RETROSPECTIVE REVIEW OF INFORMATION SUBMITTED AND ACTIONS TAKEN IN RESPONSE TO PREA 2003

Executive Summary

Section IV of the Food and Drug Administration Amendments Act of 2007, the Pediatric Research Equity Act (PREA 2007), requires the internal committee, Pediatric Review Committee (PeRC), to conduct a retrospective review of information submitted and actions taken in response to PREA 2003. The PeRC has produced this report in response to section 505B(f)(5) of the Federal Food, Drug, and Cosmetic Act (the Act).

When performing the retrospective review, members of the PeRC queried the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) databases for new drug applications (NDAs) or biologics license applications (BLAs) and supplements to such applications that had triggered PREA 2003 and were approved during the period covering January 1, 2004, to September 27, 2007. FDA selected this time frame because it encompassed the time period after passage of PREA 2003 and before passage of PREA 2007 (and, thus, before the establishment of and oversight provided by the PeRC).

Pediatric assessments were reviewed for quality and consistency, and waivers and deferrals were reviewed for appropriateness. Although most of the assessments were of good quality and the waivers and deferrals were appropriate, there are some elements in the process that need improvement. The establishment of the PeRC provides a mechanism for addressing many of these elements. The PeRC made general recommendations to review divisions based on the retrospective review. Many of these recommendations will also be incorporated into the draft guidance for industry *How to Comply with the Pediatric Research Equity Act* when it is finalized.

I. BACKGROUND

Statutory Requirement

The PeRC has produced this report in response to section 505B(f)(5) of the Act. PREA, which was enacted on December 3, 2003, amended the Act by adding section 505B (21 U.S.C. 355B), and was reauthorized and expanded in PREA 2007. PREA 2007 requires the PeRC, established under section 505C of the Act, to conduct a retrospective review of information submitted and actions taken in response to PREA 2003. PREA 2007 states in part:

> ‘‘(5) RETROSPECTIVE REVIEW OF PEDIATRIC ASSESSMENTS, DEFERRALS, AND WAIVERS.—Not later than 1 year after the date of the enactment of the Pediatric Research Equity Act of 2007, the committee referred to in paragraph (1) shall conduct a retrospective review and analysis of a representative sample of assessments submitted and deferrals and

waivers approved under this section since the enactment of the Pediatric Research Equity Act of 2003. Such review shall include an analysis of the quality and consistency of pediatric information in pediatric assessments and the appropriateness of waivers and deferrals granted. Based on such review, the Secretary shall issue recommendations to the review divisions for improvements and initiate guidance to industry related to the scope of pediatric studies required under this section."

This study was conducted from August 2008 to April 2009. It was conducted internally by members of the PeRC and other FDA staff in CDER and CBER. This group selected a representative sample of applications to include in the review, conducted the review, and assisted in the drafting of this report. Additional details of how the selection was made and the process that was used to review the applications are discussed at length in section II of this report.

Definitions of Terms Used in this Report

Deferral – A deferral is issued when a pediatric assessment is required but has not been completed at the time the NDA, BLA, or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if FDA finds that the drug or biological product (hereafter *product*) is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

Full Waiver – FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients.

Partial Waiver – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted on the grounds that a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

Pediatric Assessment – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

Pediatric Page – The Pediatric Page is the form that the review divisions complete for all NDAs, BLAs, or supplemental NDAs or BLAs. This form indicates whether the application triggers PREA, and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If FDA is waiving or deferring any or all pediatric studies, the Pediatric Page also includes the reason(s) for the waiver and/or deferral.[1]

Pediatric Plan – A pediatric plan is a statement of intent submitted by the applicant outlining the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant plans to conduct (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and, under PREA 2007, must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and (3) submit the study reports.

Pediatric Rule – The Pediatric Rule was a final rule issued by FDA on December 2, 1998 (63 FR 66632), and suspended by court order on October 17, 2002. Under the Pediatric Rule, approval actions taken on or after April 1, 1999, on applications that were submitted for changes in active ingredient, indication, dosage form, dosing regimen, or route of administration, were required to include pediatric assessments for indications for which applicants were receiving or seeking approval in adults, unless the requirement was waived or deferred. PREA 2003 codified elements of the suspended Pediatric Rule and attempted to fill gaps left by the Pediatric Rule's suspension.

PeRC – The Pediatric Review Committee (PeRC) is the internal review committee established under section 503C of the Act. This committee includes employees of FDA with expertise in pediatrics, biopharmacology, statistics, chemistry, legal issues, pediatric ethics, and other appropriate expertise. With regard to PREA, the committee consults on pediatric plans and assessments and reviews all requests for deferrals and waivers before the approval of an application that triggers PREA.

PMC/PMR – Postmarketing commitments (PMCs) and postmarketing requirements (PMRs) are studies that FDA requires an applicant to conduct after approval of a product. Under PREA 2003, all deferred pediatric studies were referred to as required postmarketing commitments that were posted along with the status of the studies on the FDA Web site. Under PREA 2007, these required PMCs are referred to as PMRs and additional details about the progress of the studies are posted on the FDA Web site.

[1] The Pediatric Page was developed by CDER, and was not routinely used by CBER before the passage of PREA 2007.

Written Request – A Written Request is a specific document from FDA, issued under section 505A of the Act, in which FDA requests submission of specific studies to determine if the use of a product could have meaningful health benefits in the pediatric population. FDA may issue a Written Request for those studies at the request of an interested party or on its own initiative. Issuance of a Written Request to an applicant does not require the applicant to conduct pediatric studies described in the Written Request. It is the applicant's decision whether to conduct the studies and possibly gain pediatric exclusivity. It is FDA's policy to offer applicants the opportunity to qualify for pediatric exclusivity for studies required and conducted under PREA. Under this policy, however, FDA will not issue a Written Request for, or grant pediatric exclusivity for, studies that have been submitted to FDA before the Written Request is issued.

II. STRATEGY FOR RETROSPECTIVE REVIEW

Application Selection Strategy

PREA 2003 (and PREA 2007) requires all NDAs, BLAs, or supplements to an NDA or BLA that an applicant submits under section 505 of the Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (section 505B(a) of the Act). Generally, the pediatric age range for product labeling, and thus for which an assessment is required, is birth through 16 years (21 CFR 201.57(b)(9)(iv)).

When performing the retrospective review, members of the PeRC queried CDER and CBER databases for NDAs and BLAs (and supplements to such applications) that had triggered PREA 2003 and were approved during the period covering January 1, 2004, to September 27, 2007. FDA selected this time frame because it encompassed the time period after passage of PREA 2003 and before passage of PREA 2007 (and, thus, before the establishment of and oversight provided by the PeRC). This time frame is also expected to better identify for PeRC the scientific and procedural matters on which the review divisions need to focus.

The initial lists of products identified 1,129 waivers, deferrals, and pediatric assessments, as shown in Table 1. These product applications were sorted by review division and included those applications and supplements during the selected time period that contained: (1) pediatric assessments; (2) full waivers; (3) partial waivers; or (4) deferrals. A subset of product applications from each list was chosen for the retrospective review.[2] As shown in Table 2,

[2] For each list of applications and supplements approved by CDER, every fifth application was chosen for retrospective review. If there were so few products in a particular review division that there would not have been a selection for that division using this methodology, the first product in that division was chosen and then the count of five was begun again. Upon detailed review of the applications, some errors in classification were discovered (e.g., product was not identified as an orphan and therefore was counted among the PREA numbers when it did not trigger PREA). When these errors were discovered, another application from that review division

CDER review divisions were sorted by the mail code number that, until recently, was used to identify that division (e.g., Cardio Renal is 110, Neurology is 120).

was selected in its place. In some instances, additional applications outside the stated review window were reviewed because of the potential to provide additional information. Because of small numbers, sorting by review divisions in CBER was not practical, so for each list of applications and supplements approved by CBER, every other application was chosen for review.

Table 1. Number of Waivers, Deferrals, and Assessments Identified (January 1, 2004 to September 27, 2007)

Review Division	Waivers	Deferrals	Assessments	Total
107 – Biologic Oncology	5	1	0	6
110 – Cardio-Renal	32	10	11	53
120 – Neurology	40	42	11	93
130 – Psychiatry	27	19	7	53
150 – Drug Oncology	29	0	11	40
160 – Medical Imaging/Hematology	6	10	7	23
170 – Anesthesia, Analgesia, Rheumatology	36	37	16	89
180 – Gastroenterology	23	26	12	61
510 – Metabolic and Endocrine	87	36	29	152
520 – Anti-infective and Ophthalmology	28	12	31	71
530 – Antiviral	15	38	14	67
540 – Dermatology and Dental	40	8	26	74
560 – Nonprescription Clinical	23	16	20	59
570 – Pulmonary	55	40	45	140
580 – Reproductive and Urology	44	8	4	56
590 – Special Pathogens and Transplant	17	27	15	59
CBER (OVRR, OBRR)	17	8	8	33
Total	524	338	267	1,129

Table 2. Review Cohort of Waivers, Deferrals, and Assessments Reviewed for Inclusion in the Retrospective Review, Sorted by Division (January 1, 2004 to September 27, 2007)

Review Division	Waivers	Deferrals	Assessments	Total
107 – Biologic Oncology	1	1	0	2
110 – Cardio-Renal	6	1	1	8
120 – Neurology	3	5	3	11
130 – Psychiatry	5	2	1	8
150 – Drug Oncology	6	0	0	6
160 – Medical Imaging/Hematology	2	1	0	3
170 – Anesthesia, Analgesia, Rheumatology	4	4	2	10
180 – Gastroenterology	4	4	1	9
510 – Metabolic and Endocrine	13	4	4	21
520 – Anti-infective and Ophthalmology	4	1	5	10
530 – Antiviral	2	5	2	9
540 – Dermatology and Dental	5	1	3	9
560 – Nonprescription Clinical	3	1	2	6
570 – Pulmonary	7	4	5	16
580 – Reproductive and Urology	9	1	0	10
590 – Special Pathogens and Transplant	3	4	1	8
CBER (OVRR, OBRR)[1]	9	4	4	17
Total	86	43	34	163

[1] It should be noted that the waiver count for CBER products included in the retrospective review (nine) includes two applications that included a total of four partial waivers for vaccinations where the population studied was in the middle of the pediatric age range. For purposes of this report, each is counted twice, because in both cases it was determined that the waiver for one pediatric age group was appropriate and the waiver for the other age group was not appropriate.

Strategy to Determine Quality and Consistency of Assessments

When reviewing the assessments for quality and consistency, FDA medical officers from CDER and CBER reviewed the approval packages and other relevant documents (e.g., pediatric pages, product labeling, Written Requests, approval letters, and medical reviews). Their review was designed to answer the following list of questions, based on the elements in each assessment, using a yes/no/not applicable response.

1) Did the assessment use the appropriate formulations for each age group?
2) Is there adequate data to assess the safety and effectiveness of the product?
3) Is there adequate data to support the dosing and administration for each pediatric subgroup?
4) Was there a Written Request that potentially influenced the conduct of the studies? (CDER only)

5) Were the studies conducted consistent with the PREA PMC/PMR in those cases where there was a PMC/PMR?[3]
6) Did the studies lead to labeling changes that reflected the outcome of the studies?

Medical officers provided an explanation of each yes/no response based on review of relevant documents.

Strategy to Determine Appropriateness of Waivers

When reviewing the full waivers and partial waivers for appropriateness, FDA staff examined the relevant documentation, including approval letters, clinical reviews, and/or Pediatric Pages to identify the stated reason for the waiver or partial waiver, and then determined whether the waiver or partial waiver was appropriate. To make this determination, the first criterion was whether the reason for waiver or partial waiver was one of the following reasons provided for in the statute:

1) Studies are impossible or highly impractical (because, for example, the number of patients in the waived population is so small or the patients are geographically dispersed)[4]
2) There is evidence strongly suggesting that the product would be ineffective or unsafe in the waived population
3) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in the waived population AND the product is not likely to be used by a substantial number of patients in that pediatric age group
4) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed (for partial waivers only)

If the review division identified a reason other than those reasons above for granting a waiver, the waiver was judged to be not appropriate and no further review by a medical officer was required. If the review division selected any of the reasons above, and the indication was one for which FDA routinely waives pediatric studies (e.g., treatment of breast cancer), no further medical officer review was required. However, if the waiver raised any questions at all, a second review by a medical officer was conducted. Additionally, waivers granted for reasons 2 and 3 were referred to a medical officer for a second review because those reasons tend to be the ones that tend to raise the most issues. For the waivers or partial waivers with a second review by a medical officer, the medical officer stated whether he or she agreed that the waiver was properly granted and explained the scientific rationale for concurrence or nonconcurrence.

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[3] Note that when all necessary pediatric studies are included in the original application, no PREA PMC/PMR is needed. In addition, as a result of confusion caused by timing gaps after the Pediatric Rule was suspended, some products that had pediatric studies deferred before the passage of PREA 2003, but which were later brought within the scope of PREA 2003, were never properly recorded as PREA PMCs/PMRs.

[4] Reasons given by the review divisions that were included in this category were that the disease does not exist in children, the disease is rare in children, or children are too geographically dispersed.

Strategy to Determine Appropriateness of Deferrals

When reviewing deferrals, FDA staff examined the relevant documentation, including the Pediatric Page, the approval letter, and the clinical review, to determine the reason for granting the deferral. Under the statute, appropriate reasons for deferral include: (1) the product is ready for approval for use in adults before pediatric studies are complete; (2) pediatric studies should be delayed until additional adult safety or effectiveness data have been collected; and (3) there is another appropriate reason for deferral. FDA staff also examined the approval letter for each application reviewed to see if it contained PMC/PMR language indicating that a plan had been submitted and studies deferred. FDA used the following criteria to determine if the deferral was appropriate:

1) If the approval letter instructed the applicant to submit its plan, the deferral was considered to be inappropriate because the plan had not been submitted before approval in accordance with the law.[5]
2) If the approval letter had PREA PMC/PMR language, the deferral was considered to be appropriate.
3) If the approval letter simply stated that FDA was deferring studies, FDA examined the action package for separate letters granting the deferral, meeting minutes, or any other documents that provided information about the deferral. If there was documentation regarding a PREA PMC/PMR and the date the studies are due, the deferral was considered to be appropriate if the deferral criteria were met. In the absence of such documentation, the deferral was considered to be inappropriate.

III. RESULTS OF ANALYSIS

Below is a sampling of the issues FDA identified in its retrospective review of pediatric assessments and grants of waivers and deferrals under PREA 2003.

Assessments

Overall Quality of Assessments Submitted to Fulfill Postmarketing Requirements: The assessments submitted in response to PREA PMRs were generally of good scientific quality and the data were robust, providing adequate information to assess the safety and effectiveness of each product, resulting in labeling when products were efficacious. In the majority of cases, sufficient pharmacokinetic data were obtained to guide dosing and the age groups selected were appropriate.

[5] PREA 2003 (as does PREA 2007) required the applicant to submit the pediatric plan before approval of its product. Thus, although some approval letters before passage of PREA 2007 included language requiring the applicant to submit its pediatric plan within 120 days after approval, deferrals in the context of submission of a pediatric plan subsequent to approval were considered presumptively inappropriate.

Scientific quality problems were identified, particularly in the early years of PREA 2003. These included recurring issues of inadequate approaches for dose selection. In the instances where efficacy was not established, there were a variety of possible explanations for this failure. Some of the studies may not have had adequate prior dose finding studies and the single dose selected for use in the pivotal trial was not the dose that would have resulted in efficacy. Some studies were not large enough to demonstrate a difference between the product being studied and the control. Although difficulty in enrolling patients in pediatric clinical trials is a well-established barrier to successful studies, more often, the studies were too small to demonstrate an effect because statistical estimates were not performed before initiation or were unrealistic. For cases where studies did not demonstrate efficacy, it is possible that the process could have benefitted from a more detailed pediatric plan being submitted by the applicant before approval, or by the review division making more specific recommendations on that plan before study initiation.

With 17 review divisions within CDER and few or no pediatricians in some divisions, approaches in the implementation of PREA, including the level of detail in reviewing pediatric protocol plans, were quite variable. The current process involving review by the PeRC has added an opportunity to provide more pediatric input into the decision making concerning the need for pediatric studies and additional consistency to the process.

Review of applications for this retrospective review indicated that many of the pediatric postmarketing requirements listed in the approval letters were described in general terms in one to three sentences. Although this is a typical format for PMCs/PMRs included in approval letters, the lack of details regarding PREA PMCs may have contributed to the broad range in quality of studies submitted to fulfill the PREA requirement. Where there was evidence of specific discussion and documentation of the studies needed to fulfill the PREA requirements before commencement and/or submission of the studies, the PREA assessments generally were of higher quality.

The benefit of documented discussion is illustrated by one product for which the language in the approval letter describing the required postmarketing commitment was vague. However, there was documentation of discussions with the applicant during which the review division provided specific advice regarding the design of the required studies in pediatric patients. The division had documented its detailed advice on the applicant's proposed pediatric plan. When the full study reports were submitted and it was clear that the applicant had not conducted the studies as it had committed to do, and safety and efficacy had not been established, the review division was able to tell the applicant that it had failed to meet the requirements in the PMC and did not release it from the obligation to study pediatric patients. If the review division had not documented its discussions with the applicant regarding the design of the pediatric studies, the vague language concerning the PREA PMC in the approval letter would have made it more difficult to reject the submitted assessments as being insufficient to meet

PREA requirements. Unfortunately, documentation of such discussions for other applications were not always available.

The importance of detailed discussions between the applicants and FDA and documenting scientific advice was borne out in reviewing products that had both a PREA requirement and a Written Request (a total of three products). For these products, the pediatric development program and resulting pediatric assessments tended to be more complete. This may have been because applicants who received Written Requests had increased communication with FDA about the pediatric studies that FDA believed were necessary to label the product for relevant pediatric populations, and/or because those studies were described in greater detail in the Written Request than in a typical PREA PMC.

Consistency of Assessment Format: Before passage of PREA 2007, some studies conducted in response to a PREA PMC were not submitted in a supplemental NDA or BLA, but rather as final study reports to the investigational new drug application, annual report, or other general correspondence. In these cases, there was no timeline for review of the information submitted, and no mechanism for labeling unless the division requested a labeling supplement from the applicant.

Timing of Studies: In some cases, pediatric pharmacokinetics were integrated into phase 3 studies. Although appropriate in some cases, it is preferable that characterization of product absorption, distribution, metabolism, and elimination in pediatric patients, as well as appropriate doses, are determined early in the product development program before studies to determine safety and efficacy. There is evidence that initiation of a phase 3 study in pediatrics with a single empiric dose is associated with a greater potential for the study to fail to demonstrate efficacy.

Demographics: Because PREA requires studies only in the specific indication or indications for which the triggering application is approved, in some cases the required studies were applicable to older children but not to younger children and newborns. Studies in the neonatal/infant population were frequently waived because the indications for which the product was being approved in adults do not occur in the neonatal/infant population; however, that particular population often has unique medical conditions that do not occur in adults. Because of this fact, opportunities to study important potential uses may have been missed because there was no legal requirement under PREA to conduct those studies. For example, under PREA a product approved for the treatment of chronic myeloid leukemia in adults might have the potential for activity against neuroblastoma in younger children, but studies could not be required as it is not the same indication as that in the application that triggered PREA.

Age-Appropriate Formulation: An age-appropriate formulation was used in all studies that were reviewed. In most cases, an age-appropriate formulation (e.g., intravenous solution, oral suspension, tablets/capsules for older children) was already available before the conduct of the pediatric studies. In some cases, new oral formulations (e.g., suspensions, solutions) were

developed for studies in pediatric patients who could not swallow a tablet, but in most of these cases, efficacy was not established in the populations requiring the new pediatric formulations, no indication was obtained for use in these populations, and, thus, the new formulations have not been marketed. (See additional comments on formulations under Waivers.)

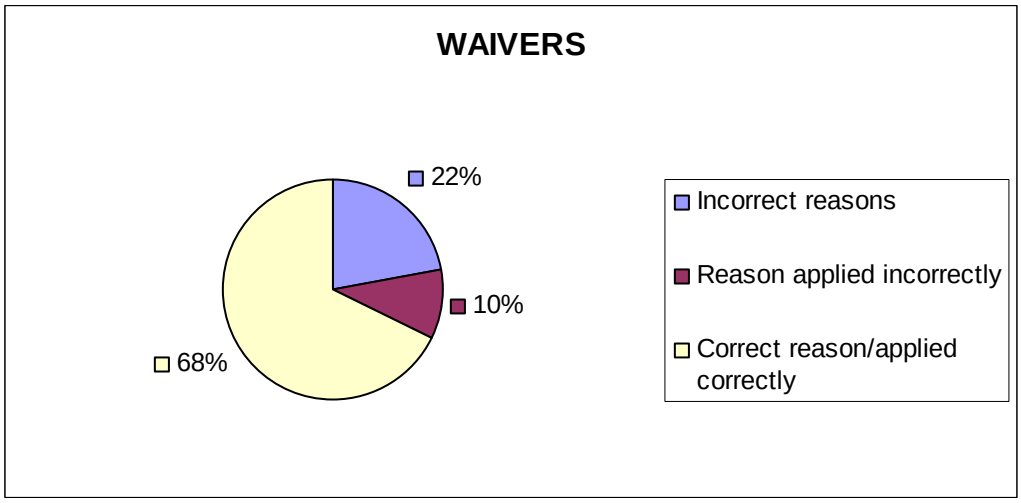
Additional Information Regarding Assessments

Labeling: Results from pediatric assessments were not consistently incorporated into labeling. Even in those cases where the results of pediatric studies were reported in labeling, the section of labeling where information was included was not consistent. For example, some labeling contained information regarding pediatric use in the Clinical Pharmacology section when an indication was not granted and failed to provide any information in the pediatric use subsection of labeling; others provided relevant information in the pediatric use subsection of the labeling.

Waivers

Although the majority of the waivers that FDA staff reviewed were appropriate, it appears that a number of waivers granted under PREA 2003 were granted in error, as shown in Figure 1. Of the 87 waivers that were reviewed, 19 (22 percent) were granted for reasons that were not consistent with criteria defined under PREA. In addition, 9 (10 percent) of the waivers that were reviewed and were granted using appropriate reasons provided in the law (as described in section II, Strategy for Retrospective Review) should not have been granted because the waiver criteria appear to have been applied incorrectly to the products at issue and thus were not in fact met.

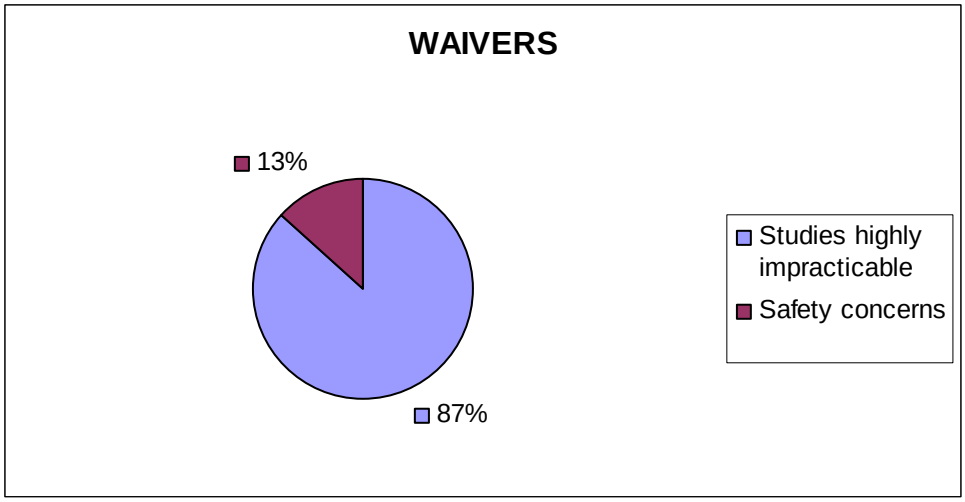
Figure 1. Breakdown of Reasons for Waivers Granted



Most of the waivers were granted for reasons permitted under PREA 2003. Of these waivers, 59 (87 percent) were granted because studies would be impossible or highly impracticable; the remainder of the waivers was granted because of safety concerns, as shown in

Figure 2. None of the applications in the review received waivers because the product did not represent a meaningful therapeutic benefit over existing therapies and would not be expected to be used in a substantial number of pediatric patients. In addition, none of the partial waivers reviewed were granted because the applicant could not develop an age-appropriate formulation.

Figure 2. Breakdown of Waivers Granted Appropriately



The Pediatric Page may have contributed to inappropriate waivers being granted. For waivers that were granted for reasons that were not permissible under PREA 2003 (or for that matter, are not under PREA 2007), the main reason cited was "products in this class for this indication have been studied/labeled for the pediatric population." Although this reason was not included in PREA 2003 (and is not included in PREA 2007), until recently it was listed as a waiver option on the Pediatric Page.[6] The Pediatric Page has since been revised to eliminate this option for granting a waiver and to reflect only those grounds for waiver that are permissible under the statute. In some of the cases where this impermissible reason was cited, it is possible that it would have been appropriate to waive studies under the criteria provided in the statute. For some of these therapies, it is possible that there was no meaningful therapeutic benefit over existing therapies labeled for pediatric use and the product would not be expected to be used in a substantial number of patients in that age group, because of the number of already approved and labeled products in that class for that indication.

[6] It should be noted that the Pediatric Page (the form provided for review divisions to document their actions with respect to the Pediatric Rule) was not revised to reflect the reasons for waiver when PREA 2003 was enacted. Reasons for waiver or partial waiver under the Pediatric Rule were more expansive and included such rationale as "Products in this class for this indication have been studied/labeled for the pediatric population," and "other." Neither of these reasons is considered to be a valid reason for waiver under PREA. (See Appendix A for Pediatric Page used under PREA 2003.)

In two cases reviewed, partial waivers were granted because the formulation was not appropriate for the pediatric population. PREA 2003 required (and PREA 2007 continues to require) that an applicant develop an age-appropriate formulation to fulfill the requirements if one is needed. Thus, waiver decisions based on inadequacy of existing formulations without evidence that reasonable attempts to develop an age-appropriate formulation have failed were in error.

Other reasons for waiver that were cited, but are not consistent with PREA 2003 included the following:

1) There are ongoing studies in response to an outstanding Written Request
2) Safety and effectiveness of the product have been established in pediatric patients on the basis of studies in adults
3) Adult studies are ready for approval
4) Another formulation is already approved in the age group
5) Safety and efficacy have been established in women of childbearing age
6) A full waiver was granted for another dosage form of the product
7) The product has no meaningful therapeutic benefit over existing therapies[7]
8) No reason was given

Deferrals

Of the 43 deferrals reviewed, 42 (98 percent) were consistent with requirements under PREA 2003. Overall, the deferrals granted were consistent with statutory criteria for deferral with the exception of a few that did not include a date by which the applicant would submit the studies.[8]

[7] This reason is inconsistent with PREA 2003 because the relevant waiver criterion is that the product would provide no meaningful therapeutic benefit over existing therapies, AND that it is unlikely to be used in a significant number of pediatric patients in the relevant population(s).

[8] Although a timeline for submission of studies was not a requirement under PREA 2003, it is standard practice for PMCs to include a study schedule, which should include a date that studies will be submitted. FDA enforced the deferral requirements of PREA 2003 through the PMC reporting regulations.

The most common reason provided for a deferral was that the product was ready for approval in adults. There were a few deferrals on this basis where it is unclear why the applicant had not initiated pediatric studies earlier in development. This may have been due to the common practice of fully developing a product for use in adults before beginning pediatric development. Although this practice is appropriate in some circumstances (e.g., where specific concerns about safety are identified or where there is a question of efficacy), in many cases, a delay is not justified by existing data. Although there is no requirement that applicants begin pediatric studies before completion of the development of the product in adults, it would be beneficial for the applicants to consider pediatric product development early in the overall development program, beginning studies at the time that there is sufficient data to move into this population. Timelines thought by FDA to be appropriate for pediatric product development were first described in the 1998 Pediatric Rule.

The one deferral that was not appropriate based on the reasons provided was a complicated case for a class of drugs that had a significant safety signal. In this case, FDA was unsure whether it was appropriate to study the class of drugs in pediatric patients. Rather than deferring on the ground that additional safety data were needed, and setting a deferral date far enough in the future to allow for additional studies at a later date (which would have been the appropriate reason for deferral), the approval letter indicated that FDA would soon hold an internal meeting to decide whether pediatric studies would be required. In light of the significant safety signal, a deferral was appropriate, however. If the division later determined that studies were not needed, or if safety concerns prevented study in the pediatric population, FDA could then have released the applicant from the PREA PMC and waived the studies because of safety concerns.

IV. SUMMARY AND RECOMMENDATIONS

PeRC Oversight

FDA has actively worked to improve how the review divisions in CDER and CBER apply PREA. PREA 2007 required the establishment of the PeRC to review all assessments, waivers, deferrals, and pediatric plans. By providing high level oversight, the PeRC aims to significantly reduce inconsistencies or errors made in the application of PREA and thereby improve the quality and consistency of the PREA process. It should be noted that the recommendations made by PeRC to the divisions are not binding, but most divisions seriously consider PeRC's input in their final decision making concerning their approach to pediatric product development. If an application triggers PREA, the PeRC requires the review division to provide information about the application so it can review plans to waive or defer pediatric studies or to require submission of a pediatric assessment before approval. This oversight by a group of experts in pediatric product development will help eliminate inconsistent and inappropriate use of waiver and deferral criteria identified by the retrospective review, ensure that pediatric assessments submitted in response to a PREA postmarketing requirement fully

meet the PREA requirements, and that information from the studies is communicated through labeling.

One improvement the PeRC already has made is to update the Pediatric Page to reflect the requirements of PREA 2007 (see Appendix B). This change has led review divisions to more consistently apply PREA in the correct manner by more accurately setting out the grounds for them to consider in determining whether PREA has been met, or whether a waiver or deferral is appropriate. The more detailed Pediatric Page also allows for more precise documentation of the actions taken under PREA. Furthermore, the PeRC's involvement in the PREA process has led to increased interaction between the review divisions and the pediatric product development experts who sit on PeRC. This interaction has contributed to increased understanding across both CDER and CBER of the challenges involved in developing and labeling products for use in pediatric populations.

FDA has provided mandatory training on how to implement PREA with the passage of PREA 2007 and voluntary training sessions continue. These sessions are designed to help ensure the uniform application of PREA across review divisions.

Recommendations

PeRC makes the following general recommendations to review divisions based on the retrospective review:

- To correct problems of consistency between pediatric assessments in response to a Written Request and those only in response to the PREA requirement, consideration should be given to the pediatric development program early in the overall product developmental process. Review divisions should seek to engage applicants to begin discussing the approach to pediatric studies with review divisions as early as possible. Though the law simply requires this assessment before an action is taken on a submitted application, the PeRC recommends the assessment take place before but not later than the end of phase 2.

- Pediatric studies should begin when there is sufficient evidence to support the safety of studies in the pediatric population and there is a reasonable demonstration of a sufficient prospect of direct benefit either from animal studies (absent a comparable human adult population) or studies in the adult population to justify the risks.

- If pediatric studies are not already underway, review divisions should request applicants to submit more detailed plans for pediatric studies when submitting their NDA or BLA. In circumstances where a Written Request was issued for a study required under PREA, the expectations of studies to be conducted and the level of discussion with the applicant was greater. If all pediatric plans submitted to meet the requirements of PREA contained elements at a level of detail similar to that provided in a Written Request, FDA would be better able to assess the scope of studies needed to provide adequate data for dosing, safety, and efficacy for

use in the appropriate pediatric populations. Documentation of discussion regarding the details of the plan (similar to the documentation of studies needed to obtain pediatric exclusivity outlined in a Written Request) will help applicants and FDA assure the sufficiency of submitted studies to fulfill the PREA requirements. In Europe, industry must submit detailed plans to the European Medicines Agency (EMEA) when they submit their pediatric investigational plan;[9] thus this is a reasonable approach to request in the United States. This process also will assist in the scientific discussions that occur on a monthly basis between FDA and EMEA on pediatric proposals submitted to the EMEA and their relation to studies submitted to or being proposed in the United States.

- Descriptions in approval letters of PREA postmarketing requirements should be more extensive. For example, instead of stating "pediatric studies in pediatric patients 2-17 years," the PREA PMR could state "a pharmacokinetic and pharmacodynamic study of 3 doses of drug x and a double-blind, multicenter, active-controlled noninferiority study of drug x compared to drug y 2 times daily for 6 months for the treatment of pediatric patients ages 2-16 years with disease X." Documentation regarding fulfillment of PREA requirements should be fully captured in the reviews and approval letters completed by FDA upon taking an approval action. Failure to document could lead to PREA PMRs not being captured and tracked, or being misunderstood by the applicant or FDA. This problem, in part, has been addressed by establishment of the PeRC because documentation is submitted, reviewed, and then discussed by the PeRC.

- When pediatric assessments are not submitted as an application with labeling, the review divisions should inform the applicants that PREA 2007 requires that information in the pediatric assessment be included in labeling, and request that the applicant submit a labeling supplement.

- PREA requires that waivers must be granted based on the criteria set forth in the law. The involvement of the PeRC in the waiver process should help eliminate the granting of waivers that do not meet the statutory criteria.

- Information from pediatric studies should be incorporated into labeling in a consistent manner. A pediatric labeling guidance could supplement the labeling rule. Consistency in placement and language may increase the ability of clinicians and patients/guardians to find information in the label, especially when combined with labeling formatting.

[9] Guidance on preparing a pediatric investigational plan for the EMEA can be found at http://www.emea.europa.eu/htms/human/paediatrics/pips.htm.