending at the point in time when the ANDA is submitted, the filed labeling may vary, and the labeling may vary while the ANDA is being reviewed until the ANDAs are approved. Unfortunately, this competition has led to the fossilization of the labeling for most approved oncology drugs, especially for those used to treat children. There is no economic incentive to continuing to update the labeling for the pioneer or generic drug sponsors.

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<sup>5</sup> See *Cutler v. Kennedy*, 475 F. Supp. 838 (DDC 1979).

<sup>6</sup> Pub. L. No. 98-417, 98 Stat. 1585 (1984)

<sup>7</sup> See FDA brochure "Facts about Generic Drugs," available at

<https://www.fda.gov/downloads/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/ucm305908.PDF>

## **B. The Phantom NDA**

The specialty pharma industry arose as extended release dosage forms became more prevalent due to the superiority of dosing once-daily for purposes of patient compliance. Prior to the Waxman-Hatch Act, FDA had permitted approval of these dosage forms with combinations of clinical trials and bioavailability studies. For example, nitroglycerin patches were approved on the basis of the DESI finding for nitroglycerin paste.<sup>8</sup> Multiple theophylline controlled release dosage forms were approved on the basis of theophylline effectiveness. The drug products were approved under §505(b) of the Act and used labeling of the pioneer products at the time of the filings as the “reference product,” the §505(b) equivalent of the RLD.

After the Waxman-Hatch was enacted, an administrative glitch was perceived to exist. If a company had an approved NDA application under §505(b)(1), supplementing the application with a controlled release dosage form was straightforward. If a company had an approved ANDA under §505(j), there was no direct statutory mechanism to amend the ANDA to create a new controlled release dosage form that had never before been approved or used for the API. FDA created further restrictions by refusing to accept under §505(b) any application that could be filed under §505(j). FDA recognized that forcing companies to file §505(b)(1) applications for immediate release products that were never going to be marketed was unreasonable.

As a predecessor to the wide-spread use of the §505(b)(2) pathway, FDA created the phantom NDA policy. A company could file an application directly under §505(b)(2) for a new dosage form without having to obtain a meaningless NDA, thereby avoiding unnecessary human clinical exposure and risk. This phantom approach facilitated the approval of meaningful new safe and effective dosage forms. The new application was based on the safety and effectiveness, including the labeling, of the reference product. The explosion of the specialty pharma industry rendered this perception irrelevant as FDA established a more expansive interpretation of §505(b)(2) of the Waxman-Hatch At.

## **C. §505(b)(2) application**

The specialty pharma industry grew exponentially after FDA’s initial hesitancy about the role of §505(b)(2) applications. As with the formalization of the generic process, §505(b)(2) was originally thought of as a codification of Paper NDA’s. As the complexity and costs of technology increased, and needs for increased market exclusivity grew, §505(b)(2) applications expanded beyond simple once-daily dosage forms. Applications were developed by sponsors with no relationship to the holder of the approval for the initial drug product, or reference product. Unique listings in the Orange Book, i.e. the Approved List of Therapeutically Equivalent Drug Products were permitted. These listings create independent drug products with separate market exclusivity and patent listings. The foundation for the §505(b)(2) was the finding of safety and effectiveness for the original API, i.e. the reference drug. That standard evolved because FDA and the holders of the approved application for the reference drug learned more about the API from its labeling history and pharmacovigilance. A §505(b)(2) applicant must conduct a comprehensive pharmacovigilance review as part of the comprehensive summary of safety and effectiveness. As multiple dosage forms have arisen for APIs with multiple, unrelated holders of approvals, the importance of FDA as the repository of these data and the authors of the labeling has become essential.

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<sup>8</sup> See 58 Fed. Reg. 38045 at 38129 (July 15, 1993).

Analogously to the ANDA process, the sponsor for a §505 (b)(2) application must provide notice to the reference product that is closest to the new product and upon which the new product is based in its application. The original drug for which the finding of safety and effectiveness is made is the referenced drug for the §505(b)(2) application. Of course, the labeling of the reference drug continues to evolve. Therefore, FDA and the sponsor of the application continue to modify the labeling of the §505(b)(2) in part on the basis of the information in FDA's files and knowledge base.

Subsequently, in response to a Citizen Petition, FDA administratively established its §505(b)(2) policy.<sup>9</sup> The Agency concluded that it was relying on the finding that a drug approved under §505(b)(1) is safe and effective, in essence an expansion of the Paper NDA policy, and a company can rely on that finding as the basis for expanding uses of APIs under §505(b)(2). We thus have had a conflation of the RLD and the reference drug, and the application is approved under §505(b).

#### **D. Conclusion**

For over 50 years, FDA has cleverly adapted the reference drug concept as public health needs have evolved. The reference drug concept has evolved to ensure that drug products are safe, effective, and properly labeled. The adaptations have historically arisen when the agency has determined that, based on public health needs, steps are necessary for contemporary standards must be applied to marketed drug products. It has done so administratively, often, and the courts have unanimously supported the agency's action.

### **History of Attempts to Assist with Pediatric Research**

#### **I. Development of Pediatric Exclusivity and Pediatric Research Provisions**

##### **A. Pre-1997**

As early as the mid-1970s, FDA wanted to encourage pediatric drug development because healthcare professionals did not have adequate information about the use of prescription drugs in pediatric patients. In 1975, FDA issued a proposed rule to improve the information provided in prescription drug labeling.<sup>10</sup> FDA published the final rule in 1979,<sup>11</sup> making clear that labeling should inform physicians about the existence or lack of data supporting the safe and effective use of prescription drugs in children. The final rule permitted the labeling to state that safety and effectiveness in children (or specific age groups) had not been established.<sup>12</sup>

Because the 1979 final rule did not successfully encourage pediatric labeling,<sup>13</sup> the Agency proposed to amend the prescription drug labeling regulations in 1992<sup>14</sup> to clarify that controlled pediatric studies

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<sup>9</sup> See FDA Docket Nos. 2004P-023 11CP1 and SUP 1,2003P-0 1 761CP 1 and EMC 1, 2004P-01711CP1, and 2004N-0355.

<sup>10</sup> 40 Fed. Reg. 15392 (April 7, 1975).

<sup>11</sup> 44 Fed. Reg. 37434 (June 26, 1979).

<sup>12</sup> 44 Fed. Reg. 37434, 37453, 37465 (June 26, 1979) (new 21 C.F.R. § 201.75(f)(9)).

<sup>13</sup> 57 Fed. Reg. 47423, 47423 (October 16, 1992).

<sup>14</sup> 57 Fed. Reg. 47423 (October 16, 1992).

were not always required for pediatric labeling. Such studies could be waived if other data provided labeling information for children.<sup>15</sup> The 1994 final rule<sup>16</sup> provided for different methods of establishing substantial evidence in support of pediatric labeling claims, including adequate and well-controlled trials in adults along with supporting studies in children (*e.g.*, pharmacokinetic and pharmacodynamic assessments).<sup>17</sup> Sponsors were also required to survey existing data to determine if adequate and well-controlled studies in adults or other information could support modification of the labeling to address use in children and, if so, to submit a supplemental NDA.<sup>18</sup>

FDA also implemented a “Pediatric Plan” in 1994 “designed to focus attention on and encourage voluntary development of pediatric data both during the drug development process and after marketing.”<sup>19</sup> This 1994 effort was similarly unsuccessful in achieving FDA’s goals.<sup>20</sup>

## **B. 1997-2001**

In August 1997, FDA issued a proposal for what became widely known as the “Pediatric Rule.”<sup>21</sup> As proposed, the Pediatric Rule required pediatric studies when a drug is widely used in children, or is indicated for a significant or life-threatening illness but the label does not contain sufficient information for its use in children. FDA could require sponsors to develop a pediatric formulation in certain cases, unless reasonable attempts to do so failed. The proposed rule would also permit full or partial study waivers in certain cases.<sup>22</sup> However, a product could be considered misbranded or an unapproved new drug if no supplemental NDA was submitted and no waiver was granted.<sup>23</sup>

Before the Pediatric Rule was finalized, Congress enacted the Food and Drug Administration Modernization Act of 1997 (“FDAMA”)<sup>24</sup> to encourage (but not require) pediatric drug development in

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<sup>15</sup> 57 Fed. Reg. 47423, 47424 (October 16, 1992).

<sup>16</sup> 59 Fed. Reg. 64240 (December 13, 1994).

<sup>17</sup> 59 Fed. Reg. 64240, 64249 (December 13, 1994) (final 21 C.F.R. § 201.57(f)(9)(iv)).

<sup>18</sup> 59 Fed. Reg. 64240, 64240 (December 13, 1994).

<sup>19</sup> FDA, “The Pediatric Exclusivity Provision – January 2001 Status Report to Congress” (January 2001), *available at* <http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm315263.htm>, at 4 (hereinafter “Pediatric Exclusivity Report to Congress”).

<sup>20</sup> Pediatric Exclusivity Report to Congress, at 4.

<sup>21</sup> 62 Fed. Reg. 43900 (August 15, 1997).

<sup>22</sup> For example, a full waiver could be granted if the necessary studies would be impossible or “highly impractical,” or evidence strongly suggests that the product would be ineffective or unsafe in all pediatric age groups. 62 Fed. Reg. 43900, 43913-43914 (August 15, 1997) (proposed 21 C.F.R. § 201.23(c)(2)). Partial waivers could be granted if a sponsor made one of several other showings. 62 Fed. Reg. 43900, 43914 (August 15, 1997) (proposed 21 C.F.R. § 201.23(c)(3)).

<sup>23</sup> 62 Fed. Reg. 43900, 43914 (August 15, 1997) (proposed 21 C.F.R. § 201.23(d)).

<sup>24</sup> Pub. Law No. 105-115 (November 21, 1997), at § 111.

the face of few incentives but many deterrents for conducting pediatric studies.<sup>25</sup> FDAMA added new § 505A to the Act, giving FDA the ability to request that sponsors of new or approved § 505(b)(1) NDAs submit pediatric studies. If the sponsor agreed to the written request, completed and submitted the pediatric studies to FDA,<sup>26</sup> and the Agency accepted them, then the sponsor would receive six-month “pediatric exclusivity” added to the end of any existing patent or exclusivity protections.<sup>27</sup> Significantly, the new provision provided that any pediatric study required by regulation that met the “completeness, timeliness, and other requirements” for pediatric exclusivity “shall be deemed to satisfy the requirement for market exclusivity pursuant to this section.”<sup>28</sup>

Following the enactment of §505A, FDA still believed that such exclusivity incentives were not sufficient to obtain the needed pediatric labeling.<sup>29</sup> Therefore, FDA finalized the Pediatric Rule in 1998 to require pediatric studies in certain circumstances,<sup>30</sup> including when the drug is used in a “substantial number” of pediatric patients,<sup>31</sup> or provides a “meaningful therapeutic benefit” over existing treatments for children.<sup>32</sup> The final Pediatric Rule exempted any drug with an orphan drug designation from the study requirements,<sup>33</sup> as FDA believed that “[i]mposition of a pediatric study requirement on an orphan drug could conflict with the balance struck by the Orphan Drug Act, by further raising the cost of marketing the drug.”<sup>34</sup> FDA did not want to add an additional burden on sponsors of orphan drugs because of the already small patient population. However, FDA did not foreclose the possibility that one drug could be eligible for both orphan and pediatric exclusivities.

### C. 2002

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<sup>25</sup> S. Report 105-43 (July 1, 1997), at 51. Such deterrents included product liability, study recruitment and ethical concerns, and limited financial benefits.

<sup>26</sup> A “pediatric study” was considered to be at least one clinical investigation, including a pharmacokinetic study at FDA’s discretion, in pediatric age groups in which the drug was anticipated to be used. FFDCA § 505A(g), *codified at* 21 U.S.C. § 355a(g) (1997).

<sup>27</sup> FFDCA § 505A(a), (c), *codified at* 21 U.S.C. § 355a(a), (c) (1997).

<sup>28</sup> FFDCA § 505A(i), *codified at* 21 U.S.C. § 355a(i) (1997).

<sup>29</sup> 63 Fed. Reg. 66632, 66633 (December 2, 1998).

<sup>30</sup> 63 Fed. Reg. 66632 (December 2, 1998).

<sup>31</sup> FDA defined “substantial number” as 50,000. 63 Fed. Reg. 66632, 66636 (December 2, 1998).

<sup>32</sup> FDA defined “meaningful therapeutic benefit” to mean the drug (1) “would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population”; or (2) “is in a class of drugs or for an indication for which there is a need for additional therapeutic options.” 63 Fed. Reg. 66632, 66670 (December 2, 1998) (final 21 C.F.R. § 314.55(c)(5)(1)-(2)).

<sup>33</sup> 63 Fed. Reg. 66632, 66670 (December 2, 1998) (final 21 C.F.R. § 314.55(d)).

<sup>34</sup> 63 Fed. Reg. 66632, 66634, 66640 (December 2, 1998).

Congress renewed the pediatric exclusivity provisions in the Best Pharmaceuticals for Children Act (“BPCA”) in January 2002, with several changes.<sup>35</sup> Congress expanded the definition of a “pediatric study” to include studies in neonates in certain cases.<sup>36</sup> Congress also included a new subsection describing the written request process involving sponsors of drugs that are already approved. This new provision provided direction for the completion of pediatric studies when the sponsor does not agree to perform the requested studies, whether the product is on-patent<sup>37</sup> or off-patent.<sup>38</sup> The BPCA also added new statutory sections describing priority review status for supplemental NDAs describing pediatric labeling changes;<sup>39</sup> dissemination of pediatric information;<sup>40</sup> clarification of how Hatch-Waxman exclusivity and pediatric exclusivity interact;<sup>41</sup> and the prompt review of generic drugs when pediatric information is added to labeling.<sup>42</sup> Finally, Congress retained the 1997 statutory language stating that pediatric studies required by regulation were eligible for pediatric exclusivity.<sup>43</sup>

At this time, the pediatric study “landscape” was subject to two sets of provisions. First, the 1998 Pediatric Rule established conditions under which pediatric studies could be *mandated*. Second, the 2002 BPCA established statutory provisions allowing sponsors to *voluntarily* conduct pediatric studies and receive six-month pediatric exclusivity for their efforts. After several special interest groups challenged FDA’s ability to require drug sponsors to conduct studies in, or develop special drug formulations for, certain patient populations, the Court in Association of American Physicians and Surgeons, Inc. v. FDA<sup>44</sup> held that the Pediatric Rule exceeded FDA’s statutory authority, and was invalidated. The Court highlighted the numerous incompatibilities between the Pediatric Rule and the BPCA, particularly the mandatory-voluntary dichotomy. The Court concluded that the Pediatric Rule “usurps it [the BPCA] by superimposing an often-incompatible regime,”<sup>45</sup> and invalidated those regulations. The practical effect of this holding was that FDA could only encourage pediatric studies through awarding pediatric exclusivity, not require such studies.

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<sup>35</sup> Pub. Law No. 107-109 (January 4, 2002).

<sup>36</sup> FFDCa § 505A(a), *codified at* 21 U.S.C. § 355a(a) (2002).

<sup>37</sup> In the case of an on-patent drug, FDA has the option, but not the obligation, to refer the drug to the Foundation for the National Institutes of Health to conduct the studies outlined in the written request. FFDCa § 505A(d)(4), *codified at* 21 U.S.C. § 355a(d)(4) (2002); U.S. Government Accountability Office (“GAO”), Report GAO-07-557, “Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act” (March 2007), *available at* <http://www.gao.gov/products/GAO-07-557>, at 3.

<sup>38</sup> In the case of an off-patent drug, Congress amended the Public Health Service Act to cover studies in this situation. 42 U.S.C. § 284m; GAO, Report GAO-07-557, at 3.

<sup>39</sup> FFDCa § 505A(i), *codified at* 21 U.S.C. § 355a(i) (2002).

<sup>40</sup> FFDCa § 505A(j), *codified at* 21 U.S.C. § 355a(j) (2002).

<sup>41</sup> FFDCa § 505A(k), *codified at* 21 U.S.C. § 355a(k) (2002).

<sup>42</sup> FFDCa § 505A(l), *codified at* 21 U.S.C. § 355a(l) (2002).

<sup>43</sup> FFDCa § 505A(h), *codified at* 21 U.S.C. § 355a(h) (2002).

<sup>44</sup> 226 F.Supp.2d 204 (D.D.C. 2002).

<sup>45</sup> 226 F.Supp.2d at 221-222.

#### D. 2003-Present

In December 2003, Congress enacted PREA<sup>46</sup> to provide FDA with the statutory authority it was deemed to lack when it promulgated the Pediatric Rule and which implemented many of these provisions in new FFDCa § 505B.<sup>47</sup> New § 505B addressed requirements applicable to both new and marketed drugs, including obtaining waivers or deferrals of pediatric studies.<sup>48</sup> The Agency was permitted to impose pediatric study requirements on drugs already on the market when the pediatric exclusivity incentives under FFDCa § 505A did not provide the pediatric information necessary for the safe marketing of that drug for children. As a result, FDA was first required to ask the sponsor for voluntary studies under the exclusivity incentives of FFDCa § 505A before invoking the mandatory study provisions in FFDCa § 505B.<sup>49</sup>

PREA defined what was intended by a “meaningful therapeutic benefit,”<sup>50</sup> provided that study assessments must be submitted,<sup>51</sup> and addressed discussion meetings with the Agency.<sup>52</sup> PREA also exempted drugs with orphan designations from complying with the new section.<sup>53</sup> Finally, PREA amended § 505A(h) to provide that any pediatric study required by a *provision of law* (including a regulation) that also met the exclusivity requirements would be eligible for pediatric exclusivity.<sup>54</sup>

Both BPCA and PREA were prevented from sunseting with the enactment of the Food and Drug Administration Amendments Act of 2007 (“FDAAA”).<sup>55</sup> FDAAA amended the exclusivity provisions<sup>56</sup> to expand the definition of a “pediatric study” to include, at FDA’s discretion, pre-clinical studies.<sup>57</sup> The legislation also added a new section on the review of written requests and pediatric studies by an internal review committee.<sup>58</sup> Changes were also made to the pediatric study requirements of PREA.<sup>59</sup>

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<sup>46</sup> Pub. Law No. 108-155 (December 23, 2003).

<sup>47</sup> *Codified at* 21 U.S.C. § 355c; S. Report 108-84 (June 27, 2003), at 6.

<sup>48</sup> FFDCa § 505B(a), (b), *codified at* 21 U.S.C. § 355c(a), (b) (2003).

<sup>49</sup> FFDCa § 505B(b)(3), *codified at* 21 U.S.C. § 355c(b)(3) (2003); S. Report 108-84 (June 27, 2003), at 8.

<sup>50</sup> FFDCa § 505B(c), *codified at* 21 U.S.C. § 355c(c) (2003).

<sup>51</sup> FFDCa § 505B(d), *codified at* 21 U.S.C. § 355c(d) (2003).

<sup>52</sup> FFDCa § 505B(e), *codified at* 21 U.S.C. § 355c(e) (2003).

<sup>53</sup> PREA does not apply “to any drug for an indication for which orphan designation has been granted under section 526.” FFDCa § 505B(g), *codified at* 21 U.S.C. § 355c(g) (2003).

<sup>54</sup> FFDCa § 505A(h), *codified at* 21 U.S.C. § 355a(h) (2003).

<sup>55</sup> Pub. Law No. 110-85 (September 27, 2007).

<sup>56</sup> At some point prior to enactment of FDAAA, the title of 21 U.S.C. § 355a(h) was changed from “Relationship to regulations” to “Relationship to pediatric research requirements.” There were no changes to § 355a(h) made by FDAAA.

<sup>57</sup> FFDCa § 505A(a), *codified at* 21 U.S.C. § 355a(a) (2007).

<sup>58</sup> FFDCa § 505A(f), *codified at* 21 U.S.C. § 355a(f) (2007).

In 2012, both the pediatric research and exclusivity provisions were permanently reauthorized by the Food and Drug Administration Safety and Innovation Act (“FDASIA”).<sup>60</sup> Among other changes, FDCA § 505A(h) was, on its face, limited. Instead of retaining the previous broadly-read language stating that any pediatric study required under law or regulation could also be eligible for pediatric exclusivity, Congress facially narrowed the language by rewriting it to only refer to PREA studies as being eligible for pediatric exclusivity. Although Congress stated that it was providing a clarification,<sup>61</sup> the inartfully-drafted new language in this provision could be read to exclude any required pediatric studies that are not PREA pediatric studies from being eligible for pediatric exclusivity, which would be contrary to over thirty years of government policy and statutory incentive.

### E. The Pediatric Landscape Today

Today, unless waived or deferred, all applications or supplements for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must contain data gathered using appropriate formulations for each required age group that are adequate to assess the safety and effectiveness in all relevant pediatric subpopulations and that support dosing and administration in each pediatric subpopulation.<sup>62</sup> For those products already marketed, FDA may require the sponsor to submit pediatric studies as supplements in certain circumstances.<sup>63</sup> If a study is performed as required under PREA, the drug may qualify for exclusivity under BPCA only if the exclusivity provisions are also met. Any studies conducted to qualify for pediatric exclusivity must be submitted *after* the written request for studies is issued,<sup>64</sup> but the completion of studies pursuant to a written request is not a guarantee that FDA will grant pediatric exclusivity.<sup>65</sup> To make a pediatric exclusivity decision, FDA considers whether the studies fairly responded to the written request, were appropriately conducted, and

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<sup>59</sup> Sponsors were required to annually submit information about the status of a deferred study (§ 505B(a)(3)(B)), and new provisions were added regarding the review of pediatric plans, assessments, deferrals, and waivers (§ 505B(f)), labeling changes (§ 505B(g)), the dissemination of pediatric information (505B(h)), and adverse event reporting (§ 505B(i)).

<sup>60</sup> Pub. Law No. 112-144 (July 9, 2012).

<sup>61</sup> “This section...also would clarify...that studies conducted under PREA could be included in a written request.” H.R. Report 112-495 (May 25, 2012), at 23. Note that this House Report accompanied a bill related to the one that eventually passed and was enacted as FDASIA.

<sup>62</sup> FDCA § 505B(a)(1), (2), *codified at* 21 U.S.C. § 355c(a)(1), (2).

<sup>63</sup> FDCA § 505B(b)(1), *codified at* 21 U.S.C. § 355c(b)(1).

<sup>64</sup> *See, e.g.*, FDA, “Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act” (September 2005), *available at* [www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079756.pdf](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079756.pdf), at 14 (hereinafter “Draft PREA Guidance”).

<sup>65</sup> GAO, Report GAO-11-457, “Pediatric Research: Products Studies under Two Related Laws, but Improved Tracking Needed by FDA” (May 2011), *available at* <http://www.gao.gov/products/GAO-11-457>, at 15, fn. c (“According to agency officials, FDA can deny a sponsor pediatric exclusivity, but still approve labeling changes based on the studies conducted.”).

were properly submitted.<sup>66</sup> These standards were established to avoid medically specious studies from providing market exclusivity.

## **II. Summary**

In summary, for more than 20 years FDA and Congress have attempted to address novel questions of pediatric safety for newly approved new drugs with mixed success. But again, neither has addressed the issue of contemporary labeling for historically approved drugs on the basis of data existing in FDA files or the literature.

### **Food and Drug Administration Amendments Act of 2007**

After almost two decades of focusing accelerating the new drug approval process, Congress shifted focus in the Food and Drug Administration Amendments Act of 2007 (“FDAAA”)<sup>67</sup> to the safety of drugs that were on the market and under development. FDA was granted authority to work with companies to require additional safety studies, limit distribution of drugs, revise labeling, and mandate labeling changes. These amendments complemented the historic FDA authority to review the required annual reports for NDAs, pharmacovigilance data, literature, and other information gathered by FDA to monitor approved drugs and improve their labeling.

The Agency unilaterally updated labeling for drugs when new evidence, not available when the drugs were originally approved, established the basis for the new information being called to the attention of prescribers and patients, through Federal Register notices or direct orders under the Administrative Procedures Act. FDA’s authority to act through rulemaking is, of course, indisputable. Further, under FDA case law, reconsideration of previously submitted or existing evidence is new evidence.

### **Conclusions and Recommendations**

A public health need exists for contemporary pediatric oncology drug product labeling. The patient, provider and payor communities will benefit from FDA updating this labeling. The lack of such labeling is contrary to the public health and health care economics. Historically, FDA has faced analogous situations where contemporary labeling of pharmaceutical products was necessary, and the Agency has unilaterally created procedures to address these issues. Creating reference products and reference product labeling has been a hallmark of FDA regulation for the efficient enforcement of the FDCA to establish safe and effective drug usage. The FDA procedures were transparent to ensure accuracy. Often they were multistep to provide public participation and confidence in the process, although that has not always been legally necessary.

Congress and FDA have long recognized the need to address safety questions associated with pediatric drug usage for unknown safety questions, and they have tediously worked on procedures. But they have never found a need to address the issue of updating labeling for old pediatric drugs, or even drugs approved for use only in adults. The need for full and accurate labeling of approved pharmaceuticals is a vital element in providing appropriate and cost effective health care. The ability of FDA to utilize data and information in its files to support labeling actions is indisputable. The availability of FDA to review existing data to provide evidence for new labeling is irrefutable. Theoretical arguments that unknown companies could utilize the public data to create some type of market exclusivity for pediatric uses for

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<sup>66</sup> GAO, Report GAO-11-457, at 13.

<sup>67</sup> Pub. L. No. 110-85, 121 Stat. 823 (2007).

these products have never been borne out in the decades and decades of addressing pediatric drug usage. These arguments also ignore the practical impact of health care formularies on the delivery of pharmaceuticals.

There is no legal impediment to FDA creating a procedure that establishes full and accurate contemporary reference labeling for pediatric oncology products. The Agency could publish the labeling as proposed or even final labeling in the Federal Register and take comments. Alternatively, it could make a copy the reference label available on its website and accept public to comment to ensure the labeling's completeness and adopt suggestions. FDA has a long history of such action, and in this time of public need such action is practical. Holders of approvals for these applications would be permitted a time to phase in the recommended labeling which would consistent with FDA historic action, Further because most of the pediatric oncology products are parenterals, and they are in drug shortage situations, the reference labeling could serve as the basis for facilitating new generic applications, which is consistent with sound public policy.