

The Pediatric Advisory Committee's Role in Adverse Event Report Review as mandated by the Best Pharmaceuticals for Children Act

Section 17 of the Best Pharmaceuticals for Children Act (BPCA) mandates the review of adverse events reports received during the one-year after a drug has been granted pediatric market exclusivity¹. The FDA's Office of Pediatric Therapeutics (OPT) is authorized to carry out this mandate and is directed by law to refer such adverse event reports to the Pediatric Advisory Committee (PAC) for their review and recommendations regarding any regulatory actions.

Source of post-marketing safety information

The Adverse Event Reporting System (AERS) is the primary source of post-marketing safety information. AERS is a computerized database that supports the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA receives adverse drug reaction reports from manufacturers as required by regulation. In addition, health care professionals and consumers may submit adverse event reports voluntarily through the FDA's MedWatch program. These reports also become part of the AERS database.

FDA codes all reported adverse events using a standardized international terminology, MedDRA (the Medical Dictionary for Regulatory Activities). To detect drug safety signals and to monitor drug safety, the drug adverse event reports in AERS are evaluated by FDA clinical reviewers in the Office of Drug Safety (ODS). The AERS reports may form the basis for further epidemiological studies when appropriate. As a result of reported adverse events, the FDA may take regulatory actions to improve product safety and to protect the health of the public. Examples of these actions may include: updating a product's labeling information, sending out a "Dear Health Care Professional" letter, or re-evaluating an approval decision.

The BPCA-mandated adverse event review and role of the Pediatric Advisory Committee

During the Drug Adverse Event portion of the PAC meeting, PAC committee members will hear presentations of drug safety reviews from medical officers in the Division of Pediatric Drug Development (DPDD) and other FDA scientists and outside experts as deemed necessary to provide appropriate context for the adverse events under review. The focus of the FDA oral presentations to the PAC is to review the drug specific one-year post-marketing adverse events, but will be supplemented by data necessary to assist the committee in its deliberations. To allow the PAC to focus on those drugs that may have significant safety concerns, the PAC and FDA at the February 14-15, 2005, PAC agreed on the following approach:

1. For those drugs with few or no adverse event reports during the one-year post-exclusivity period and for which the FDA has determined that there are no new

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safety concerns, the DPDD Medical Officer will present a brief oral summary and provide a rationale for why the Agency does not think a detailed presentation to the PAC is not needed. However, the PAC will continue to receive the full range of data and written reports as part of the background package.

2. For drugs where the FDA has determined that the drug may have a possible new safety concern, there will be a more extensive oral presentation from the DPDD Medical Officer as well as other presentations from the FDA if needed. These presentations may be supplemented by invited outside experts and sponsors, if they choose to present. PAC members may also hear from the public during the Open Public Hearing. These detailed adverse event review presentations may be utilized for drugs where the FDA has received reports of serious adverse events that are unexpected (unlabeled) and/or clinically significant including cases that may have resulted in death, hospitalizations, required medical intervention or considered life threatening. This approach may also be used when new safety concerns are suggested by an increase in the frequency and/or severity of an expected adverse drug reaction or identification of a new sub-group of users at unusually high risk for an adverse drug reaction.

All the verbal FDA presentations to the committee are supplemented by relevant written materials contained in a PAC background package. These materials include detailed written drug use reviews and reviews of adverse events prepared by staff from the Office of Drug Safety, summaries of the clinical and pharmacology/toxicology reviews of the pediatric studies conducted by the sponsor in order to obtain pediatric market exclusivity, the most current product label and, when appropriate, relevant scientific articles. The FDA will not ask PAC members specific questions or solicit committee advice on the completed pediatric clinical trials conducted for exclusivity. The clinical trial summaries are included in the PAC package to provide a regulatory history and context for the safety reviews and potential regulatory action.

The primary focus of the FDA presentations to the PAC and subsequent public PAC discussion is on the post-marketing adverse events reports received by the Agency during the one-year post-exclusivity period. The goal of the PAC discussion is to identify any drug related safety issue and to also consider appropriate regulatory actions to protect the public from potential harm. The FDA may ask the committee specific question(s) regarding these adverse event reports or/and any recommendations for possible regulatory action. As described in Section 17 of the BPCA, the Pediatric Advisory Committee plays an important role in this mandated process.

In evaluating the relationship between the reported adverse events and the suspect drugs, the PAC should consider the limitations of FDA's spontaneous adverse event data including under-reporting, variable quality and completeness of reports, difficulty in establishing drug-event causal association or quantifying absolute risk. The PAC evaluation should also weigh the potential safety risk against the known benefits of a drug product when used for its approved indication.

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Any regulatory action that the PAC may recommend to the Agency should also weigh the anticipated benefits and any unanticipated adverse public health consequences of the action. Possible unanticipated consequences of a regulatory action could include a shift in drug use to other medications with unfavorable risk-benefit ratio associated with their use in pediatric patients.

The information on drug use data, key efficacy and safety findings of the exclusivity trials, the approved drug label and other pertinent literature and the presentations regarding the adverse event reports should help provide the context in which to assess the risks and benefits of these drugs.

The PAC's advice and recommendations regarding the safety of medicines in children form an important component of FDA's assessment of adverse drug events. We look forward to hearing the Committee's recommendations.

¹BPCA section pertaining to Adverse Event Reporting

SEC.17. ADVERSE-EVENT REPORTING.

b) Drugs With Pediatric Market Exclusivity.--

(1) In general.--During the one year beginning on the date on which a drug receives a period of market exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act, any report of an adverse event regarding the drug that the Secretary of Health and Human Services receives shall be referred to the Office of Pediatric Therapeutics established under section 6 of this Act. In considering the report, the Director of such Office shall provide for the review of the report by the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee, including obtaining any recommendations of such subcommittee regarding whether the Secretary should take action under the Federal Food, Drug, and Cosmetic Act in response to the report.

(2) Rule of construction.--Paragraph (1) may not be construed as restricting the authority of the Secretary of Health and Human Services to continue carrying out the activities described in such paragraph regarding a drug after the one-year period described in such paragraph regarding the drug has expired.