



***Dissemination of Information about Off-label Uses by Children Should be Generally Prohibited***

In thinking about the implementation of Chapter V, Subchapter D as it relates to children, it is necessary to analyze the three different possible types of information that might be disseminated:

- Type 1: Information about a drug that has been tested for safety for use by adults, but not for use by children, in which the additional information beyond that already on the label is only about use of the drug by children;
- Type 2: Information about a drug that has been tested for safety for use by adults, but not for use by children, in which the additional information beyond that already on the label is about a new indication or new use not specifically involving the use of the drug by children; and
- Type 3: information about a drug that has been tested for safety for use by children, in which the additional information beyond that already on the label is about a new indication or new use.<sup>1</sup>

The dissemination by the manufacturer of the different types of information should be treated differently by the regulations, both because of different risks to the public and because of different effects on policies aimed at developing additional data regarding the safety of drugs for children,

***Dissemination of Information about Off-label Use by Children is Not Included in Chapter V, Subchapter D because Children are Not a "Use"***

In general, the Foundation does not believe that children should be considered a "use" for a drug but rather a "user" of a drug. In its description and implementation of various sections of the Federal Food, Drug, and Cosmetic Act (FDCA), the FDA has interpreted the word "use" to

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<sup>1</sup> Arguably, this last type of information could be further subdivided as

(CL) information about a drug that has been tested for safety for use by children, but not for use by adults, in which the additional information beyond that already on the label is only about use of the drug by adults; and

(b) information about a drug that has been tested for safety for use by children, but not for use by adults, in which the additional information beyond that already on the label is about a new indication or new use not specifically involving the use of the drug by adults.

We do not make this further distinction because the situation will be rare (since few drugs are approved for children and not for adults) and the potential risks to safety are small (since it can be generalized that most drugs that are safe for children can be expected to be safe for adults).

be essentially equivalent to the conditions prescribed in the labeling of a drug. This interpretation would be consistent with the plain language of the statute, but for the fact that the FDA interprets “use by children” to be a “condition prescribed.”

A plain reading of the statutory language suggests that “under the conditions prescribed” refers to how a drug is to be taken (e.g., what dosage and how often) not by whom. This reading is supported by the statute’s legislative history, which indicates that the phrase “under the conditions proscribed” replaced language in an earlier bill that read “when used in the dosage, or with the frequency or duration, prescribed.”<sup>2</sup> It appears Congress replaced this limited and specific language with more general language in order to include additional conditions of use, e.g., the time a drug should be taken, whether a drug should be taken with or without food, or whether a drug will adversely interact with other drugs. All of these conditions of use are analogous to dosage and do not contemplate the classification of subgroups of the population as “uses” of the drug or “conditions of use” of the drug.

For the most part, the FDA’s subsequent interpretations of “under the conditions prescribed” (e.g., restricting distribution to certain facilities or to physicians with special training or experience, or conditioning distribution on the performance of specified medical procedures<sup>3</sup>) are consistent with this plain reading. Such conditions are “dosage-like” conditions of use, which expressly describe how - rather than by whom -- a drug is to be taken. Indeed, one of the few things a “condition prescribed” cannot be is “children,” for children are users, not a use.

With this in mind, the Foundation would first argue that the terms of Chapter V, Subchapter D do not require or even allow the dissemination of information about off-label use of any sort by children unless data supporting the safety and efficacy of the product in children have been submitted to the FDA and the directions for use by children have been included in the label. Dissemination of information described above as Types 1 and 2 should not be permitted.

### ***Dissemination of Information about Off-label Use by Children is a Risk to Safety***

The new off-label dissemination policy embodied in Chapter V, Subchapter D is clearly premised on the understanding that the drug at issue has been approved for at least one use. Obviously, an approved application includes basic safety data and a determination has been made by the FDA that benefits of the product outweigh potential risks and adverse events. Chapter V, Subchapter D was not adopted as a means of promoting new chemical entities whose safety profile is unknown. Rather, it was enacted as a means of allowing information to be circulated regarding already approved drugs whose safety profiles have been reviewed at least once by the

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<sup>2</sup> See S. 5, 75th Cong. § 17 (1937); see also H.R. 300, 75th Cong. § 17( 1937).

<sup>3</sup> See 21 C.F.R. 314.520 (1996).

agency, **Had** Congress **wanted to allow the dissemination of information about unapproved** drugs, it clearly **could** have done so; it did not.

However, very **few** approved drugs on **the market today** have been tested for safety in pediatric patients. This **has** been noted in the FDA's commentary to accompany proposed "Regulations Requiring **Manufacturers** to Assess **the Safety** and Effectiveness **of New Drugs and Biological Products in Pediatric Patients,**" (Docket **No. 97N-0 165**). As these proposed regulations **point** out, this **failure** to test a **drug** for safety when used by children poses a potential risk to the **health of** pediatric patients (which the proposed **1997** regulations **are** intended to address),

Drugs **without** pediatric information have, in effect, **never** met the approval standards for **safety** in children. They **thus do** not meet the premise on which Congress predicated **the new Chapter V, Subchapter D. Safety data** relevant to children have not been submitted to the agency. **The** agency **has** not determined that benefits **of the product** to children outweigh potential risks and adverse events in children. Instead, these drugs **are** comparable to **drugs** for which dissemination of information is not **allowed**, i.e., unapproved drugs.

Dissemination of information by manufacturers could, therefore, **be** dangerous to the public health. As **the** agency noted in its **1997** proposed rule on pediatric **drugs**, drugs that **are** safe when used by **adults** may pose significant **safety** risks for children. **The** Congress **has** also noted these risks in its consideration **of the new Section 505A.** **The** dissemination by manufacturers **of informat ion** for an off-label use of a drug by children when **the drug's** initial **approved** use **has** never been tested for pediatric safety **may** pose even more risk. **The** Foundation believes **that** Congress did not contemplate this special circumstance and did not intend this result. Thus, dissemination of information of Types 1 and 2 **should be** prohibited.

***Dissemination of Additional Information Regarding Off-label Uses of a Drug Tested for Safety for Use in Children is the Only Appropriate Application of Chapter V, Subchapter D to Pediatric Patients***

The Foundation does acknowledge that dissemination of information of Type 3 is within the scope of activities **covered** by Chapter V, Subchapter D. If a drug has been **tested** in children and approved as **safe** and effective for one **use**, **information** about another use by children is akin to the off-label information about **a new use of an adult drug** that the Congress clearly discussed and considered. Thus, if a drug **has** been **shown to be safe and effective** when taken by children for **asthma**, **information** about its off-label use by children for allergies might **be allowed**. Similarly, if a drug is approved to be **taken** by children in a **100-milligram dose three times a day**, information about children taking the drug in a **300-milligram dose once a day** might be allowed. The Foundation remains concerned that **the information be accurate, balanced, and regularly reviewed**, but it **cannot** request that **the agency** overrule this policy adopted by the Congress.

***Allowing Dissemination of Information Targeted Toward Children Will Impede Other Statutory and Regulatory Measures Designed to Improve Pediatric Information***

The 1997 FDA regulations regarding pediatric use and the new Section 505A of the FDCA demonstrate that both the agency and the Congress are concerned about the development of adequate pediatric data for the safe use of drugs by children. These two measures lay out complementary and important methods of requiring and encouraging research activities by manufacturers and should be treated as at least as important as the effort to allow the dissemination of information about off-label uses of approved drugs. The Foundation would argue, therefore, that if there are any ambiguities in the meaning or Congressional intent surrounding Subchapter D of Chapter V, they should be resolved in a manner most likely to advance the development of pediatric data. With that in mind, the Foundation believes that the dissemination of information regarding off-label use of a drug by children would significantly impede the development of pediatric data.

***Loss of Usual Market Incentives to do Research***

In addition to the safety risks outlined above, permitting distribution of information regarding off-label use by children will defeat basic marketplace incentives to develop pediatric studies. Clearly the major incentive for a manufacturer to do research on a new aspect of a drug is so that it may add new directions, indications, or sorts of uses to the drug's label and thus promote wider sales of the drug. While it has been acknowledged by many (including the Foundation) that such market forces are often inadequate to encourage manufacturers to perform the appropriate studies in pediatric populations, these forces may encourage pediatric research in some instances or in combination with other incentives and requirements. The permission for manufacturers to disseminate information about off-label uses by children would interrupt and lessen such usual market incentives by allowing the promotion of pediatric sales long before pediatric studies have been completed and reviewed.

***Inappropriate Extension of Incentives for Manufacturers***

Furthermore, allowing distribution of off-label information targeted towards increasing sales to children will impede a delicately-achieved balance regarding incentives provided to manufacturers in exchange for conducting pediatric research. Under Section 505A, manufacturers may obtain six months of extra marketing exclusivity in exchange for completing pediatric studies. There was a lively Congressional debate in the drafting of Section 505A regarding what would constitute a sufficient incentive for manufacturers to conduct pediatric studies. It was clear to Congress that pediatric testing is urgently needed -- so much so that Congress was willing in some cases to offer extra market exclusivity to get manufacturers to produce pediatric studies. The conclusion reached by Congress was that six months of additional marketing exclusivity would be sufficient (or more than enough) incentive. Allowing distribution of off-label information would give manufacturers a windfall of at least 36 months to promote pediatric sales over and above the statutory award of exclusivity and, more significantly,

to do so without being required to complete their research first. By speaking so specifically on the topic of pediatric exclusivity in Section 505A, and by implicitly ratifying the FDA's 1997 regulations in Section 505 A(i)<sup>4</sup>, Congress laid out a clearly defined system of regulation for pediatric studies. A general provision such as Subchapter D of Chapter V should not be used to impede these targeted activities.

### ***Clarification of Time Frames is Needed***

This proposed regulation could also create confusion in relation to the time limits suggested in the proposed 1997 regulations on pediatric research. The proposed pediatric regulations suggest a compliance date (by which time the manufacturer must have submitted adequate pediatric data as part of a New Drug Application (NDA)) of twenty-one months for drug applications submitted to the FDA before the rule's effective date or fifteen months for those drug applications submitted on or after its effective date. While the Foundation continues to believe that the compliance times in the proposed pediatric regulation are too long (as was discussed in the Foundation's comments on that proposed rule), the time frame in the final pediatric regulation will be significantly less than the 36 months allowed in this more general rule regarding dissemination of information on off-label uses. At the very least, the FDA must clarify that any time limits established in this dissemination regulation will not override time limits created under separate regulatory and statutory authority. If, under FDA separate authority, manufacturers are required to conduct pediatric tests within a shorter timeframe than that mandated by the dissemination regulation, manufacturers must not be allowed to avoid such a shorter timeframe by voluntarily beginning dissemination of information. To allow such an outcome would have the perverse effect of delaying research because a manufacturer circulates information about fragmentary research. As discussed above, the Foundation believes that the dissemination option should not even exist in regard to children: Manufacturers should not have the option of disseminating information regarding off-label use of a drug by children despite an absence of pediatric studies. If the FDA insists that manufacturers have the option to disseminate pediatric information, the regulation must make clear that it cannot be used to defeat time limits established under separate authority.

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<sup>4</sup> In Section 505A, providing additional market exclusivity when pediatric studies are conducted, Congress explicitly acknowledges that the FDA may require pediatric studies. The law states that "if any pediatric study is required pursuant to regulations promulgated by the Secretary" and meets the requirements of the new law, market exclusivity should be provided. The Conference Report also refers to data collected before or after a "request or requirement by the Secretary," further emphasizing the point that Congress recognized and accepted that the FDA would be requiring pediatric studies.

### ***Exemptions – Ethical and Cost Considerations***

While Subsection (d) of Section 554 provides for the possibility of an exemption to the completion of study requirements of the other parts of that section, the Foundation would argue that exemptions should be granted only in extremely limited circumstances, Congress has clearly indicated that exemptions are to be rare, Subchapter D was designed as a way of allowing some information dissemination, but only when manufacturers have committed themselves to completing the research to get new uses on a product label, Such an outcome attempts to balance the dangers of off-label uses with the guarantee of proper clinical studies, If a manufacturer is unwilling or unable to conduct the clinical studies necessary to submit an SNDA, the appropriate response of the agency should be to forbid dissemination of off-label information by the manufacturer. Manufacturers are not the only, or even the best, source of information about most drugs, The usual reason for manufacturers to disseminate information about their products can be anticipated to be the increase of sales of that product for a use not demonstrated to be safe and effective. The public interest both in safety and in the development of safety data should outweigh such sales goals.

If the FDA insists on permitting dissemination of Type 1 and Type 2 information described above, the agency must take special care to keep pediatric exemptions extremely rare. As described above, children are in an exceptional situation regarding drugs. Most drugs are approved without basic safety information for children. Therefore, allowing manufacturers to promote an off-label use of a drug in children is a risky proposition, even with the distant prospect of the eventual completion of clinical studies of the use in children. Granting an exemption from the study requirement, considering the dangers particular to children, can almost never be justified.

The agency must also take care in how it interprets evidence that a new use represents “standard medical treatment or therapy” as an element of ethical considerations. Given the present dearth of pediatric information on drugs, many physicians are forced by circumstances to prescribe drugs without pediatric information to children. Manufacturers must not be allowed to take advantage of a situation of their own creation. “Standard” treatment or therapy is not the same as a treatment or therapy that is regularly used because physicians have no other choice, Any more lenient interpretation would virtually eliminate the requirement for completing any pediatric research. While the Foundation is extremely sensitive to the question of withholding potentially effective treatment from patients<sup>5</sup>, it believes that research on “standard” treatments can be ethically developed.

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<sup>5</sup> Indeed, one of the bases for the Foundation’s vigorous pursuit of pediatric research regulations and incentives is to end the practice of withholding potentially safe and effective drugs from children because of a lack of appropriate data.

The cost considerations allowing an exemption must also be very stringent. Permitting a manufacturer to avoid completing clinical studies based on costs is actually an ethical decision. It is, in effect., placing a monetary value on people's lives and safety. The Foundation is particularly concerned about the use of this exemption when children are involved. To date, manufacturers have rarely found safety and effectiveness information for children lucrative enough to motivate studies. If manufacturers are now allowed to put a price tag on children's safety, claiming that cost considerations prohibit them from gathering clinical safety and effectiveness information about a use they are promoting, that price tag must be extremely high. In its worriments on the 1997 pediatric regulations, the Foundation opposed any granting of a waiver of research requirements because of cost concerns. While the Foundation recognizes that the Congress explicitly allowed for the granting of a exemption for reasons of cost, it would argue that exemptions from research requirements should almost never be granted in the case of information described above as Types 1 or 2. In those situations, the risks and potential costs of failure to conduct research on safety in children dramatically outweigh the manufacturer's interest in promoting sales to children.

Finally, the Foundation would argue that, given the importance of decisions made regarding whether or not to grant an exemption, the entire exemption process must be made public.<sup>6</sup> Ethical and cost decisions must not be made behind closed doors, without a public opportunity to participate in decisions as to the ethics and value of children's health and safety. All information should be made public from the moment a manufacturer requests an exemption, so that interested parties can have input into the decision, Moreover, if such an exemption is granted (or is deemed granted), all information regarding that exemption must be made public so that interested parties such as the Foundation will be able to play a role in keeping the FDA informed as to when it should revoke an exemption.

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<sup>6</sup> The Foundation would further point "out that any information that is disseminated, along with information provided to the FDA before dissemination begins, must be accessible to the public. Interested parties such as the Foundation, who are not members of industry or the FDA, will play an important role in public safety. First, patients and their advocates must be able to obtain all information being disseminated to their health care providers in order to make the most informed decisions about care; to achieve that end, all disseminated information should be placed on the public docket. Second, patients and their advocates will often be among the best-informed sources of information on the off-label uses suggested by the manufacturers. As the FDA determines what additional information it should require a manufacturer to disseminate, both before dissemination begins and once it has started, the public will be able to play an important role in providing balanced information. Third, interested parties deserve to know whether promised clinical studies will be conducted and, as described in the text accompanying this footnote, to have the information necessary to participate fully in decisions regarding exemptions. Finally, patients and their advocates must be able to monitor the progress or delay of clinical trials.

### ***Prominently Displayed Statements Regarding Absence of Pediatric Data***

The FDA should **ensure** that manufacturers disclose **the absence** of pediatric information in the prominently **displayed** statement required under § 99.103. As can be seen **from** the agency's discussion of **the** proposed 1997 pediatric **regulations**, many physicians prescribe drugs **to** children **for** both approved and off-label indications **of** drugs that **have been** tested **only** in adults despite **the absence of** any pediatric **information**. When dissemination **of** information about off-label uses of Q drug **in** adults is permitted, **it can be** expected **that many** physicians will construe this information **as being** applicable to children. This means **that** physicians might inadvertently prescribe drugs to **children** for a promoted **off-label** use without even **the most basic safety information** in children.

**The** presence or absence **of** children in trials described in disseminated information should be made explicit and **clear to** the recipients of such information. **If there have been** no **safety or** effectiveness studies conducted in pediatric patients, the information should note that **fact**. Therefore, the FDA should require an additional statement for **drugs that have not** undergone the pediatric testing required by **the** FDA to **prove safety and** effectiveness. Immediately following the sentence required under § 99,103 (a)(1)(i) ("This information concerns **a use** that has not **been** approved by the Food and Drug Administration and is being disseminated under section 551 *et seq.* of **the** Federal Food, Drug, and Cosmetic Act."); manufacturers should **be** required to state: "Safety and effectiveness **in** pediatric patients **have** not been established for this product **for the use** that has been approved by the FDA or **for the use** suggested by this information," With this disclaimer or one similar to it, misunderstanding **of** disseminated information might be Minimized.

### ***Miscellaneous***

**The** FDA should require manufacturers to keep records of **the** individual recipients **of** disseminated information. If **the** manufacturer **had the** ability to send out the information **in the first place**, it is not **too** much to expect the manufacturer to **be able to send out** subsequent information or warnings to the same individuals. Considering the **health and safety issues at stake**, the FDA must be assured that every person receiving disseminated information **can** be contacted with subsequent **data**.

Manufacturers must **cease** dissemination if they **fail to comply** with **the** statutory and regulatory requirements. **It is essential that the** FDA be quickly informed of this failure to comply. Therefore, there should be no doubt **that** a manufacturer must notify **the** FDA of any failure to comply as soon **as the** manufacturer **realizes the failure** and ceases dissemination. **The last sentence of § 99.401(e), addressing** cessation **of** dissemination, should be **changed to read:** "A manufacturer shall notify **FDA** immediately if it **ceases dissemination** under this **paragraph.**"

The Foundation must also take issue with the discussion in the "Analysis of Impacts" section accompanying the proposed regulation. While **the** FDA has discussed **the** potential

benefits of the proposed rule, related to public health gains, the agency has not seen fit to address the potential costs to public health, Before an SNDA is approved by the FDA, there is no established safety and effectiveness for an off-label use. Allowing promotion of off-label uses will likely lead to more occasions when a drug is used off-label in a way that clinical studies later demonstrate is unsafe or ineffective. There will be dangers to the public health arising from both the adverse effects of an off-label use and the failure to use an approved therapy in favor of an off-label use later shown to be ineffective. Considering the absence of pediatric information for the majority of drugs and the limited number of approved treatment options for children, the costs to the public health of such risks to children could prove to be especially dire. The FDA should take note of these potential costs to public health in its analysis,

### **Conclusion**

The Foundation believes that the application of this regulation to drugs not tested for safety in children is inappropriate. Dissemination of information regarding off-label use by children (whether Type 1 or Type 2) is a risk to children's health and will impede other efforts to promote pediatric research. The Foundation would urge that the FDA strictly limit the applicability of Ibis regulation to minimize these outcomes.

The Foundation instead looks forward to working with the agency on the implementation of the 1997 regulations regarding pediatric use and of Section 505A of the FDCA. These actions will have the effect of genuinely improving pediatric research and giving children the full benefits of new therapies as they are developed.

Sincerely,



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