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Food and Drug Administration
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RE: Guidance for Industry: Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act: Docket No. 98D-0265

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing over $21 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

The FDA Modernization Act, enacted on November 21, 1997, provides for six months of additional market exclusivity for drugs for which FDA requests, and a manufacturer conducts, a pediatric clinical trial. The purpose of the provision is to increase pediatric use information for already-marketed and newly-approved drugs. FDA has issued a Guidance for Industry, "Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act," that sets forth the procedures by which drug sponsors can request that FDA issue a request for a pediatric study and sponsors can submit reports of completed studies. PhRMA is pleased to submit these comments in response to that Guidance.

Congress clearly intended that the pediatric provision of the FDA Modernization Act (FDAMA) would expedite the submission to FDA of studies involving pediatric patients. On May 20, 1998, FDA published the list of priority drugs for which FDA had determined that information about pediatric use may produce health benefits in the pediatric population. FDA also determined that a Guidance document would assist drug sponsors in submitting information FDA wanted to facilitate its issuance of

requests for pediatric studies and ensure consistency across drug review divisions. FDA did not issue the Guidance, however, until the end of June 1998, seven months after enactment of the statute. In addition, FDA issued no Written Requests for pediatric studies until after its Guidance issued.

PhRMA commends FDA for releasing a Guidance that addresses most of the issues of concern to the Agency and the industry related to the procedures for obtaining Written Requests from FDA and submitting pediatric study reports. Although PhRMA would have liked to see the Guidance released at the time the Priority List was published, so studies could begin immediately, PhRMA is pleased that FDA has issued a Guidance and is attempting to ensure consistency in review of requests across review divisions. PhRMA does have some comments on the Guidance.

1. <u>For Already-Approved Drugs, Studies Submitted Before a Request is Received Should Qualify as Pediatric Studies</u>

The Guidance contains one policy that will undercut the Congressional purpose behind the pediatric provision in FDAMA. The legislative history of FDAMA makes it clear that pediatric studies initiated or completed prior to a Written Request from FDA will allow a drug to qualify for the statute's pediatric exclusivity. *See* H. Rep. No. 105-399, at 93 (1997). FDA has stated that studies performed prior to an official FDA request will be permitted to qualify for pediatric exclusivity. It will not, however, allow studies that were <u>submitted</u> to FDA prior to such a request to "be used to request pediatric exclusivity." Thus, any applicant that, acting in good faith, submitted pediatric studies prior to receiving a Written Request from FDA would be unfairly penalized by the denial of the incentive and reward of exclusivity. This policy could cause companies to delay submitting pediatric studies, contrary to the intent of Congress. Alternatively, it could result in companies conducting additional studies to duplicate those already conducted, thereby wasting the resources of sponsors and medical facilities capable of conducting pediatric studies.

Although this policy may provide administrative convenience for FDA, it is a counterproductive policy. PhRMA strongly urges FDA to revise this policy to allow it to issue official Written Requests for those studies that have already been submitted prior to the Written Request and that meet the statute's criteria. Nothing in the statute would prohibit this change in policy and the change, if made, would meet the statute's and Congress' purpose.

PhRMA recognizes the difficulty FDA would experience in making determinations about studies previously submitted or conducted. The case for allowing FDAMA pediatric exclusivity for studies submitted or conducted as a result of the 1994 Pediatric Labeling Rule is particularly strong. As an alternative, certainly FDA must allow studies submitted on or after November 21, 1997, even if submitted before FDA issued a Written Request. Otherwise, FDA's delay in implementing the FDAMA pediatric exclusivity provision and issuing Written Requests and the position taken in the Guidance would unduly penalize sponsors who have shown initiative pending the FDA's implementation of the pediatric exclusivity provision and would be contrary to Congressional intent. PhRMA recommends that FDA change this policy and accept studies submitted before FDA issued a Written Request.

2. For Drugs Awaiting Approval of a New Drug Application, FDA Should Not Create Administrative Hurdles to the Submission of Pediatric Study Data

In the Guidance, FDA describes how a sponsor may obtain pediatric market exclusivity for a drug that is not yet approved under a New Drug Application. As written, however, the Guidance encourages sponsors to delay (1) initiation of pediatric clinical trials and, as a consequence, (2) submission of a pediatric NDA, pediatric information within an NDA for use in adults, or a Supplement, until a Written Request has been granted.

In item 2 in section II. A. of the Guidance, FDA states that "the reports of studies should be submitted after the Agency makes the Written Request." This concept is repeated in section III. C, where the Guidance states that "studies submitted before FDA issued a Written Request should not be used to request pediatric exclusivity." With these comments, FDA is in effect telling sponsors to delay – "Do not conduct or submit studies until you run the bureaucratic gauntlet to obtain your Written Request."

FDA's approach is fundamentally inconsistent with the clear intent of Congress in the FDA Modernization Act as well as the President in his statements – to stimulate urgent attention to pediatric drug development. There is no basis in the statute for FDA's policy. Application of FDA's policy as set forth in this Guidance and existing regulations governing new drug applications will eliminate the Congressionally-established incentive to conduct pediatric studies for a group of drugs, those for which sponsors submitted NDAs before FDA issued this Guidance.

PhRMA can provide a compelling example of the conflict between the FDA's policy as expressed in the Guidance and Congressional intent to encourage pediatric studies:

One PhRMA member is concurrently developing adult and pediatric uses of a new drug that was in Phase III when FDAMA was enacted. In late 1997 and early 1998, the company submitted documents requesting a Written Request from FDA, but no such request was forthcoming due to lack of a Guidance or procedure within FDA for issuing pediatric study requests. The company prepared its NDA in accordance with 21 CFR § 314. The NDA included reports of studies in children – the NDA regulations simply do not allow a sponsor to withhold such pediatric results due to the administrative lack of a Written Request for a pediatric study – rather, such pediatric data are material to FDA's thorough evaluation of the safety and efficacy of the new drug. Withholding such pediatric results would place the sponsor in conflict with the final pediatric rule of December, 1994, which requires the sponsor to propose appropriate content for the "Pediatric Use" subsection of a drug's draft labeling. The NDA was submitted to FDA prior to issuance of the Guidance that states that studies submitted before a Written Request is issued should not be used to request pediatric exclusivity.

This example illustrates the dysfunctional nature of this requirement – the Guidance's refusal to consider data submitted prior to a sponsor's receipt of a Written Request is inconsistent with FDA's effort to encourage submission of complete NDAs, including information about use of the drug in children. PhRMA urges FDA to delete from the Guidance the prohibition on the use of already-submitted data.

In its place, PhRMA recommends that FDA establish a process and timelines by which pediatric protocols, identified as such, would be submitted to the sponsor's IND and reviewed by FDA in a defined, timely fashion. FDA's acceptance of these protocols would result in a Written Request and written agreement, such that completion of these studies and submission of a study report would qualify for exclusivity. However, PhRMA specifically reminds FDA that review and approval of an NDA must not be dependent upon a sponsor's conducting or completing any pediatric study, and discussions regarding pediatric drug development should under no circumstances hinder or delay the submission, review, or approval of an NDA for an adult indication.

3. FDA Should Institute a Streamlined Written Request System

In light of the large number of drugs on FDA's Priority List and the pace at which FDA has issued written requests for pediatric studies, PhRMA urges FDA to establish a streamlined process for reviewing proposed study requests and issuing

Written Requests. As of November 10. 1998, almost a year after enactment of the FDA Modernization Act and almost 6 months after publication of the Priority List, FDA's pediatric web site indicates that FDA has issued Written Requests for pediatric studies of 10 drugs. Assuming that FDA proceeds at the same rate of 10 requests each six months, when the pediatric provision sunsets in five years, FDA will have issued Written Requests for 20 percent of the drugs on the Priority List. This pace is inconsistent with the importance Congress attached to the effort to encourage pediatric labeling of prescription medicines and with FDA's own expressed interest in encouraging pediatric labeling. FDA, in PhRMA's opinion, simply must find a way to issue Written Requests more promptly.

One possibility would be to deem that inclusion of a drug on the Priority List constitutes a Written Request for the sponsor to conduct a pediatric study of the drug. FDA could then move directly into a discussion of study protocols with a sponsor that submits a proposal to conduct one or more pediatric studies. Other alternatives no doubt could be proposed, but PhRMA urges FDA to move more promptly to issue Written Requests and to work with sponsors to move pediatric studies out of the planning stages so that pediatric use information can be added to product labeling as soon as possible.

4. <u>For Already-Marketed Drugs Not in Tier 1, FDA Should Use a System Based on Date of Submission of a Request</u>

FDA has set up a difficult priority schedule for review of proposals for Written Requests. The timing for FDA review and issuance of a Written Request and performance of requested studies is nearly impossible for those drugs with short periods of patent life or exclusivity remaining, especially those drugs having exclusivity periods expiring before March 31, 1999, which is the closing date for FDA's tier 1 review. However, a tremendous number of drugs on the FDA's Priority List fall into tier 2 of the FDA's priority schedule, and some of those drugs also have short remaining patent or exclusivity periods.

After FDA completes its review of manufacturers' proposed pediatric studies for drugs for which patent or exclusivity expiration is on or before March 31 1999, the Guidance states that FDA will process the tier 2 requests in the order received. FDA would not distinguish among these requests on the basis of patent or exclusivity expiration. A system based on order of receipt at FDA allows those sponsors that anticipate that studies may take a longer time to submit proposed studies to FDA as soon as possible.

Sponsors may anticipate longer studies for a variety of reasons, such as small patient populations resulting in extended recruitment efforts or an illness in which signs of improvement appear slowly. Thus, sponsors can influence the order in which they receive a Written Request from FDA by the time in which they submit proposed study requests to FDA.

However, in light of the many resource requirements facing the Agency, PhRMA is concerned that tier 2 proposed study requests may, in the future, not receive the prompt attention that they deserve. Therefore, PhRMA recommends that FDA establish a time schedule for the review of proposed study requests, and urges that FDA commit to review and respond to all proposed study requests within 90 days of receipt. In addition, FDA should conduct an initial review of all requests when received and notify the submitter, within 10 working days, if the request lacks any necessary information. The submitter would then be able to supply the missing information in a timely manner, after which the 90 day review clock could start. This two-step system – initially reviewing proposed study requests to determine whether they are complete and then reviewing them within 90 days of receipt – would ensure that sponsors' requests would receive prompt consideration and that reviewing divisions would be working on the same review schedules.

5. For Unapproved Drugs, FDA Should Give Highest Priority to Consideration of Requests Related to Applications nearing Approval

For unapproved drugs, FDA should assign the highest priority to proposed requests for studies that have already been submitted and as to which the date of likely approval is approaching. While determination of exclusivity can occur after approval, the statutory language of the Food, Drug, and Cosmetic Act Section 505A(a) suggests that the Written Request must occur prior to approval of the application. Both FDA and applicants will, of course, want to avoid any delay in approval of the new applications for pediatric indications or dosage forms. Thus, the highest priority should be given to applications nearing approval, particularly applications that have been granted accelerated review status by FDA.

6. FDA Should Change the Signatory of Written Requests from the Director of the Office to the Director of the Reviewing Division

In Section IV. A. the Guidance states that each FDA Written Request must be signed by the applicable Office Director at FDA. This is inconsistent with other authority within FDA and will cause delays in issuance of Written Requests due to the need for "new mechanisms" for the Office Director to sign letters. In addition, it removes a valuable dispute resolution mechanism from the process.

Inconsistent: Within FDA, it is now commonplace for the Director of each reviewing division to have signature authority for action letters (*e.g.*, decisions of approval versus not approved), letters of agreement from milestone meetings (*e.g.*, End of Phase II or Pre-NDA meeting), and letters addressing disputes between a sponsor and a review team within the Division. Each such letter has as much or more impact on a drug development program as the Written Request for pediatric studies. Yet, the Guidance has elevated the Written Request to the Office Director – this is inconsistent and inappropriate.

Delays: Designating the Office Director as signatory will cause delays for two reasons. First, the Office Director is usually not a participant in ongoing FDA/sponsor discussions of pediatric development for a new drug. Therefore, a new mechanism must be created to route the documentation for a proposed Written Request from the reviewing division to the Office Director for review, comment, and finalization. Second, while the Division Director could simply build a Written Request for pediatrics into the development process as part of the End-of-Phase II or Pre-NDA meeting, for example, the Office Director does not have this convenient option because Office Directors do not always attend such meetings. Therefore, a new mechanism must be created to obtain the Office Director's involvement and agreement in a Written Request.

Dispute Resolution: Sponsors interact with reviewing divisions on an ongoing basis throughout development of a new product. In this multi-year process, the first (and often most important) avenue for dispute resolution between the reviewing division and sponsor is the Office Director. These Office Directors have considerable drug development experience and bring a wider perspective to bear on disputes. By requiring the Office Director to be the signatory to a Written Request, the FDA removes the Office Director as the first avenue for discussion and resolution of a dispute regarding pediatric studies; rather, the first avenue for discussion and resolution of disputes would be the Office of Review Management – an office that seems inappropriate for such a task, given the extraordinary demands the Office faces.

7. The Methods for Submitting Pediatric Study Reports Should Not Be Limited to Submission of a Supplemental or New Drug Application

FDA's Guidance states that the term "filing" as used in the pediatric provision has a specific legal meaning which requires that reports of studies must be submitted as a Supplement or New Drug Application. The underlying objective of the FDA Modernization Act is the filing of supplemental applications to expand the availability of informed treatment options for pediatric patients. Yet Congress recognized that, in order for the FDA Modernization Act's incentives to work, all bona fide pediatric studies that otherwise qualify should allow the applicable drug to earn the six months of additional exclusivity, including studies that fail to find clinical effectiveness. Studies can be unsuccessful for a variety of valid medical, scientific, and toxicological reasons that cannot be known in advance. Therefore, the statute requires a report of a completed study, not a New Drug Application or Supplemental application. In addition, there is nothing in the legislative history which indicates that study reports must be submitted in the form of a Supplement or New Drug Application.

According to the statute, studies can qualify for exclusivity even if they are unsuccessful and do not lead to new pediatric indications, dosing information or formulations. It is likely, however, that most pediatric studies will support and lead to the filing of a Supplemental application. For studies that find a lack of clinical effectiveness or identify safety concerns, a description of such findings would typically be included in the appropriate section(s) of the product labeling. This information will enable health providers to assess fully the treatment options available for their pediatric patients. For studies that find evidence of clinical effectiveness, the change in the product label would include this information on the drug's use in children.

One method to avoid delays and additional work for sponsors in preparing and FDA staff in reviewing full supplemental applications would be for FDA and the sponsor to agree on the limited content of a completed study report. The agreed-upon content could be limited to information generated by the pediatric study, any additional confirmatory information used to support a labeling change, and any proposed changes in product labeling resulting from the study. If necessary, the sponsor might reference information already submitted in the new drug application for the product. This agreement could be reached during the discussions prior to FDA's issuing of a Written Request.

PhRMA recommends that FDA not require that a sponsor file a supplement as a report of a completed pediatric study, but allow submission of a study report, to be followed by a supplemental application, or a limited supplemental application, as appropriate.

In addition, PhRMA notes that FDA has established guidelines for the quantity and quality of information that is sufficient to support changes in product labeling. Indeed, FDA rejected some number of the supplemental applications that proposed labeling changes that were submitted to FDA in response to the 1994 pediatric rule because FDA concluded that the information was not sufficient to support a labeling change. PhRMA recommends that FDA apply those same rules to proposed labeling changes to incorporate information from pediatric studies, rather than requiring, *a priori*, that labeling changes result from a pediatric study.

In its 1994 pediatric rule, FDA required sponsors to review the available literature and submit supplemental applications. PhRMA members report that many of those supplemental applications are still pending at FDA. While FDA has expressed publicly its disappointment that the 1994 rule did not result in more products bearing labeling for use in children, FDA has never provided information about the number of supplemental applications submitted, the number that resulted in additional pediatric information in product labeling, or the number on which FDA has not yet acted. PhRMA recommends that FDA devote the necessary resources to review those applications and provide a public report of the number of supplemental applications submitted and the number that resulted in revised product labeling.

8. <u>FDA Should Explain How it Will Implement the Interim Extension Provisions of the Statute</u>

The Guidance does not address the possibility, contemplated by the statute, that patent or market exclusivity expiration will occur after submission of reports of studies but prior to an FDA determination that the requirements of the Written Request and thus of the statute have been met. *See* Food, Drug, and Cosmetic Act Section 505A(e). Particularly in light of the fact that patent and market exclusivity will expire in the relatively near future for several important drugs, PhRMA recommends that the Guidance address how FDA will address this situation.

The statute requires that ANDAs for products with pending pediatric exclusivity determinations will not be approved for a period of up to 90 days. FDA staff have articulated in public meetings their understanding of the statutory requirement, but the

Guidance does not clearly state that position. PhRMA urges FDA to make this policy explicit in the Guidance.

9. FDA Should Clarify How to Obtain a Written Request Under Section 505A(a) to Study an Approved Drug for a Use in Children Different from the Approved Adult Use

The Priority List states that FDA believes that studies in pediatric populations of uses approved in adults may benefit the public health. Likewise, in the Guidance, FDA references studies in children of uses approved for adults. Yet, in the Priority List FDA notes that "Studies in support of an application for approval of a use that is currently not approved in adults may be eligible for exclusivity under 21 U.S.C. § 355a(a)(sic)." *See* "List of Approved Drugs for which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population," Docket No. 98N-0056 (May 20, 1998). In the Guidance, FDA notes that it might publish in the *Federal Register* a request for pediatric studies for a use not approved in adults. Yet the Guidance does not provide a clear indication of how a sponsor interested in conducting such studies should seek a Written Request from FDA.

While most drugs are not used uniquely for off-label uses in children, some drugs have important uses in children that are not uses included in the adult labeling. Often, but not always, such uses occur in newborns, for conditions that do not occur in adults. Examples of drugs used for children for uses not approved for adults include the use of:

- corticosteroids as prophylaxis to prevent respiratory distress syndrome;
- theophylline or aminophylline for apnea of prematurity;
- chemotherapy agents for childhood leukemias;
- pyridoxine/vitamin B-6 for treatment of pyridoxine-dependent seizures in neonates;
- cardiovascular drugs in congenital heart disease and primary pulmonary hypertension;
- inhaled tobramycin in cystic fibrosis;
- psychoactive drugs to treat attention deficit disorder, autism, and other central nervous system conditions in children;
- treatment of juvenile rheumatoid arthritis with NSAIDs and other drugs (recognizing differences between juvenile rheumatoid arthritis and arthritis in adults);
- steroids and antimetabolites to treat nephrotic syndrome in children;

- GI drugs to address immature gut motility; and
- drugs used for obstructive pulmonary diseases in older patients might be useful in treating chronic lung disease of prematurity in infants.

As these examples illustrate, unique pediatric diseases is still a major issue across therapeutic categories and pediatric age ranges. Even where the drug is used in both pediatric and adult indications, the dosing levels for children can be so drastically different – both higher and lower -- that efficacy and safety in children may not be extrapolated from studies in adults. More data regarding optimum dosing, treatment schedules and combination use could provide effective results for pediatric conditions which previously had not been as well treated as their adult counterparts.

In addition, some diseases that occur in both children and adults are significantly different in children. Examples of such diseases include Attention Deficit Disorder, many types of cancers, RSV bronchiolitis, and certain mental health diseases such as oppositional defiant disorder.

The FDA Modernization Act pediatric provision, section 505A(a) of the Food, Drug, and Cosmetic Act, authorize exclusivity for pediatric studies of uses of drugs in children that are not approved uses for adults. The Guidance should clearly state that FDA will consider proposed pediatric studies for uses in children that are not approved in adults. The procedures for obtaining a Written Request should be the same for drugs applicable under section 505A(a) as for those eligible under 505A(c).

FDA should treat those proposed study requests as if they were proposed requests for drugs on the Priority List, rather than requiring sponsors to file citizen petitions to include the drug and its use on the Priority List and then negotiate the terms of a Written Request. FDA should not apply to these uses of drugs the "number of drug mentions" criterion that FDA used to decide what drugs to include on the Priority List, because in many instances the populations requiring these uses of the drugs are small, but the use is vital. For example, the number of childhood cancers such as glioma, glioblastoma, neuroblastoma, rhabdomyoscarcoma, medulloblastoma, etc. totals no more than 25,000 patients in the United States. Such an exemption from the "number of drug mentions" criterion is consistent with the policy of the Orphan Drug Act.

10. FDA Should Clarify the Criteria to Determine When a Pharmacokinetic Study Will Be Sufficient

Congress recognized that in some situations it would not be necessary to involve children in full effectiveness trials, or to expend the resources of health care facilities capable of conducting pediatric studies on effectiveness trials. To avoid involving children in unnecessary trials, Congress explicitly stated that pharmacokinetic studies could be sufficient for pediatric exclusivity.

To implement this aspect of the statute, the Guidance notes that a pediatric clinical study may, at the Agency's discretion, be a pharmacokinetic study, but provides no indication of what criteria will be applied to determine that a pharmacokinetic study is sufficient. If sponsors apply criteria different from those that FDA will apply, they may suggest only a pharmacokinetic study in the request to FDA for a Written Request. FDA could prevent delays and the time and resources involved in resolving disputes over whether a pharmacokinetic study will be sufficient by specifying the criteria that will be used to make that determination. For products with a short time remaining on the existing patent or market exclusivity, a disagreement about whether a pharmacokinetic study is sufficient may prevent completion of a pediatric study prior to the expiration of market exclusivity. In addition, review divisions might apply different criteria, resulting in inconsistent application of the Agency's authority to determine that a pharmacokinetic study is sufficient.

PhRMA recommends that FDA rely on the criteria in the 1994 Pediatric Labeling rule – "the course of the disease and the effects of the drug are sufficiently similar in children and adults to permit extrapolation from the adult data to children" – to determine when a pharmacokinetic study is sufficient. The Agency and sponsors have had three years of experience with those criteria. The Agency has not said that it has had any difficulty applying the criteria and we are not aware that they have caused any problems among product sponsors. If FDA wants to expand those criteria, they could consider criteria such as the class of drugs, the indication, and whether there might be unique pediatric safety issues.

PhRMA urges FDA to include the criteria in a guidance document so that both industry and the FDA divisions will be clear about what criteria to apply to determine when a pharmacokinetic study will be sufficient and children will not need to be involved in effectiveness studies unnecessarily.

11. FDA Should Clarify that "Older" Data and Results of Literature Reviews Can Be Used in Support of a Clinical Study in a Supplemental Application for Pediatric Labeling

The Guidance states that data collected prior to the FDA's Written Request will not be accepted unless they support a change to labeling and that literature reviews will not qualify for pediatric exclusivity. *See* the Guidance at page 4. These statements could be read to mean that a sponsor who has conducted a clinical trial and intends to submit a supplemental application to add pediatric use information to labeling or to modify existing pediatric use information in labeling may not use the results of a literature review, or existing data, in addition to the clinical trial results, to support the labeling language. This should not be FDA's intent. Clearly, any labeling change sought in a supplement should be grounded in all available information, regardless of whether the information is sufficient to meet the requirements of the FDAMA pediatric provision. PhRMA urges FDA to clarify that the limitation on the use of existing data and literature reviews applies solely to the requirement for a clinical trial to obtain the pediatric provision's market exclusivity. FDA should explicitly state that data collected before receipt of a written request and information from literature reviews can support a label change.

12. A Citizen Petition to Add a Drug to the Priority List Should Not Be Dependent on the Number of Mentions of the Drug

The number of times that a drug is mentioned, or the number of prescriptions written for the drug, should not be a criterion for an FDA response to a citizen petition to include the drug on FDA's Priority List. First, the number FDA has selected is too large. For example, 50,000 prescriptions exceeds the number of patients with cystic fibrosis in the U.S. by 10,000. Second, prescription numbers may capture outpatient use but fail to reflect use with the sickest pediatric in-patients. Third, current use of a given medication even for a large population of pediatric patients may be limited by the absence of a suitable pediatric formulation. The AAP has repeatedly stated that "defining substantial numbers of patients would be inexact." The task should be to define clinical utility in the broadest possible context; if a drug is currently or likely to be used to treat pediatric patients, it should qualify for the FDA's Priority List.

13. Confidentiality of Data

FDA should clarify that it intends to comply with its obligations for maintaining confidentiality of submissions to FDA consistent with the requirements of the Freedom of Information Act (FOIA) and the Agency's confidentiality regulations.

14. Report to Congress

Subsection (k) of Section 101 of the FDA Modernization Act requires FDA to report to Congress not later than January 1, 2001 (one year before this part of FDAMA sunsets) on the results of the market incentive provision. In order to compile accurate and comprehensive information to file that report and to provide information to the public and interested persons during the years between now and 2001, PhRMA recommends that:

- FDA should provide a status report on pediatric initiatives in its annual report to Congress in November 1998, as well as in November 1999 and 2000, and then provide the final report requested in the statute on January 1, 2001.

- Each status report should include an accounting for all Supplements submitted pursuant to the December, 1994 final pediatric rule. It is important that any report of the results of the FDAMA provision take account of the efforts underway within the pharmaceutical industry when FDAMA was enacted to increase pediatric use information on product labels, in response to the 1994 rule. FDA staff members have indicated that the 1994 rule resulted in few, if any, changes to labeling, and the preamble to the 1997 proposed mandatory rule stated that the mandatory rule was grounded in the lack of approved labeling changes resulting from the 1994 rule. Yet FDA has provided no accounting of the effects of the 1994 rule, so an initial report should indicate, both for the 1994 rule and for the FDAMA provision:

    ◊ the number of supplemental applications submitted,
    ◊ the number of those applications that resulted in labeling changes,
    ◊ the number of supplemental applications that were approvable,
    ◊ the number of supplemental applications not approved,
    ◊ the number of supplements pending review, and

◊ the number of studies undertaken as a result of sponsors' efforts to respond to the 1994 rule, and as a result of a Written Request under the FDAMA section 101 provision.

- Each status report should include the number of Proposed Pediatric Study Requests submitted to FDA by sponsors, and how many of those requests had been acted upon by FDA as of the time of the report.

- Each status report should include a complete roster of all Written Requests issued for drugs on the "List of Approved Drugs for which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population."

- Each status report should include a complete roster of Written Requests issued for drugs prior to approval of an NDA.

15. Notification to the Public

The Guidance should clarify how the public will be notified regarding a sponsor's successful completion of a study and achievement of the six month pediatric exclusivity. PhRMA recommends that the current process for notification of patent and other exclusivity periods through the *Orange Book* be used to identify products that have received six months of additional market exclusivity.

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PhRMA is pleased to submit these comments to FDA on its Guidance for Industry on Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act.

Sincerely,

Marjorie E. Powell