

COPY  
PhRMA

April 3, 1998

0501 98 MAY 19 10:11

**BY MESSENGER**

Murray Lumpkin, M.D.,  
Deputy Director,  
Center for Drug Evaluation and Research  
Food and Drug Administration  
HFD-002  
5600 Fishers Lane  
Rockville, MD 20857

Rebecca A. Devine, PhD  
Associate Director for Policy,  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
S200N, HFM10  
1401 Rockville Pike  
Rockville, MD 20852-1448

**RE: PhRMA Recommended Proposed Regulation for Pediatric Studies of  
Drugs Under Section 111 of the FDA Modernization Act (FDAMA)**

Dear Drs. Lumpkin and Devine:

We are writing on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA) to provide industry input on the pediatric studies provision of the FDA Modernization Act (Section 111), in the form of a recommended prototype of a proposed implementing regulation. In addition, PhRMA will later be submitting comments on the FDA's proposed list of drugs for which the Agency will be requesting pediatric studies.

The enclosed recommended approach was developed by the PhRMA Pediatrics Work Group, and we hope that you and your staffs, and interested members of the public, find this input useful. The Work Group is available at your convenience to discuss this proposal and answer any questions. We look forward to the opportunity to provide any appropriate assistance to the Agency in furtherance of the timely implementation of this important provision, which increases incentives for pharmaceutical researchers to conduct pediatric studies and develop information about the uses of drugs in children.

98D-0265

C1

*Pharmaceutical Research and Manufacturers of America*

1100 Fifteenth Street, NW, Washington, DC 20005 • Tel: 202-835-3400

Murray Lumpkin, M.D.  
Rebecca A Devine, PhD  
April 3, 1998  
Page 2

Sincerely yours,



Stephen Spielberg, M.D.

R. W. Johnson Pharmaceutical Research Institute  
Chair, PhRMA Pediatrics Work Group  
(908/704-4875)



John Siegfried, M.D., Deputy Vice President  
Marjorie Powell, Assistant General Counsel  
PhRMA (202/835-3545; 202/835-3517)

cc: Jane Axelrad, Associate Director for Policy, CDER  
Khyati Roberts, Executive Operations Staff, CDER

April 3, 1998

## **PROPOSED PEDIATRIC REGULATION**

### **I. Introduction**

The recently enacted Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997), among other things, creates special incentives for the sponsors or holders of applications for new drugs to conduct studies regarding the use of the drugs in children. Children frequently suffer from the same diseases as adults, but they can demonstrate different tolerances than adults to the pharmaceuticals that have been approved to treat those diseases and may require special dosing and treatment considerations. For example, infants may have greater difficulty clearing some substances from their systems due to their metabolism and lack of physiological development. Accordingly, it is important that adequate information exist for the safe and effective use of drugs in children in general and in specific pediatric subpopulations in particular. In some cases, there is a need for special pediatric formulations of a drug to be developed. In others, pediatric dosing information can be provided in drug labeling. In the absence of pediatric use information for a particular drug, physicians can be left in the difficult position of having either to prescribe the drug without knowing its precise effects in children or use a potentially inferior alternate treatment for which pediatric information is available. Both the safety and efficacy of therapy can suffer as a result.

The FDA Modernization Act addresses these concerns by increasing the incentives for pharmaceutical researchers to conduct pediatric studies and develop information about the use of drugs in children. Before passage of the FDA

Modernization Act, the incentives were inadequate for many to conduct pediatric studies.

As Congress found when drafting the FDA Modernization Act:

[T]here is little incentive for drug sponsors to perform studies for medications which they intend to market primarily for adults and whose use in children is expected to generate little additional revenue. Pediatric studies pose ethical and moral issues relating to using new unapproved drugs in young patients. Second, there are substantial product liability and medical malpractice issues. Third, pediatric patients are more difficult to attract into studies. Fourth, for some drugs, pediatric use represents more difficult issues of drug administration and patient compliance than adult use.

S. Rep. No. 105-43, at 51 (1997).

For a new drug under development, before the FDA Modernization Act a manufacturer obtained no additional period of exclusivity (the period during which no generic drugs can be approved) for the new drug if it included pediatric studies in its new drug application (NDA). Yet conducting pediatric studies would create additional research and development expenses and could delay the preparation, submission, and approval of the NDA and thereby shorten the effective patent life of the drug remaining after approval by FDA. For a drug already approved and marketed, before the FDA Modernization Act a company could conduct pediatric studies, file an NDA supplement for a new pediatric indication, and gain three years of exclusivity specifically for the new pediatric indication. However, the patient population for the pediatric indication was often unlikely to be large enough to provide an adequate incentive to conduct the necessary studies. In addition, subsequent marketers could bring a generic product onto the market without the pediatric indication and circumvent the additional exclusivity period. Although the generic company could not market its product for the pediatric indication, because the indication was not approved for its product, physicians could still

prescribe the generic product for the pediatric indication and pharmacists could dispense it.

Section 111 of the FDA Modernization Act responds to this situation by providing an additional six months of exclusivity for a drug when the sponsor or holder of a licensing application for the drug conducts a pediatric study or studies requested by FDA. This new incentive should help raise the priority of pediatric drug development and increase competition among researchers and manufacturers to assure that new therapeutic advances will be made available to children and that drug labeling will include information about proper dosing and administration for pediatric patients. To encourage the effective use of the new incentive, the FDA Modernization Act creates a flexible system in which FDA, in consultation with experts in pediatric research, can identify drugs and diseases for which additional pediatric information or drug development may produce health benefits. A drug sponsor, in collaboration with FDA, can design and conduct a study or studies as scientifically appropriate for a drug and disease based on what is already known about the drug or similar drugs in children, or based on data from adults about the drug's pharmacokinetics.

Prior FDA initiatives have similarly sought to create a flexible system to promote the development of pediatric information about prescription drugs. In 1979, FDA promulgated a regulation to establish a "Pediatric use" subsection on drug labeling and encourage drug labeling to include adequate information about indications and usage, and dosage and administration, in pediatric patients. 44 Fed. Reg. 37,434 (June 26, 1979). In 1994, FDA further encouraged manufacturers to provide more pediatric information on drug labels by expanding the ways in which companies could include pediatric uses in

labeling based upon efficacy studies in adults and supporting safety and dosing information related to pediatric use, rather than full clinical trials in pediatric patients. 59 Fed. Reg. 64,240 (Dec. 13, 1994). The desire for further pediatric information for a number of drugs commonly used in pediatric patients led FDA in 1997 to propose a regulation that would compel manufacturers of certain drugs to conduct pediatric studies. 62 Fed. Reg. 43,900. The 1997 proposed rule has yet to be finalized, and the new statutory incentives created by the FDA Modernization Act, if successful, may very well obviate the need for additional regulations.

## **II. The Food and Drug Administration Modernization Act of 1997**

Section 111 of the FDA Modernization Act creates a new section 505A of the Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. § 355a, to provide an additional six months of exclusivity when the sponsor or holder of a drug application conducts a pediatric study or studies at the request of FDA for a new drug or for drugs already on the market designated by FDA. The six months of exclusivity are provided for the drug by extending the periods during which FDA cannot approve an NDA submitted under 21 U.S.C. § 505(b)(2) or an abbreviated new drug application (ANDA) submitted under 21 U.S.C. § 505(j) for any indication because of the innovator's market exclusivity under section 505 of the FFDCA (21 U.S.C. § 355), orphan drug exclusivity, or applicable patents. This incentive may not benefit drugs that are already off-patent or drugs for which all market exclusivity periods have expired, since there are no existing exclusivity periods to extend. Creative alternatives independent of the FDA Modernization Act can be explored to provide incentives to conduct pediatric studies for such drugs, such as public and private research funding.

For drugs that have yet to be approved, the sponsor qualifies for the additional six months of exclusivity under the FDA Modernization Act when (1) FDA determines that information relating to the use of the drug in the pediatric population may produce health benefits in that population, (2) FDA makes a written request for a pediatric study or studies, including a timeframe for completing the study or studies, (3) the sponsor completes the study or studies within the timeframe established by FDA, and (4) the sponsor submits study reports to FDA that are acceptable under the statute. For already approved and marketed drugs, the same essential criteria apply. The FDA Modernization Act directs FDA to consult with experts in pediatric research to develop an initial list of approved drugs for which additional pediatric information may produce health benefits in pediatric patients, and then to publish the list. FDA must update the list at least annually. FDA published a draft list on March 16, 1998 (63 Fed. Reg. 12815).

For both marketed drugs on the pediatric list and new drugs under development, any type of pediatric study, as long as it is clinical in nature (*i.e.*, conducted in humans), can qualify for exclusivity. The FDA Modernization Act explicitly provides that pediatric studies as defined in the Act can include pharmacokinetic or similar studies, and, therefore, the FDA Modernization Act does not limit exclusivity to situations in which a controlled double-blind effectiveness study or similar investigation has been conducted.

Moreover, there is no requirement that the study or studies be successful in demonstrating safety and effectiveness in a pediatric population to trigger the additional six months of exclusivity. The incentive is provided to conduct and submit the research; how that research turns out is unknowable in advance. As long as the study or studies are

properly carried out and submitted to the FDA, the drug will qualify for exclusivity, even if the results do not support approving a pediatric formulation or labeling to recommend pediatric use. In most cases, the pediatric study or studies should provide a basis for some labeling change regarding pediatric use, and FDA expects that most companies will file supplements based on the pediatric data. For example, the results if negative may suggest labeling that would caution against pediatric use. Nevertheless, the additional six months of exclusivity is earned under Section 111 once the pediatric study or studies are conducted and reported, and is not contingent on the filing of a labeling or other supplement.

As required by the statute, the additional exclusivity period, once earned, applies to the drug as a whole and not just to whatever pediatric indication or formulation might result from the requested study or studies, if any. Providing exclusivity merely for the pediatric indication or formulation would not be a sufficient incentive for manufacturers, because follow-on producers could circumvent the exclusivity by nominally selling their product for other indications while knowing that physicians could prescribe the product, and pharmacists dispense it, for the pediatric indication. In addition, the market for the pediatric indication or formulation might be too small to justify conducting pediatric studies. Thus, Congress recognized that meaningful incentives can only be provided if completing a pediatric study or studies as required for a particular drug causes the exclusivity periods to be extended for six months as against any follow-on product containing the same active moiety as that tested.

### **III. Implementation of the Pediatric Studies Provisions of the FDA Modernization Act**

The FDA Modernization Act does not require that regulations be promulgated to implement the Act's pediatric studies provisions. Nevertheless, FDA has determined that publishing a regulation will provide clarification and the mechanism by which this provision will be implemented. In particular, this proposed rule seeks to clarify (1) how FDA will identify drugs and diseases for which pediatric studies might be beneficial; (2) how FDA will make requests for pediatric studies; (3) what types of studies will qualify for extended exclusivity; and (4) how FDA will monitor and track the effectiveness of the new incentives. The proposed rule also makes conforming amendments to the existing regulations on exclusivity.

#### **A. Identifying Drugs Eligible for Extended Exclusivity**

The overarching goal established by the FDA Modernization Act is to promote the investigation and, if appropriate, labeling of as many drugs as possible which may potentially provide a health benefit to children. With that objective in mind, FDA's approach to determining which existing drugs and which new drugs are candidates for pediatric studies will be flexible and inclusive. The focus will be on therapeutic need and the likely use of the drug in pediatric patients. Nearly any medication, except those targeted solely at unique diseases of adulthood or those associated with unique toxicity to developing children, is a potential candidate for a pediatric study or studies. Maternally administered drugs indicated for the treatment of the mother or the fetus can qualify for extended exclusivity under the FDA Modernization Act, providing an important incentive to conduct what can be difficult studies related to pregnancy.

In deciding whether to request a pediatric study or studies for a particular drug, FDA may consider criteria such as the number of patients with the targeted disease or in need of the medication, pediatric utilization of currently marketed compounds without suitable formulations or labeling, disease severity, disease and current treatment morbidity, societal costs due to the absence of pediatric information, and pediatric safety issues and the importance of pediatric labeling information for proper administration and dosing. In general, suitability for pediatric study will be determined by therapeutic class. That is, although FDA will make requests for pediatric studies for specific drugs, FDA will generally determine the suitability of pediatric studies by therapeutic class and will not ordinarily pick and choose within a class. The agency will request pediatric studies for multiple drugs within an appropriate therapeutic class, because significant benefits exist to having several medications in a class formulated, studied, and labeled. For example, it is often difficult to determine in advance whether a given drug can be formulated for pediatric patients or whether safety and efficacy in pediatrics can be established for a particular drug. Providing an incentive for sponsors to conduct pediatric studies of multiple products for the same indication will increase the likelihood that some acceptable pediatric formulation or pediatric drug will be developed or that pediatric labeling will be approved. Moreover, if one product in a therapeutic class may produce health benefits, presumably other products in that class may produce health benefits.

For new drugs, FDA expects that the discussion of pediatric drug development will become a routine part of FDA's interaction with drug sponsors during the development and review process (*e.g.*, regulatory milestone meetings). Review and approval of an NDA is not dependent upon a sponsor's conducting or completing any

pediatric study, however, and discussions regarding pediatric drug development should under no circumstances hinder or delay the submission, review, or approval of an NDA.

For already marketed drugs, FDA has developed a draft initial list of marketed products for which additional pediatric information may produce health benefits. *See* 63 Fed. Reg. 12815 (March 16, 1998). FDA invites input on which specific drugs or therapeutic categories should be included on the pediatric list. Those wishing to request that FDA include a drug on the initial pediatric list should submit information to Docket No. 98N-0056. After that docket closes, those wishing to request that FDA add a drug to the pediatric list should submit information to the Executive Operations Staff, Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, HFD-6, WOCII, Rockville, MD 20857. Requests can include any reasonable basis to demonstrate that the drug may produce a potential health benefit in at least a portion of the pediatric population. The sponsor may wish to include information such as the number of pediatric patients with the pertinent disease or in need of the medication, pediatric utilization of currently marketed compounds, the severity of the disease at issue, and special pediatric safety concerns including those related to dosing and administration. FDA will consider the request in accordance with the criteria outlined above and respond in writing to the request within 45 days. Those in disagreement with FDA's determination may appeal the matter to the Director of the Center for Drug Evaluation and Research and to the Commissioner. If such an optional appeal is not taken, FDA's determination shall constitute final Agency action.

## **B. FDA Requests for Pediatric Studies**

Under Section 111, FDA must request a pediatric study or studies in writing with a timeframe for completing the study or studies to trigger the FDA Modernization Act's extended exclusivity provisions. FDA anticipates requesting pediatric studies in a wide range of products. As a starting matter, FDA's inclusion of a drug on the initial list it is publishing of drugs for which pediatric study may produce health benefits shall constitute a request for pediatric study. The sponsor or holder of an approved NDA for such a drug may write to FDA to propose a timeframe and protocol for a pediatric study or studies. FDA's return acceptance of such a proposal shall satisfy the written request requirement of Section 111. Such a return acceptance will be sent within 45 days of receipt by FDA of the sponsor's or holder's proposal.

For a new drug or a marketed drug not on FDA's initial pediatric list, sponsors or holders of NDAs may also submit written proposals to FDA to conduct a pediatric study or studies on the drug. FDA's return acceptance of such a proposal, which FDA will send within 45 days of its receipt of the proposal, shall satisfy the written request requirement of Section 111. Where FDA requests a pediatric study or studies on a marketed drug not already on the pediatric list, either on its own initiative or in response to a company's proposal, the request shall automatically cause the drug to be added to the pediatric list. FDA believes that this flexible procedure will minimize the administrative burdens of implementing Section 111.

Studies that have been initiated or completed prior to passage of the FDA Modernization Act can still qualify for the exclusivity incentive. Sponsors or holders of NDAs that pursued a pediatric study or studies in advance of the legislation should not be

penalized for taking such steps. Furthermore, no perverse incentives should be created that might lead an NDA sponsor or holder to abort a study or decide not to pursue a labeling supplement or new formulation based on a past study in order to await a new FDA request to conduct a pediatric study or studies that could allow a drug to qualify for extended exclusivity. NDA sponsors or holders that have already initiated or completed a pediatric study or studies, including Phase IV (postmarketing approval) studies, are permitted to request and will obtain written confirmation from FDA that the study or studies will be considered to have been requested by the FDA and allow the drug to qualify under the FDA Modernization Act, as long as the study or studies are or were conducted and reported in accordance with commonly accepted scientific principles and protocols within a reasonable time frame. The drugs that are the subject of such a study or studies shall automatically be added to FDA's pediatric list.

FDA requests for pediatric studies and acceptances of proposals shall come from the Director of the Center for Drug Evaluation and Research (CDER) or the Director's designee. When the Director delegates such tasks, the delegate's determination may be appealed to the CDER Director. The CDER Director's determinations may be appealed to the Commissioner. FDA's rejection of an NDA sponsor or holder's proposal to conduct a pediatric study or studies shall constitute final agency action subject to judicial review, unless such determination is appealed, in which case the determination following appeal shall constitute final agency action subject to judicial review.

**C. Types of Studies Qualifying for Extended Exclusivity**

Any pediatric study that is clinical in nature can potentially qualify for exclusivity under the FDA Modernization Act. Section 111 provides that FDA may enter into

written agreements with the sponsor or holder of an NDA concerning the protocol for a pediatric study or studies. Where the NDA sponsor or holder submits a written proposal for a pediatric study protocol and FDA indicates its acceptance of the protocol in response, such response from FDA shall constitute both a request from FDA to conduct the study or studies and an agreement for the protocol or protocols. If the drug that is the subject of such an agreement is not already on FDA's pediatric list, it shall automatically be added to the list. Where the sponsor or holder of an NDA and FDA does not enter into a written agreement concerning study protocol, the FDA Modernization Act specifies that the study or studies shall be conducted and reported in accordance with commonly accepted scientific principles and protocols.

FDA's determinations concerning study protocols shall be made by the CDER Director or the Director's designee. When the Director delegates such tasks, the delegate's determination may be appealed to the CDER Director. The CDER Director's determinations may be appealed to the Commissioner. Where no appeal is taken, FDA's initial determination shall constitute final agency action subject to judicial review. Where an appeal is taken, FDA's determination following appeal shall constitute final agency action subject to judicial review.

In keeping with the ultimate goal of developing additional pediatric information, FDA will apply flexible and inclusive criteria to determine what particular study or studies are appropriate for a given drug or class of drugs. FDA's determinations will be based on discussions with the drug sponsor, and may include consideration of the drug's chemical class, indication (including severity of disease), adult pharmacokinetics, adult pharmacodynamics, and available safety and efficacy data. Depending upon these

considerations, appropriate studies might address pharmacokinetics, pharmacodynamics, safety (from post-market through controlled safety trials), or efficacy (for difficult to extrapolate indications or novel pediatric indications). Existing literature on the drug may support a proposed pediatric study or studies; however, the extended exclusivity provided for by the FDA Modernization Act cannot be based on a literature survey alone. The more extensive the existing literature, the less the need for an extensive pediatric study and the more likely a limited pharmacokinetic study may be appropriate.

Qualifying studies may target the pediatric population as a whole, or particular age groups, and may relate to new pediatric indications, formulations, or labeling, even if other pediatric indications or formulations were previously approved for the same drug. In addition to maternally administered drugs for the mother or the fetus, generally relevant categories within the pediatric population that a study or studies may target include (1) neonates (birth to 1 month); (2) infants (1 month to two years); (3) children (2 years to 12 years); and (4) adolescents (12 years to 16 years). These age ranges represent generally pertinent categories. The age ranges studied for any given drug should include the targeted population as relates to the current availability of formulations, disease prevalence, safety, and the ability to evaluate efficacy end-points with age. Studies in neonates and infants often present special problems. For example, children below a certain age may be unable to swallow pills, but there may be no existing liquid, chewable or injectable formulation of a product. Where a disease is prevalent in a certain pediatric subpopulation but obstacles exist to the feasibility of conducting studies in the subpopulation, sponsors or holders of NDAs may qualify for extended exclusivity under the FDA Modernization Act by conducting a study or studies in those pediatric

populations for which studies are feasible. In such circumstances, it may be appropriate for the NDA sponsor or holder to commit to conduct a study or studies subsequently in the less feasible pediatric populations – for example, after a drug has been successfully studied in older children or after a new formulation for younger patients has been developed. Extended exclusivity under Section 111 shall be earned once the first study or studies are completed and reported, notwithstanding a commitment to conduct a subsequent study or studies in a different pediatric population. The sponsors or holders of NDAs shall report on the progress of all commitments to conduct subsequent studies in accordance with Section 130 of the FDA Modernization Act (FDCA § 506B; 21 U.S.C. § 356b), which establishes reporting requirements for postmarketing approval studies.

In certain instances, FDA may only request a pediatric study or studies on specific indications for which a drug is approved, because not all of the drug's approved indications may be relevant to pediatric patients. As required by Section 111 of the FDA Modernization Act, completion and reporting of such a study or studies would allow the entire drug to qualify for six months of extended exclusivity. The extended exclusivity would neither be limited to the pediatric indications studied nor to the corresponding adult indications. If the exclusivity were limited to certain indications, the incentive created by Section 111 would be rendered a nullity because other manufacturers could market the same drug for other indications with the knowledge that physicians could still prescribe the drug and pharmacists dispense the drug for the indications that had received the nominal exclusivity extensions.

**D. Completing and Reporting Studies**

Extended exclusivity is earned under Section 111 when the study or studies are completed and reported to FDA in accordance with the NDA sponsor or holder's agreement with FDA on study protocols or, in the absence of such an agreement, in accordance with commonly accepted scientific principles. Where bona fide delays occur in the completion of a study, the NDA sponsor or holder may notify FDA and propose a revised time schedule. The absence of an objection from FDA within 45 days to the revised schedule shall constitute acceptance of the schedule.

Once a study or studies are completed, the reporting requirements of Section 111 may be satisfied by the submission of abbreviated reports of study findings. Full study data may be submitted later, if needed and requested by FDA.

Studies can qualify for exclusivity even if they are unsuccessful and do not lead to new pediatric indications, dosing information or formulations. Studies can be unsuccessful for a variety of valid medical, scientific, and toxicological reasons that cannot be known in advance. 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. Although 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, the Act's incentives apply to a requested study or studies once the study or studies are completed and reported, and the study or studies need not lead to the filing of a supplemental drug approval application related to pediatric use to allow the applicable drug to qualify for the incentive. Nevertheless, FDA expects that

most pediatric studies will support and lead to the filing of some supplemental application. For studies that find a lack of clinical effectiveness or identify safety concerns, a description of such findings should 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.

If a study or studies are stopped for bona fide safety or effectiveness reasons, and the manufacturer files with the FDA a report describing the conduct of the study or studies, the results seen, and the reasons for stopping the study or studies, this would be regarded as a “completed” study or studies for purposes of Section 111 of the FDA Modernization Act.

FDA will publish a notice of any determination it makes that a study or studies have qualified for six months of additional exclusivity. FDA’s determinations concerning study protocols shall be made by the CDER Director or the Director’s designee. When the Director delegates such tasks, the delegate’s determination may be appealed to the CDER Director. The CDER Director’s determinations may be appealed to the Commissioner. Where no appeal is taken, FDA’s initial determination shall constitute final agency action subject to judicial review. Where an appeal is taken, FDA’s determination following appeal shall constitute final agency action subject to judicial review.

**E. Extending the Exclusivity Periods**

For those drugs that qualify, the applicable exclusivity periods described in 21 C.F.R. 314.107, 314.108 and 316.31 during which FDA will not approve any follow on drugs shall be extended by six months. This extension is for the drug as a whole, as

defined by its active moiety or moieties, and not just for the new pediatric indication or formulation. As referenced above, providing extended exclusivity for only the formulation or indication would be insufficient and could be circumvented. In addition, as also explained above, even unsuccessful studies can qualify for extended exclusivity, and in such cases there would be no new pediatric indication or formulation to grant exclusivity. Exclusivity will be extended for any drug product of the manufacturer conducting the qualifying pediatric study or studies that contains the active moiety that was the subject of the study or studies. Where the extended exclusivity applies to a patented drug, the six-month exclusivity extension would apply to all listed patents held by the manufacturer for the drug.

**F. Additional Extensions of Exclusivity for Further Pediatric Studies**

Drugs that have already earned one six-month extended exclusivity period based on the conduct of a requested pediatric study or studies under Section 111 of the FDA Modernization Act can qualify for additional six month extensions of exclusivity within certain limitations. The subsequent six-month extensions of exclusivity can only apply to supplemental new drug applications that have not already received a six-month extension of exclusivity. *See* 21 U.S.C. § 505A(h); H.R. Rep. No. 105-310, at 54 (1997). For example, a hypertension drug administered twice a day that earns an extension of exclusivity after completing a pediatric study or studies can earn a subsequent six months of exclusivity for an application for a once-a-day formulation if it conducts a further qualifying pediatric study or studies requested by FDA during or following the submission and approval of the supplemental application. Additional exclusivity cannot

be obtained to extend any exclusivity periods based on orphan drug status or applicable patent terms that have already been extended by one six-month period.

**G. Monitoring and Tracking**

Pursuant to Section 111(k) of the FDA Modernization Act, FDA must conduct a study and report to Congress by not later than January 1, 2001 on its experience with these pediatric studies provisions. The study and report shall include an examination of (1) the effectiveness of the program in improving information about important pediatric uses for approved drugs; (2) the adequacy of the incentive provided; (3) the economic impact of the program on taxpayers and consumers, including the impact of the lack of lower cost generic drugs on patients, including lower income patients; and (4) suggestions for modifications of the program. In order to fulfill these responsibilities, FDA will track its experience with pediatric studies requested under the FDA Modernization Act. Any assessment must recognize that there will be some time lag between formulation development, protocol planning, carrying out and analyzing data from a study, and applying for and obtaining FDA approval for new indications, formulations or labeling. Nevertheless, if these provisions are successful, one would expect to see measurable improvements in the availability of pediatric information about prescription drugs by 2001.

**IV. List of Subjects**

21 C.F.R. Part 314

A new Subpart I shall be added as follows:

**Subpart I – Pediatric Studies of Drugs**

**§ 314.600 Scope.**

This subpart applies to drugs for which pediatric studies are conducted in accordance with the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (21 U.S.C. § 355a) and which, therefore, qualify for an additional six months of exclusivity.

**§ 314.601 Definitions.**

- (a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.
- (b) The following definitions of terms apply to this part:
  - (1) *Health Benefit* means any potential benefit related to therapy.
  - (2) *Drug* means any drug product that contains the same active moiety as that used in the pediatric study or studies.
  - (3) *Accepted Scientific Principles and Protocols* means established principles and protocols in the relevant scientific community.
  - (4) *Clinical Study* means any study conducted in humans, including a pharmacokinetic study.

**§ 314.602 Exclusivity for New Drugs.**

- (a) If, prior to approval of an application that is submitted under section 505(b)(1) of the act, FDA determines that information relating to the use of a new drug in a pediatric population may produce health benefits in that population, FDA makes a written request for a pediatric study or studies (including a timeframe for completing such study or studies), and such study or studies are completed within

the specified timeframe and reports are submitted in accordance with 21 C.F.R. § 314.607:

- (1)(i) if the application involves a drug that contains a new chemical entity, the periods referred to in 21 C.F.R. § 314.108(b)(2) shall be deemed to be five years and six months rather than five years, and four years and six months rather than four years, the period referred to in 21 C.F.R. § 314.108(b)(3) shall be deemed to be fifty-four months rather than forty-eight months, and the periods referred to in 21 C.F.R. § 314.107(b)(3) shall be deemed to be eight years rather than 7 ½ years;
  - (ii) if the application involves a drug that contains an active moiety that has been previously approved in another application under section 505(b) of the act, the period referred to in 21 C.F.R. § 314.108(4) is deemed to be three years and six months rather than three years;
  - (iii) if the application is a supplemental application, the period referred to in 21 C.F.R. § 314.108(5) is deemed to be three years and six months rather than three years; and
  - (iv) if the application involves a drug designated as an orphan drug under 21 C.F.R. part 316, the periods referred to in 21 C.F.R. Subpart D are deemed to be seven years and six months rather than seven years; and
- (2)(i) with respect to each listed patent for the drug, if the drug is the subject of –
- (a) a listed patent for which a certification has been submitted under 21 C.F.R. § 314.50(i)(i)(2) or 21 C.F.R. § 314.94(a)(12)(i)(A)(2) and for

which a pediatric study or studies were submitted prior to the expiration of the patent (including any patent extensions); or

(b) a listed patent for which a certification has been submitted under 21 C.F.R. § 314.50(i)(i)(3) or 21 C.F.R. § 314.94(a)(12)(i)(A)(3), the date on which FDA approval of a new drug application under section 505(j) or section 505(b)(2) of the act shall become effective, as provided in 21 C.F.R. §314.107(b)(1) & (2), shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

(ii) with respect to each listed patent for the drug, if the drug is the subject of a listed patent for which a certification has been submitted under 21 C.F.R. § 314.50(i)(i)(4) or 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under 21 C.F.R. § 314.107(b)(3), (b)(4) & (c) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(b) Discussion of pediatric drug development will become a routine part of FDA's discussions with drug sponsors during the drug approval process. FDA will request a pediatric study or studies for any new drug for which there is a therapeutic need in a pediatric population. Review and approval of a new drug application is not dependent upon a sponsor's conducting or completing a pediatric study or studies, however, and discussions regarding pediatric drug

development should under no circumstances hinder or delay the submission, review, or approval of a new drug application.

- (c) Any extension of exclusivity recognized under this section shall apply to any drug product of the sponsor conducting the pediatric study or studies containing the active moiety that was the subject of FDA's request and the subsequent pediatric study or studies.

**§ 315.603 List of Drugs for Which Additional Pediatric Information May Produce Health Benefits**

- (a) By May 20, 1998, FDA, after consultation with experts in pediatric research, shall develop, prioritize, and publish an initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population.
- (b) FDA shall update and publish at least annually the list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population. Drugs may be added to the list in accordance with the various mechanisms provided for in this subpart.
- (c) Any drug that may produce a health benefit in a pediatric population is eligible for the list. In determining which drugs or classes of drugs to place on the list, FDA may consider such criteria as the number of patients with the targeted disease or in need of the drug, pediatric utilization of currently marketed compounds without suitable pediatric formulations or labeling, disease severity, disease and current treatment morbidity, societal costs due to the absence of pediatric information, and pediatric safety issues and the importance of pediatric labeling information for proper administration and dosing. FDA will place all drugs from an identified

class on the list. Maternally administered drugs indicated for the treatment of the mother or the fetus may be included on the list.

- (d) Drug sponsors and other interested parties may request that FDA include a drug on the pediatric list. Those interested in submitting a request should submit pertinent information to the Executive Operations Staff, Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, HFD-6, WOCII, Rockville, MD 20857. Requests can include any reasonable basis to demonstrate that the drug may produce a potential health benefit in at least a portion of the pediatric population. The sponsor may wish to include information such as the number of pediatric patients with the pertinent disease or in need of the medication, pediatric utilization of currently marketed compounds, the severity of the disease at issue, and special pediatric safety concerns including those related to dosing and administration. FDA will respond in writing to the request within 45 days. Those in disagreement with FDA's determination may appeal the matter to the Director of the Center for Drug Evaluation and Research and to the Commissioner, and seek judicial review in accordance with 21 C.F.R. § 10.45. Where the person does not appeal FDA's determination, FDA's determination shall constitute final Agency action subject to judicial review in accordance with 21 C.F.R. § 10.45.

**§ 315.604 Exclusivity for Already-Marketed Drugs.**

- (a) If FDA makes a written request to the holder of an approved application under section 505(b)(1) of the act for a pediatric study or studies (including a timeframe

- for completing such study or studies), the study or studies are completed within the specified timeframe, and reported in accordance with 21 C.F.R. § 314.607 –
- (1)(i) if the application involves a drug that contains a new chemical entity, the periods referred to in 21 C.F.R. § 314.108(b)(2) shall be deemed to be five years and six months rather than five years, and four years and six months rather than four years, the period referred to in 21 C.F.R. § 314.108(b)(3) shall be deemed to be fifty-four months rather than 48 months, and the periods referred to in 21 C.F.R. § 314.107(b)(3) shall be deemed to be eight years rather than 7 ½ years;
  - (ii) if the application involves a drug that contains an active moiety that has been previously approved in another application under section 505(b) of the act, the period referred to in 21 C.F.R. § 314.108(4) is deemed to be three years and six months rather than three years;
  - (iii) if the application is a supplemental application, the period referred to in 21 C.F.R. § 314.108(5) is deemed to be three years and six months rather than three years; and
  - (iv) if the application involves a drug designated as an Orphan drug under 21 C.F.R. part 316, the periods referred to in 21 C.F.R. Subpart D are deemed to be seven years and six months rather than seven years; and
- (2)(i) with respect to each listed patent for the drug, if the drug is the subject of –
- (a) a listed patent for which a certification has been submitted under 21 C.F.R. § 314.50(i)(i)(2) or 21 C.F.R. § 314.94(a)(12)(i)(A)(2)

and for which a pediatric study or studies were submitted prior to the expiration of the patent (including any patent extensions); or

(b) a listed patent for which a certification has been submitted under 21 C.F.R. § 314.50(i)(i)(3) or 21 C.F.R. § 314.94(a)(12)(i)(A)(3), the date on which FDA approval of a new drug application under section 505(j) or section 505(b)(2) of the act shall become effective, as provided in 21 C.F.R. §314.107(b)(1) & (2), shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

(ii) with respect to each listed patent for the drug, if the drug is the subject of a listed patent for which a certification has been submitted under 21 C.F.R. § 314.50(i)(i)(4) or 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under 21 C.F.R. § 314.107(b)(3), (b)(4) & (c) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(b) Any extension of exclusivity granted under this section shall apply to any drug product of the manufacturer conducting the pediatric study or studies containing the active moiety that was the subject of the pediatric study or studies.

**§ 315.605 FDA Requests for Pediatric Studies.**

- (a) *General.* FDA requests for a pediatric study or studies must be in writing and include a timeframe for completing the study or studies. Such requests will come from the Director of the Center for Drug Evaluation and Research or a delegate thereof. A request for a pediatric study may be generated through any one of the mechanisms described in this section.
- (b) *Drugs on the Pediatric Drug List.* FDA's inclusion of a drug on the pediatric list described in 21 C.F.R. § 315.603 shall constitute a request for pediatric study. The holder of an approved NDA for such a drug may write to FDA to propose a timeframe and protocol for the pediatric study or studies. FDA's return acceptance of such a proposal shall satisfy the written request requirement of Section 505A of the act. FDA shall respond to a proposal submitted by the holder of an approved NDA within 45 days.
- (c) *NDA Sponsor or Holder Proposals.* For a new drug or a marketed drug not on the pediatric list described in 21 C.F.R. § 315.603, sponsors or holders of new drug applications may submit written proposals to FDA to conduct a pediatric study or studies on the drug. FDA's return acceptance of such a proposal shall satisfy the written request requirement of Section 505A of the act. FDA shall respond to proposals within 45 days of receiving them.
- (d) *Additions to the Pediatric Drug List.* Where FDA requests a pediatric study or studies on a marketed drug not already on the pediatric list described in 21 C.F.R. § 315.603, either on its own initiative or in response to a proposal under this

section, the request shall automatically cause the drug to be added to the pediatric list described in 21 C.F.R. § 315.603.

- (e) *Studies Initiated or Completed Prior to November 21, 1997.* Studies that have been initiated or completed prior to November 21, 1997 can still allow a drug to qualify for the extended exclusivity provided for in this subpart. Sponsors or holders of new drug applications that have initiated or completed a pediatric study or studies, including Phase IV (postmarketing approval) studies, are permitted to request and will obtain written confirmation from FDA that the study or studies allow the drug to qualify for extended exclusivity under this subpart, as long as the study or studies are or were conducted and reported in accordance with commonly accepted scientific principles and protocols. The drugs that are the subject of such studies shall automatically be added to the pediatric list described in 21 C.F.R. § 315.603.
- (f) *Responsible FDA Official and Appeals Process.* FDA requests for pediatric studies and acceptances of proposals by NDA sponsors or holders shall come from the Director of the Center for Drug Evaluation and Research (CDER) or a delegate thereof. When the Director delegates such responsibilities, the delegate's determination may be appealed to the CDER Director. The CDER Director's determinations may be appealed to the Commissioner. FDA's rejection of an NDA sponsor or holder's proposal to conduct a pediatric study or studies shall constitute final agency action subject to judicial review in accordance with 21 C.F.R. § 10.45, unless such determination is appealed, in which case the

determination following appeal shall constitute final agency action subject to judicial review in accordance with 21 C.F.R. § 10.45.

**§ 315.606 Types of Studies that Can Qualify for Extended Exclusivity.**

- (a) *General.* Any human pediatric study can qualify for the extended exclusivity provided for in this subpart. FDA will apply flexible and inclusive criteria to determine what particular study or studies are appropriate for a given drug or class of drugs. FDA's determinations will be based on discussions with the drug sponsor, and may include consideration of the drug's chemical, class, indication (including severity of disease), adult pharmacokinetics, adult pharmacodynamics, and available safety and efficacy data. Appropriate studies might address pharmacokinetics, pharmacodynamics, safety (from post-market through controlled safety trials), or efficacy (for difficult to extrapolate indications or novel pediatric indications). Existing literature on a drug may support a proposed pediatric study; however, the extended exclusivity provided for by this subpart cannot be based on a literature survey alone. The more extensive the existing literature, the less the need for an extensive pediatric study and the more likely a limited pharmacokinetic study may be appropriate.
- (b) *Pediatric Populations Studied.* Qualifying studies may target any pertinent pediatric population and may relate to new pediatric indications, formulations, or labeling, even if other pediatric indications or formulations were previously approved for the same drug. In addition to maternally administered drugs for the mother or the fetus, generally relevant categories within the pediatric population

that studies may target include (1) neonates (birth to 1 month); (2) infants (1 month to two years); (3) children (2 years to 12 years); and (4) adolescents (12 years to 16 years). These age ranges represent generally pertinent categories. The age ranges studied for any given drug should include the targeted population as relates to the current availability of formulations, disease prevalence, safety, and the ability to evaluate efficacy end-points with age. Where a disease is prevalent in a certain pediatric subpopulation but obstacles exist to the feasibility of conducting studies in the subpopulation, as is often the case with neonates and infants, sponsors or holders of NDAs may qualify for extended exclusivity under this subpart by conducting a study or studies in those pediatric populations for which studies are feasible. In such circumstances, it may be appropriate for the NDA sponsor or holder to commit to conduct a study or studies subsequently in the less feasible pediatric populations – for example, after a drug has been successfully studied in older children or after a new formulation for younger patients has been developed. Extended exclusivity under this subpart shall be earned once the first study or studies are completed and reported, notwithstanding any commitment to conduct a subsequent study or studies in a different pediatric population.

- (c) *Agreement on Study Protocol.* FDA may, after consultation with the sponsor of an application for an investigational new drug, the sponsor of an application of a new drug, or the holder of an approved application for a drug, enter into a written agreement with the sponsor or holder for the conduct of a pediatric study or studies for the drug. Where the NDA sponsor or holder submits a written

proposal for a pediatric study protocol and FDA indicates its acceptance of the protocol in response, such response from FDA shall constitute both a request from FDA to conduct the study and an agreement for the study protocol. If the drug that is the subject of such an agreement is not already on the pediatric list described in 21 C.F.R. § 315.603, it shall automatically be added to the list.

- (d) *Responsible FDA Official and Appeals Process.* FDA's determinations concerning study protocols shall be made by the Director of the Center for Drug Evaluation and Research (CDER) or a delegate thereof. When the CDER Director delegates such responsibility, the delegate's determination may be appealed to the CDER Director. The CDER Director's determination may be appealed to the Commissioner. Where no appeal is taken, FDA's initial determination shall constitute final agency action subject to judicial review in accordance with 21 C.F.R. § 10.45. Where an appeal is taken, FDA's determination following appeal shall constitute final agency action subject to judicial review in accordance with 21 C.F.R. § 10.45.

**§ 315.607 Completing and Reporting Pediatric Studies.**

- (a) *Written Protocols.* If the sponsor or holder of the drug application and the Secretary agree upon written protocols for the study or studies, the studies requirement is satisfied upon the completion of the study or studies and submission of the reports thereof in accordance with such agreement. Not later than 60 days after the submission of the study reports, FDA shall determine if the study or studies were or were not conducted and reported in accordance with the agreement and so notify the sponsor or holder.

- (b) *Other Methods to Meet the Studies Requirement.* In the absence of an agreement between the sponsor or holder of the drug licensing application and FDA on study protocols, the studies requirement is satisfied when a study or studies have been completed and the reports accepted by FDA. Not later than 90 days after the submission of the reports of the studies, FDA shall accept or reject such reports and so notify the sponsor or holder. FDA's only responsibility in accepting or rejecting the reports shall be to determine, within the 90 days, whether the requested studies have been conducted and reported in accordance with commonly accepted scientific principles and protocols.
- (c) *Study Delays.* Where bona fide delays occur in the completion of a study, the NDA sponsor or holder conducting the study may notify FDA and propose a revised time schedule. If FDA does not object to the proposed revised schedule within 45 days, the revised schedule shall constitute the applicable timeframe for completion of the study.
- (d) *Abbreviated Study Reports.* The reporting requirements of this subpart may be satisfied by the submission of abbreviated reports of a study's findings. Full study data may be submitted subsequently, if needed and requested by FDA.
- (e) *Unsuccessful Studies.* Studies need not be successful – *i.e.*, lead to new pediatric indications, dosing information, or formulations – to qualify for the extended exclusivity provided for in this subpart. Any study that is requested, completed, and submitted as provided for in this subpart qualifies for extended exclusivity. If a study or studies are stopped for bona fide safety or effectiveness reasons, and the manufacturer files with the FDA a report describing the conduct of the study

or studies, the results seen, and the reasons for stopping the study or studies, this would be regarded as a “completed” study or studies for purposes of this subpart. Whether or not a study is successful, no supplemental application related to pediatric use must be filed to qualify the drug for extended exclusivity as a result of having conducted a pediatric study or studies. Nevertheless, FDA expects that most pediatric studies will support and lead to the filing of some supplemental application. For studies that find a lack of clinical effectiveness or identify safety concerns, a description of such findings should typically be included in the appropriate section(s) of the product labeling.

- (f) *FDA Determination.* FDA will publish a notice of any determination it makes that a study or studies have qualified for six months of additional exclusivity. FDA’s determination shall be made by the Director of the Center for Drug Evaluation and Research (CDER) or the Director’s delegate. When the Director delegates such responsibility, the delegate’s determination may be appealed to the CDER Director. The CDER Director’s determination may be appealed to the Commissioner. Where no appeal is taken, FDA’s initial determination shall constitute final agency action subject to judicial review in accordance with 21 C.F.R. § 10.45. Where an appeal is taken, FDA’s determination following the appeal shall constitute final agency action subject to judicial review in accordance with 21 C.F.R. § 10.45.

**§ 315.608 Limitations on Multiple Extensions of Exclusivity Under this Subpart.**

Drugs that have already earned one six-month extended exclusivity period based on the conduct of requested pediatric studies under this subpart can qualify for additional

six month extensions of exclusivity under this subpart within certain limitations. The subsequent six-month extensions of exclusivity can only apply to supplemental new drug applications that have not already received a six-month extension of exclusivity. For example, a drug in one formulation that earns an extension of exclusivity after completing a pediatric study or studies can earn a subsequent six months of exclusivity for a supplemental application for a new formulation if it conducts a further qualifying pediatric study or studies requested by FDA during or following the submission and approval of the supplemental application. Only one six-month extension may be added to any period of exclusivity based on an applicable patent or orphan drug status.

**§ 315.609 Special Applications.**

When FDA determines that the acceptance or approval of an application under section 505(b)(2) of the act or 505(j) of the act for a new drug may occur after submission of reports of a pediatric study or studies under this subpart, which were submitted prior to the expiration of the patent (including any patent extension) or the applicable period under 21 C.F.R. § 314.107, 21 C.F.R. § 314.108, or 21 C.F.R. part 316, but before FDA has determined whether the submission satisfies the requirements of 21 C.F.R. § 315.607, FDA will delay the acceptance or approval under section 505(b)(2) or 505(j) of the act until it has made a determination under 21 C.F.R. § 315.607. However, any such delay shall not exceed 90 days. In the event that requirements of this subpart are satisfied, the applicable six-month period under this subpart shall be deemed to have been running during the period of delay.

**§ 315.610 Sunset.**

A drug may not receive an exclusivity extension under this subpart unless an application for the drug under section 505(b)(1) of the act is submitted on or before January 1, 2002. After January 1, 2002, a drug shall receive a six-month period under 21 C.F.R. § 315.603 if (1) the drug was in commercial distribution as of the date of enactment of November 21, 1997; (2) the drug was included by FDA on the pediatric list described in 21 C.F.R. § 315.603 as of January 1, 2002; (3) FDA determines that there is a continuing need for information relating to the use of the drug in the pediatric population and that the drug may provide health benefits in that population; and (4) all the other requirements of this subpart are met.