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Food and Drug Administration
Center for Drug Evaluation & Research
Office of the Center Director
Executive Operations Staff, HFD-6
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Re: Implementation of the Pediatric Exclusivity Provision
of the Food and Drug Administration Modernization Act

Dear Dr. Roberts:

Hoffmann-La Roche Inc. ("Roche") understands that FDA is actively working on developing guidance on the implementation of the pediatric exclusivity provision of Section 111 of the Food and Drug Administration Modernization Act of 1997 (the "FDA Modernization Act" or "Act"). The Agency has solicited public comment on the *Draft List of Drugs for which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population* (the "List") published in the March 16, 1998 Federal Register (63 Fed. Reg. 12815), and Roche has submitted its comments to the Docket on that List. Roche would like, however, also to comment on issues related to implementation of the statute as a whole. Specifically, Roche is concerned that FDA implement the pediatric exclusivity provision so as not to disadvantage applicants who have been responsive to FDA requests for pediatric studies made before enactment of the Act, and who have developed new pediatric formulations and/or indications at FDA's request. Roche requests that you disseminate a copy of this letter to others at FDA working on this issue. Roche has no objection to FDA's placing a copy of this letter in the public docket created for comments on the List, if the Agency considers that appropriate.

**I. EXCLUSIVITY REQUIREMENTS UNDER SECTION 505A
OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT SHOULD BE
IMPLEMENTED TO REWARD ELIGIBLE STUDIES COMMENCED OR
COMPLETED BEFORE ENACTMENT OF THE ACT**

Section 111 creates a new section 505A of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), codified at 21 U.S.C. § 355a, which provides for six months of additional market exclusivity to be recognized when a sponsor or holder of an application for a drug conducts and submits pediatric studies of a drug at the request of FDA. The legislative history of the FDA

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Modernization Act states: "With respect to any requested studies under this provision, the conferees intend that data collected prior to a request or requirement by the Secretary may be used, in addition to data collected after such request or requirement in satisfying the provisions of this section." H. Rep. No. 105-399, at 92-93 (1997)(Exhibit A). This makes clear that the provision is to apply to drugs for which pediatric studies were undertaken prior to passage of the Act. This is also consistent with the legislative intent that the statute reward diligence in completing studies promptly. Thus, although the statute authorizes the Secretary to determine the timeframe for completing the studies, "such studies should be sought, conducted, and completed at the earliest possible opportunity." *Id.* at 92. In accordance with the intent of the statute, manufacturers should be rewarded for diligently conducting pediatric studies sought by FDA prior to enactment of the Act.

Below, Roche offers comments on how the pediatric exclusivity provision should be implemented with respect to studies commenced prior to enactment.

A. The Pediatric List

Under section 505A(b), FDA must publish, by May 20, 1998, an initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population. As noted above, Roche has already provided comments on FDA's draft List.

There is no statutory requirement that a drug be placed on the List before the pediatric studies on that drug are requested or commenced. Roche asks that FDA state clearly that placement on the List need not predate commencement or completion of pediatric studies in order for those studies to qualify a drug for pediatric exclusivity.

B. FDA Request for Pediatric Studies

For a drug to be eligible for additional exclusivity, FDA must make a written request that the sponsor conduct studies of the drug in a pediatric population. FDCA Section 505A(c). The Act defines pediatric studies to mean "at least one clinical investigation (that, at the Secretary's discretion, may include pharmacokinetic studies) in pediatric age groups in which a drug is anticipated to be used." FDCA Section 505A(g).

FDA may decide to prescribe an appropriate format for written requests made after enactment and may limit the FDA officials who can issue such requests. It cannot, however, be expected that a request made before enactment will conform to such a format. For requests made before enactment, we ask that FDA require only that there be a written record that the request was made by an FDA official, advisory committee, or other person acting in an official FDA capacity. Communications to or from the NDA reviewing division recording

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requests for studies, or transcripts and/or minutes of meetings at which FDA's requests were made known, should qualify.

In addition, FDA should confirm such prior requests in writing after enactment. The Agency should also state clearly its understanding that, as the Act's language reflects, the written request need not predate the commencement or the completion of the studies requested. An alternative, which we believe would be superior to confirming prior requests in writing, would be for FDA to adopt the suggestion of many commentators on the draft List that FDA deem the listing of a drug to be an automatic written request for studies. If listing of a drug is deemed an automatic written request, FDA should again make it clear that listing need not predate commencement or completion of the studies in question.

C. Agreement on Conduct of the Studies and Submission in Accordance With Section 505A(d)(2) or (d)(3)

The Act provides two alternatives with respect to agreement on and submission of studies. First, if FDA and the sponsor agree upon written protocols for the conduct of the studies, the studies requirement of section 505A is satisfied upon the sponsor's completion of the studies and submission of reports of the studies in accordance with the established protocols. FFDC Section 505A(d)(2). Second, under section 505A(d)(3), if there was no prior written agreement on the protocols, the requirement is satisfied if FDA finds that the studies (1) "fairly respond to the written request," (2) were "conducted in accordance with commonly accepted scientific principles and protocols," and (3) "have been reported in accordance with the requirements of [FDA] for filing."

In implementing the pediatric provision, FDA may prospectively establish specific mechanisms by which FDA and the sponsor will agree in writing on the conduct of studies. FDA should, however, make it clear that an appropriate written record of agreement on protocols for studies, such as correspondence reflecting review and comment by the reviewing division, should suffice for studies commenced before enactment of the Act. In situations in which there is no agreement in writing on the protocols for the studies, or it is unclear whether the requirement for agreement on protocols under section 505A(d)(2) has been met, the review of the study reports under section 505A(d)(3) should occur on an expedited basis.

D. Completion Within Requested Timeframe

FDA is to specify a timeframe for completion of the studies. FFDC Section 505A(c). The studies must be completed within any requested timeframe. *Id.*



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For studies requested in the future, FDA may prescribe rules for how timeframes will be specified. Before enactment of the Act, however, neither FDA nor the sponsor would have had reason to record a specific requested timeframe, although completion within a reasonable timeframe would have been the mutual understanding of those involved. For studies commenced before enactment of the Act, therefore, FDA should provide that completion within a reasonable timeframe was implied in each request for studies.

II. FDA SHOULD INTERPRET SECTION 505A(c) TO PROVIDE MEANINGFUL EXCLUSIVITY WHEN NEW FORMULATIONS OR INDICATIONS OF APPROVED DRUGS ARE DEVELOPED

The intent of the Act is to increase useful information on pediatric uses of drugs by rewarding drug manufacturers for conducting pediatric studies of drugs that may provide health benefits in the pediatric population. The FDA and the medical community often recognize the need for an approved formulation of a drug for use in a pediatric population or for information on a use of a drug that is specific to the needs of a pediatric population. This provision should be implemented so that manufacturers are provided with a meaningful incentive to develop pediatric formulations or indications by being fully rewarded for such activities. To do so an additional six month period of exclusivity should be recognized for all of a manufacturer's drug products containing the active moiety studied, including all of that manufacturer's previously approved non-pediatric formulations and indications.

It is important that FDA make clear that the additional exclusivity period recognized under the Act would not be limited to any indication or formulation approved on the basis of the requested studies. The additional exclusivity under the Act should extend the existing exclusivity of the manufacturer's already marketed drug products containing the active moiety studied, in addition to extending any new exclusivity for an indication or formulation approved on the basis of the pediatric studies done.

The Act does not contain any requirement that studies be successful or result in an approvable application in order to warrant exclusivity. Rather, the statute plainly awards exclusivity upon the submission of acceptable reports of requested studies without regard to their outcome. Section 505A(c). Where no new formulation or indication can be approved because the outcome of the studies demonstrates that pediatric use is inappropriate, according to the only possible reading of the statute, exclusivity on the previously existing approved drug would be extended. It would thus make no sense to limit the scope of exclusivity to only adding six months to

the three-year Hatch-Waxman exclusivity for a new pediatric use or formulation when that new indication or formulation is approved on the basis of successful pediatric studies. Doing so would penalize sponsors who achieve successful study results because studies leading to approved supplements would get exclusivity extensions only for the approved supplement, while studies not



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leading to approved supplements would get exclusivity extensions for the previously approved drug. As that can not be the statute's intent, it follows that the exclusivity earned must apply not only to any new pediatric indication or dosage form, but also to all of the sponsor's previously approved drug product(s) containing the active moiety studied.

Roche appreciates your consideration of its views as FDA develops its policy on the implementation of the Act, and would be happy to discuss these issues with you or others in the Agency if you would find that helpful.

Sincerely,

HOFFMANN-LA ROCHE INC.

A handwritten signature in cursive script that reads "Briana C. Buchholz".

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Enclosure

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HLR No. 1998-1314

EXHIBIT A

FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT
OF 1997

NOVEMBER 9, 1997.—Ordered to be printed

Mr. BLILEY, from the committee of conference,
submitted the following

CONFERENCE REPORT

[To accompany S. 830]

The committee of conference on the disagreeing votes of the two Houses on the amendments of the House to the bill (S. 830) to amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to improve the regulation of food, drugs, devices, and biological products, and for other purposes, having met, after full and free conference, have agreed to recommend and do recommend to their respective Houses as follows:

That the Senate recede from its disagreement to the amendment of the House to the text of the bill and agree to the same with an amendment as follows:

In lieu of the matter proposed to be inserted by the House amendment, insert the following:

SECTION 1. SHORT TITLE; REFERENCES; TABLE OF CONTENTS.

(a) **SHORT TITLE.**—*This Act may be cited as the "Food and Drug Administration Modernization Act of 1997".*

(b) **REFERENCES.**—*Except as otherwise specified, whenever in this Act an amendment or repeal is expressed in terms of an amendment to or a repeal of a section or other provision, the reference shall be considered to be made to that section or other provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.).*

(c) **TABLE OF CONTENTS.**—*The table of contents for this Act is as follows:*

Sec. 1. Short title; references; table of contents.

Sec. 2. Definitions.

TITLE I—IMPROVING REGULATION OF DRUGS

Subtitle A—Fees Relating to Drugs

Sec. 101. Findings.

anced Budget Agreements (BBA). This Act preserves the original PDUFA adjustment factor and therefore the basic understanding behind the 1992 enactment of this provision: that is, the industry willingness to pay user fees for enhanced performance in the drug approval process. Nevertheless the conferees acknowledge that the 1997 BBA places tight constraints on the appropriations process, particularly in the out years. The conferees expect the appropriators will make every effort to meet the trigger so that FDA is allowed to collect and expend user fees. However, it must be acknowledged that particularly in the fifth year of BBA, budgetary pressures on all discretionary spending will be great.

Breakdowns of the actual spending levels at FDA have not traditionally been provided to the appropriators, making it difficult to conduct oversight. Beginning in Fiscal Year 1998, appropriators will require FDA to submit a directed operating budget as part of the annual budget request. This will serve as a functional breakdown of how appropriated dollars are spent, similar to the report FDA submits annually to show how the agency spent collected PDUFA user fees.

The conferees expect the President's budgetary request for FDA for salaries and expenses to meet the PDUFA levels specified for each of these years and not be based on any assumption of the enactment of new substitutive user fees on other FDA regulated industries.

Pediatric studies of drugs (Sec. 111)

The conference agreement provides that if the Secretary determines that information about a drug may produce health benefits in a pediatric population and makes a written request for pediatric studies (including a time frame for completing the studies), and the studies are completed and are accepted by the Secretary, then the sponsor or manufacturer will qualify for 6 months of extra market exclusivity. The agreement authorizes the Secretary to determine the time frame for completing the studies, but the conferees emphasize that such studies should be sought, conducted, and completed at the earliest possible opportunity. The conferees do not intend that such studies be artificially timed for market advantage.

The agreement provides that no new market exclusivity may be applied to any new drug for which a new drug application is submitted after January 1, 2002. However, the agreement provides a continuation of the program for certain drugs already on the market on the date of enactment. The purpose of this limited extension is to ensure that, with respect to such already marketed drugs, exclusivity remains available if the Secretary determines there is a continuing need for additional information relating to the use of such drugs that may promote health benefits in the pediatric population. This is applicable only to drugs already included on the list under subsection (b) as of January 1, 2002. The Secretary will not list any additional drugs under Section 505A(b) after January 1, 2002. These drugs will be eligible for the applicable 6-month time extension if the requested studies satisfy all requirements of the section.

The conferees expect the Secretary to consult with experts in pediatric research to develop the list of drugs under subsection (b),

and to set priorities for studies on these drugs. Such experts should include representatives from the American Academy of Pediatrics, the Pediatric Pharmacology Research Unit (PPRU) Network, and the U.S. Pharmacopeia. The conferees note particularly the excellent efforts of NIH, especially through the PPRU Network, which will contribute significantly to this effort.

The conference agreement also requires that a study be conducted on the program, by January 1, 2001, that reviews all aspects of the program, including its impact on the price and availability of drugs and the availability of generic drugs.

With respect to any requested studies under this provision, the conferees intend that data collected prior to a request or requirement by the Secretary may be used, in addition to data collected after such request or requirement in satisfying the provisions of this section.

Clinical investigations (Sec. 115)

The conferees note that the requirement for the Secretary to review existing guidance and develop additional guidance, as appropriate, on the inclusion of women and minorities in clinical trials does not require participation of women and minorities in any particular trial. Furthermore, FDA is required to consult with the National Institutes of Health, which has developed inclusion guidelines for subjects in federally funded clinical research, and with representatives of the drug manufacturing industry, to ensure that ethical, scientific, and legal issues specific to privately funded clinical research are considered. The conferees expect FDA to set forth its general policy regarding: the inclusion of women and minorities in drug development research; population-specific analyses of clinical data and assessment of potential pharmacokinetic differences; and the conduct of specific additional studies in women or minorities, where appropriate.

Content and review of applications (Sec. 119)

The Secretary is required to meet with an applicant if the applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of studies, if the sponsor provides the information necessary to discuss and reach agreement on the design and size of such studies. The Secretary may refuse to meet if the sponsor does not provide such information or if the Secretary determines that such meeting is premature or would not be useful.

Positron emission tomography (Sec. 121)

The conference agreement provides for regulation of positron emission tomography (PET) drugs and replaces earlier industry guidance and regulatory standards for PET products promulgated by the FDA. The agreement provides that, until the Secretary establishes procedures under subsection (c)(1) described below, neither a New Drug Application (NDA) nor an Abbreviated New Drug Application (ANDA) is required by a licensed practitioner to produce a compounded PET product in accordance with United States Pharmacopeia (USP) standards.