Guidance for Industry

Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Revised, September 1999
Procedural

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GUIDANCE FOR INDUSTRY[1]

Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act

I. WHY IS FDA ISSUING THIS GUIDANCE?

Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act), signed into law by President Clinton on November 21, 1997, created section 505A of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355a). Section 505A permits certain applications to obtain an additional six months of exclusivity if, in accordance with the requirements of the statute, the sponsor submits requested information relating to the use of the active moiety in the pediatric population. The text of section 505A is reproduced at Attachment A. The Food and Drug Administration (FDA) plans to issue regulations through notice and comment rulemaking to further implement the pediatric exclusivity provisions of the Modernization Act. The Agency is publishing this updated guidance to assist industry in interpreting section 505A in the interim. This guidance supersedes the guidance for industry on *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act* that FDA issued in June 1998. FDA will continue to update the guidance as appropriate. This guidance will remain in effect until superseded by regulations or new guidance.

This guidance describes how studies may qualify for pediatric exclusivity under section 505A. Topics covered include (1) whether studies for certain drugs will be requested under section 505A(a) or (c), (2) the definition of pediatric studies, (3) the content and format of an FDA request for pediatric studies, (4) how an applicant can obtain an FDA Written Request, (5) the content of a written agreement for the conduct of pediatric studies, (6) the definition of commonly accepted scientific principles, (7) the filing of reports of studies, (8) acceptance of studies by FDA, (9) scope and nature of pediatric exclusivity, (10) publication of exclusivity information, (11) treatment of information submitted in support of a request for pediatric exclusivity, (12) how pediatric studies required under FDA regulations may qualify for pediatric exclusivity, and (13) what happens after January 1, 2002, the

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[1] This guidance has been prepared by the Pediatric Implementation Team in the Center for Drug Evaluation and Research (CDER) in consultation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the implementation of Section 111 of the Modernization Act and pediatric exclusivity. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

sunset date for the pediatric exclusivity provisions of the Modernization Act.

II. HOW DOES A NEW DRUG APPLICATION QUALIFY FOR PEDIATRIC EXCLUSIVITY?[2]

A. New Drug Applications

In general, a 505(b)(1) (21 U.S.C. 355(b)(1)) application[3] will qualify for pediatric exclusivity if all of the following have occurred:

1. The Agency issued a Written Request for pediatric studies:

   a. before the approval of a new drug application (NDA) submitted under section 505(b)(1) (section 505A(a)), or

   b. for an active moiety approved for adults and/or part of the pediatric population for an approved indication that occurs in the pediatric population and appears on the List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population (the List) (section 505A(c)). Refer to Docket 98N-0056 for the current list of approved priority and nonpriority drugs.[4]

2. The sponsor submitted reports of the requested studies to the NDA ***after*** the Agency made the Written Request.

3. The sponsor submitted studies that responded completely to the Written Request (section 505A(d)(2) and (3)).

4. The sponsor submitted reports of the studies in accordance with a written agreement (section 505A(d)(1) and (2)) or, if there was no written agreement, in accordance with commonly

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[2] Consult individual sections of this guidance for additional information on each step.

[3] Applications submitted under section 505(b)(1) include full new drug applications (NDAs) and 505(b)(2) applications. A 505(b)(2) application is an NDA submitted under section 505(b)(1) of the Act for which one or more of the investigations relied upon for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

[4] If a drug is not currently approved for a specific indication, a Written Request to study the use of the drug for that indication would issue under section 505A(a) of the Act, which addresses pediatric studies of unapproved drugs. A drug eligible to receive a Written Request under section 505A(a) would not be included on the list because it would not be an approved drug for purposes of the list.

accepted scientific principles (section 505A(d)(3)).

5. The sponsor submitted reports of the studies in accordance with the Agency's requirements for filing (section 505A(d)).

6. The Agency accepted the reports of studies (section 505A(d)).

B. Over-the-Counter Drugs

Over-the-counter drugs approved under section 505(b) of the Act may qualify for pediatric exclusivity by following the procedures outlined in this guidance.

C. Antibiotics (previously submitted under old Section 507 of the Act)

An application for a drug that contains an antibiotic, in which the antibiotic was the subject of any application for marketing received before November 21, 1997 (hereinafter referred to as an *old* antibiotic), is not eligible to receive pediatric exclusivity unless (1) such antibiotic has or obtains orphan drug exclusivity under section 527 of the Act and (2) the requirements for pediatric exclusivity are met. Old antibiotics are exempt from the exclusivity, patent listing, and patent certification provisions of section 505, and thus are not eligible for pediatric exclusivity that extends section 505 exclusivity, or that provides exclusivity at the end of the term of a listed patent. For further discussion of the current status of antibiotic drug applications, see FDA's guidance on *Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act* (Revised, May 1998). FDA also plans to publish a proposed rule containing a list of old antibiotics.

III. WHAT ARE PEDIATRIC STUDIES?

A. Definition of a Pediatric Study

The terms *pediatric studies* or *studies* are defined for the purposes of pediatric exclusivity as at least one clinical investigation (that, at the Agency's discretion, may include pharmacokinetic studies) in pediatric age groups in which a drug is anticipated to be used (section 505A(g)).

B. Submission of Pediatric Study Protocols to an IND

A sponsor may submit protocols for studies to obtain information relating to the use of a drug in the pediatric population to an investigational new drug application (IND). The sponsor should identify such protocols with the header PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY.

C. Studies That May Be Used to Qualify for Pediatric Exclusivity

Studies submitted in response to the required Written Request may qualify an application for pediatric exclusivity. The party seeking exclusivity need not have conducted the studies it submits in response to a Written Request. Reports of studies conducted by someone other than the party requesting exclusivity should be submitted in response to a Written Request only if the sponsor obtains the underlying data and the studies meet the requirements of the Written Request. A sponsor should obtain a right of reference if it submits reports of studies conducted by another person and should include the data underlying the reports of the studies.

Data collected prior to or after FDA issues a Written Request may be used to respond to the request. FDA does not believe it would be consistent with the intent of the statute to accept data collected prior to the Written Request if such data are already known to provide no useful information. Generally, studies conducted prior to issuance of an FDA Written Request should not be used as the basis of a proposed pediatric study request or submitted in response to an FDA Written Request unless the information would assist a physician in prescribing a drug or would assist a parent in determining whether to administer an OTC drug to their child. Therefore, FDA will not generally accept studies conducted prior to issuance of a Written Request unless the studies would potentially support a change in the labeling to incorporate pediatric information. FDA does not consider reviews of published literature to be pediatric studies that will qualify for pediatric exclusivity.

> **FDA generally will *not* accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA.**

Studies submitted to an IND before FDA issues a Written Request but not submitted as part of an NDA, an amendment to an NDA, or a supplement, may be used as part of a proposed pediatric study request (see section V).

IV. WHAT IS AN FDA WRITTEN REQUEST FOR PEDIATRIC STUDIES?

A. Description of FDA's Written Request

A Written Request is a specific document from FDA that is signed by the applicable office director(s) in which the Agency requests submission of certain studies to determine if the use of a drug could have meaningful health benefits in the pediatric population. FDA may issue a Written Request for those studies at the request of an interested party or on its own initiative. Issuance of a Written Request to a sponsor does not require the sponsor to conduct pediatric studies described in the Written Request. It is the sponsor's decision whether to conduct the studies and possibly gain pediatric exclusivity. FDA's

Written Request will include a provision for amending a Written Request. FDA does not expect to amend Written Requests in the absence of scientific or medical justification.

Generally, FDA's request will seek all necessary pediatric information for an active moiety. The Written Request will address the following issues, as appropriate:

- Type and objective of studies to be performed
- Indications to be studied
- Number of patients to be studied
- Age groups in which the studies will be performed
- Study endpoints, including primary efficacy endpoints (if appropriate)
- Timing of assessments (if appropriate)
- Entry criteria (if appropriate)
- Drug information
- Dosage form
- Regimens
- Route of administration
- Drug-specific safety concerns to be monitored or assessed
- Statistical information, including:
    - power of the study
    - statistical analyses of data to be performed
- Labeling that may result from the studies
- Format of report to be submitted to the Agency
- Timeframe for submitting reports of the studies

FDA will post the most recent template for the Written Request at http://www.fda.gov/cder/pediatric/wr_template.htm.

The Agency may use a proposed pediatric study request (see section V.A) to develop its Written Request or may use alternative information.

If an applicant believes it will be unable to meet the timeframe in a Written Request, it should contact FDA to request an extension as soon as possible. If FDA agrees to an extension, FDA will communicate the extension time in writing to the applicant in accordance with the provision for amending the Written Request.

If a sponsor believes that data resulting from a study provide a meaningful health benefit but the sponsor obtained the data in a manner different from that specified in a Written Request or the sponsor obtained data different from the data specified in the Written Request, the sponsor should contact FDA as soon as possible to discuss whether FDA believes it appropriate to issue an amended Written Request. Sponsors are reminded to obtain an amended Written Request in these situations *before* submitting any

pediatric study reports to their NDA. Reports of studies that do not completely meet the terms of a Written Request will *not* qualify an application for pediatric exclusivity.

Each Written Request can result in only one 6-month period of pediatric exclusivity, as described in section X of this guidance.

B. Studies Requested by FDA in the Written Request

FDA will request sponsors to conduct studies that will provide information that may produce health benefits in the pediatric population.

FDA will determine what studies to request in a Written Request by asking the question: [redacted] n? In answering this question, FDA will first determine what pediatric information is included in the labeling for drug products containing the active moiety, what additional pediatric information has been submitted to the Agency for inclusion in the labeling, and what additional pediatric information is included in NDAs containing the active moiety. FDA will then request a sponsor to submit reports of studies of the active moiety to add appropriate pediatric information to the labeling.

FDA might not issue a Written Request for every drug that appears on the List of Drugs for Which Additional Pediatric Information May Produce Health Benefits. A drug is included on the List simply because the drug is used in the pediatric population but insufficient pediatric information appears in the drug's labeling. FDA might not request additional pediatric studies if:

- sufficient pediatric information has already been submitted to the NDA, even if the pediatric information is not yet included in the labeling;
- sufficient pediatric information exists in the literature and the active moiety can be labeled appropriately based on submission of a supplement that contains the relevant literature;[5]
- information from the population for which the drug is labeled is sufficient to label the drug for all relevant pediatric age groups based on submission of a supplement that proposes such extrapolation.

FDA will evaluate the need for studies for all pediatric subpopulations and for all indications for which the active moiety is being used in the pediatric population. FDA will consider approved indications, pending indications, and unapproved uses.

FDA will request studies on unapproved indications under section 505A(a) of the Act. FDA will

[5] FDA would issue a Written Request if it could not label a drug based on literature reports alone, but required the raw data underlying the published literature reports.

request studies on approved indications that occur in all or part of the pediatric population under section 505A(c) of the Act. FDA will not combine requests for studies on unapproved and approved indications in one Written Request.

FDA may request that a sponsor conduct nonclinical trials before completing pediatric studies in humans. Certain toxicology studies in immature animals may be necessary to evaluate the safety of products intended for use in pediatric conditions. FDA may need to review such studies before it is able to evaluate whether information from pediatric studies using a product may produce health benefits in the pediatric population.

Sponsors are advised and encouraged to consult with FDA before beginning pediatric studies.

C. Issuance of FDA's Written Request

All Written Requests will be signed by the applicable office director(s) in CDER or CBER.

1. Prior to approval of a drug, the Agency will issue the Written Request to the sponsor of the NDA or, if there is no sponsor, may publish the Written Request in the *Federal Register*.[6]

2. For approved drugs, the Agency must issue the Written Request to the holder of the approved application (section 505A(c)).

Requests to perform phase 4 studies or other communications concerning pediatric studies are *not* official requests as described in this guidance and required under the statute.

FDA publishes a list of approved active moieties for which it has issued Written Requests. This list is available on the Internet at http://www.fda.gov/cder/pediatric.

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[6] The Agency could publish a Written Request if, for example, it believed that information on the pediatric use of a drug for an unapproved indication would provide health benefits in the pediatric population, it sought pediatric studies related to approval of the indication, and it had not received an application for that indication.

V. HOW DO I OBTAIN A WRITTEN REQUEST?

A. Proposed Pediatric Study Requests From Interested Persons

To expedite the Agency's issuance of a Written Request, interested persons are strongly encouraged to submit to the appropriate new drug review division(s) proposed pediatric study requests addressing the pediatric studies necessary to use the active moiety appropriately in pediatric subpopulations. Submitters should clearly mark their proposal with the header PROPOSED PEDIATRIC STUDY REQUEST. Sponsors should plan to submit their proposed pediatric study request with sufficient time to permit FDA to review the proposed pediatric study request, confer with the sponsor as necessary, issue a Written Request, and permit sponsors to initiate, complete, and file reports of studies before expiration of a patent or exclusivity period. FDA estimates that it could take approximately 120 days after submission of a proposed pediatric study request to issue an appropriate response.

At a minimum, any proposed pediatric study request should address the issues identified in section IV.A and the types of studies discussed in section IV.B. FDA will send an Incomplete Letter to submitters of proposals that do not address all relevant items.

Proposed pediatric study requests generally should include all pediatric age groups in which particular drug products will be studied. FDA will also consider requests to study multiple pediatric age groups in the same study, as appropriate. FDA recognizes that studies defined by age may be inappropriate in instances in which it is reasonable to define subgroups using methods other than age, such as stage of development. If data are submitted as part of a proposed pediatric study request to indicate that a drug should be studied in pediatric groups identified by characteristics other than age, FDA will consider the data in composing its Written Request.

B. FDA Prioritization and Processing of Proposed Pediatric Study Requests

Generally, FDA will process proposed pediatric study requests within each review division as a first or second priority.[7]

1. FDA will first review:

    a. proposed pediatric study requests for approved drugs that appear in the *priority* section of the list (section 505A(c) requests), and

[7] In the June 1998 version of this guidance, FDA created four priorities, two of which took into consideration the date of expiration of patent or exclusivity. FDA created these additional categories in recognition of the fact that it did not issue guidance for this law, which went into effect on November 21, 1997, until June 1998. FDA has completed the processing of proposals submitted under these categories, and has therefore removed them.

b. proposed pediatric study requests submitted for drugs that are not yet approved (section 505A(a) requests).

2. FDA will then review other proposed pediatric study requests for approved drugs that appear in the *nonpriority* section of the list (section 505A(c) requests).

Generally, FDA will review proposed pediatric study requests within each priority in the order the proposals are received by the appropriate new drug review division, as indicated by the official FDA document room receipt stamp.

C. Changes to the List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population

Persons may request changes to the List, including the addition of a drug to the priority section of the List, by submitting a citizen petition under 21 CFR 10.30. Petitioners should include in the header of the petition PEDIATRIC PRIORITY LIST so that their petition can be distinguished from other types of citizen petitions and be sent to the appropriate people.

A drug is not included and does not need to be included on the List if a sponsor wishes to receive a Written Request to conduct studies for an indication for which the drug is not approved currently (section 505A(a) requests).

Generally, an active moiety is included in the priority section of the List if:

- The drug, if approved for use in the pediatric population, would be a significant improvement compared to marketed products labeled for use in the treatment, diagnosis, or prevention of a disease in the relevant pediatric population (i.e., a pediatric priority drug); or,

- The drug is widely used in the pediatric population, as measured by at least 50,000 prescription mentions per year; or,

- The drug is in a class or for an indication for which additional therapeutic or diagnostic options for the pediatric population are needed.[8]

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[8] FDA compiled an initial working list based on recommendations from the American Academy of Pediatrics, the Pharmaceutical Research and Manufacturers Association, the National Institutes of Health, the Pediatric Pharmacology Research Units Network, the National Pharmaceutical Alliance, the Generic Pharmaceutical Industry Association, the National Association of Pharmaceutical Manufacturers, and the United States Pharmacopeia. FDA also included on this initial working list drugs identified in the *Orange Book* as having remaining patent and/or exclusivity life. After internal review of this working list, FDA published a draft list on

FDA might not include a drug on the priority section of the List even if it meets one of the above criteria if FDA believes pediatric studies should not be conducted due to safety concerns.

VI. WHAT IS THE CONTENT OF A WRITTEN AGREEMENT FOR THE CONDUCT OF PEDIATRIC STUDIES?

Sponsors seeking to fulfill a Written Request may enter into a signed written agreement with FDA for the conduct of pediatric studies. The written agreement can address items in the Written Request that the sponsor and FDA wish to clarify. In addition, the agreement can outline what will be necessary to meet the study objectives.

FDA anticipates that written agreements will be used to clarify ambiguities in the Written Request or to confirm that a particular method of fulfilling a term of the Written Request is acceptable when multiple options are available. The written agreement may include the protocol for the study to be conducted or identify how the protocol will be reviewed (for example, review of the protocol as part of phase 2 drug development).[9] However, FDA does not believe that sponsors should routinely include protocols in written agreements. Studies must meet the terms of the Written Request *and* any written agreement (section 505A(d) of the Act). Sponsors do not always follow protocols to the letter, although the studies completed are still good, scientifically sound studies. If a sponsor incorporates a protocol into a written agreement but does not follow the protocol exactly, the sponsor would not earn pediatric exclusivity unless it obtained an amendment to the written agreement.

A written agreement for the conduct of pediatric studies may be modified in writing by mutual agreement.

March 16, 1998 (63 FR 12815).

After consideration of comments received on the draft list, FDA concluded that information on any drug approved for an indication that occurs in the pediatric population may produce health benefits in the pediatric population. Therefore, all drugs approved by CDER and CBER that are approved for indications that occur in children are considered to be on the list. In considering alternative approaches to establishing priorities among the drugs on the draft list, FDA concluded that the criteria used to include drugs on the draft list best describe those drugs for which studies would be considered a high priority because they might provide a significant benefit to the pediatric population. These criteria are described in this guidance. The Agency included the drugs that met the criteria on the priority section of the list.

In May 1999 FDA removed ages from the list in an effort to reduce confusion and encourage sponsors to consult with FDA before conducting pediatric trials. FDA had found that the ages were not necessarily accurate and therefore were often more a hindrance than a help to sponsors developing proposed pediatric study requests.

[9]Any protocol should meet the requirements of 21 CFR 312.23(a)(6). Adequate and well-controlled studies should meet the requirements of 21 CFR 314.126.

VII. WHAT ARE COMMONLY ACCEPTED SCIENTIFIC PRINCIPLES AND PROTOCOLS?

Over the years, FDA has striven to describe commonly accepted scientific principles. FDA's regulations and guidances should serve as a source of information and standards for those seeking to write protocols and to use commonly accepted scientific principles of study design, conduct, and analysis. In particular, FDA recommends a review of:

- 21 CFR 312.23 (describing protocol contents),
- 21 CFR 314.126 (describing adequate and well-controlled studies),

and the guidances:

- *International Conference on Harmonization (ICH) E3: Structure and Content of Clinical Study Reports* (July 1996),
- *ICH E4: Dose-Response Information to Support Drug Registration* (November 1994),
- *ICH E6: Good Clinical Practices: Consolidated Guideline* (May 1997),
- *ICH E8: General Considerations for Clinical Trials* (December 1997),
- *Content and Format for Pediatric Use Supplements* (May 1996), and
- *Format and Content of Clinical and Statistical Sections of New Drug Applications* (July 1988).

FDA plans to use its regulations and guidances to determine whether submitted studies were conducted in accordance with commonly accepted scientific principles and protocols, as required under section 505A(d)(3).

VIII. HOW DO I FILE MY REPORTS OF STUDIES WITH FDA?

Sections 505A(d)(2) and (3) require reports of studies to be submitted in accordance with FDA's requirements for filing. The term *filing* has a specific legal meaning under the Act (see 21 U.S.C. 355, 21 CFR 314.101). Accordingly, to file reports of studies, an applicant should submit a supplement or a new drug application in accordance with the regulatory requirements for filing such documents. A supplement generally would be for a change in an approved product's labeling designed to incorporate information obtained from the pediatric studies. The sponsor of a supplement or NDA containing the reports of pediatric studies need not obtain approval for the reports of studies to be accepted by FDA and qualify an application to receive pediatric exclusivity. A sponsor must file complete reports of the study(ies) prior to the expiration of patent or exclusivity protection they wish to extend to qualify for pediatric exclusivity. A commitment to complete a study is not sufficient to qualify for pediatric exclusivity (section 505A(d)).

Reports of studies completed under protocols submitted to an IND must be submitted in accordance with 21 CFR 314.50 and should be submitted in accordance with the *Guidelines for Format and Content of Clinical and Statistical Sections of New Drug Applications* (July 1988) and *ICH E3: Structure and Content of Clinical Study Reports* (July 1996).

To ensure that reports of pediatric studies are evaluated for eligibility for pediatric exclusivity in a timely manner, an applicant should include with the application or supplement:

- A header on the cover sheet that states: SUBMISSION OF PEDIATRIC STUDY REPORTS -- PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED
- A copy of the Written Request
- A copy of the written agreement, if one existed

Applicants should send a facsimile copy of the cover sheet to the Office of Generic Drugs (OGD), FDA, Attn: Director, OGD (HFD-600), 301-594-0183(fax).

In response to a Written Request, an applicant may submit multiple supplements or NDAs at multiple times before the expiration of the timeframe in the Written Request. If an applicant makes multiple submissions, only the last submission should be marked as described above. FDA will evaluate whether an application qualifies for pediatric exclusivity after a sponsor has filed their final submission responding to a Written Request.

FDA will compare the Written Request to the reports of studies point-by-point. Therefore, FDA encourages sponsors to submit an annotated Written Request indicating where in the reports of studies the sponsor has responded to each part of the Written Request.

IX. WHAT CONSTITUTES ACCEPTANCE OF MY REPORTS OF STUDIES?

A. Definition of Acceptance

Acceptance means the Agency has determined that the studies were conducted in accordance with and are responsive to the original Written Request and either a written agreement if one existed, or commonly accepted scientific principles if no written agreement existed. FDA will also determine if the studies were reported in accordance with FDA's requirements for filing (section 505A(d)(2) and (3)). FDA will compare the Written Request to the reports of studies point-by-point.

FDA will not grant pediatric exclusivity to any product containing the active moiety studied in the Written Request until the sponsor has submitted all requested reports of studies on that active moiety and the Agency has found the studies to be responsive to the Written Request. FDA will not grant pediatric exclusivity based on a commitment to complete pediatric studies by some future date.

B. Notification of Acceptance

A sponsor who had a written agreement with FDA will be notified by CDER or CBER, as appropriate, whether the sponsor's reports of studies qualified for pediatric exclusivity, before the expiration of the 60-day period after the sponsor filed the reports of studies (section 505A(d)(2)).

A sponsor who did not have a written agreement with FDA will be notified by CDER or CBER, as appropriate, whether the sponsor's reports of studies qualified for pediatric exclusivity, before the expiration of the 90-day period after the sponsor filed the reports of studies (section 505A(d)(3)).

X. IF MY STUDY QUALIFIES FOR PEDIATRIC EXCLUSIVITY, TO WHAT WILL THE PERIOD OF PEDIATRIC EXCLUSIVITY ATTACH?

A. Pediatric Exclusivity

Pediatric exclusivity will attach to exclusivity and patent protection listed in the *Orange Book* for any drug product containing the same active moiety as the drug studied and for which the party submitting the studies holds the approved new drug application (505A(a) and (c)). For studies conducted on an unapproved drug, pediatric exclusivity will also attach to any exclusivity or patent protection that will be listed in the *Orange Book* upon approval of that unapproved drug. FDA will attach pediatric exclusivity to protections listed at any time for a drug product as approved at the time pediatric exclusivity is obtained, as described further in section X.C.

Pediatric exclusivity attaches a period of 6 months exclusivity to the exclusivity and patent protections of each drug product containing the studied active moiety and for which the party submitting the studies holds the approved new drug application. For example, if the drug product has 5-year, new chemical entity (NCE) exclusivity, the addition of pediatric exclusivity will give the applicant $5^{1/2}$ years of NCE exclusivity. Pediatric exclusivity attaching to the end of a patent term is not a patent term extension under 35 U.S.C. 156. Rather, it extends the period during which the approval of an abbreviated new drug application (ANDA) or 505(b)(2) application may not be made effective by FDA.

If a sponsor earns pediatric exclusivity for studies on a single active moiety that is also included in a combination product, that pediatric exclusivity would extend exclusivities that apply to the monotherapy and would be added to patents covering the monotherapy. Protections covering the combination therapy alone or just the other ingredient of the combination therapy would not be extended. However, if any of the protections covering the monotherapy also apply to a combination product, the pediatric exclusivity appended to the protections for the monotherapy would also apply to the same protections listed for the combination therapy. For example, if one active ingredient of a combination product has NCE exclusivity, and the sponsor earns pediatric exclusivity for a study on the active moiety protected by NCE exclusivity, the pediatric exclusivity will extend the 5-year NCE protection for the

monotherapy and for the combination therapy. If the same patent is listed for the monotherapy and for the combination therapy, pediatric exclusivity will attach to the patent as it applies to the monotherapy and the combination therapy. However, if a patent protects only the active moiety in the combination that was not studied or the combination as a whole, pediatric exclusivity would not attach to such a patent.

If a sponsor conducts studies on a combination product that contains more than one active moiety, pediatric exclusivity would attach to all of that sponsor's eligible patent and exclusivity protections for each active moiety contained in the combination product.

B. A Second 6-Month Period of Pediatric Exclusivity

Each Written Request may result in only one 6-month period of pediatric exclusivity.

Once a drug has qualified for pediatric exclusivity, a sponsor may submit additional pediatric studies meeting the statutory requirements described in this guidance in response to a Written Request different from the Written Request under which the drug first qualified for pediatric exclusivity. Pediatric studies submitted in a supplemental application for a drug that has already received one period of pediatric exclusivity may qualify the drug to receive a different 6-month period of pediatric exclusivity if submitted in response to a Written Request. The different 6-month period of pediatric exclusivity will attach only to any exclusivity period under sections 505(c)(3)(D)(iv) and 505(j)(5)(D)(iv) granted to the supplemental application for which the studies were completed.

This means:

1. A second Written Request can result in a 6-month period of exclusivity if and only if the response to the Written Request is a supplement for a new use.

2. A new use is a use that is not included in the approved labeling of an approved drug (21 CFR 99.3(g)). Expansion of a label to include a new pediatric population constitutes a new use.

3. The supplement for a new use submitted in response to the second Written Request must qualify for 3-year Waxman-Hatch exclusivity (sections 505(c)(3)(D)(iv) or 505(j)(5)(D)(iv)) or no 6-month period of pediatric exclusivity will attach.

4. The 6-month period of pediatric exclusivity attaches *only* to the 3-year exclusivity applied to the supplement for a new use containing the studies submitted in response to the second Written Request and not to any other exclusivity or patent protections applicable to the active moiety.

C. Later-filed Applications Containing the Same Active Moiety

Previously earned pediatric exclusivity will not apply to new patents or exclusivity covering later-filed applications or supplements containing the same active moiety for which a sponsor previously earned pediatric exclusivity, unless the data that earned the prior pediatric exclusivity is essential to approval of the new application or supplement.

FDA notes that if previously earned pediatric exclusivity has been applied to a patent or exclusivity that also protects the new application or new supplement, it will continue to apply. For example, if a sponsor earns a 6-month extension on 5-year NCE exclusivity, that extension will apply to all applications protected by the NCE exclusivity, regardless of when the new application or supplement is filed.

Consider the following examples:

Example 1
FDA grants pediatric exclusivity on Active Moiety 1 (AM1). The sponsor earns pediatric exclusivity as described in section X.A or X.B. After FDA grants the pediatric exclusivity on AM1, the sponsor files a different application for a drug containing AM1 or a supplement to an existing application for a drug containing AM1. FDA does not need any of the data the sponsor submitted for pediatric exclusivity to approve the new application or new supplement. FDA will not apply the previously granted pediatric exclusivity to any exclusivities or patents that apply solely to the new application or the new supplement to the application. However, if previously earned pediatric exclusivity applies to a patent or exclusivity that also protects the new application or new supplement, it will continue to apply.

Example 2
FDA grants pediatric exclusivity on AM1. The sponsor earns pediatric exclusivity as described in section X.A or X.B. After FDA grants the pediatric exclusivity on AM1, the sponsor files a different application for a drug containing AM1 or a supplement to an existing application for a drug containing AM1. Data the sponsor previously submitted for pediatric exclusivity is essential to approval of the new application or new supplement. FDA will apply the previously granted pediatric exclusivity to any exclusivities or patents that apply to the new application or the new supplement. In addition, if previously earned pediatric exclusivity applies to a patent or exclusivity that also protects the new application or new supplement, it will continue to apply.

XI. WHERE DOES FDA PUBLISH INFORMATION ABOUT PEDIATRIC EXCLUSIVITY?

A. Pediatric Exclusivity Determinations

FDA publishes pediatric exclusivity information in the Patent and Exclusivity Information section of the *Orange Book* and its supplements in the same manner as Waxman-Hatch exclusivity, patent listings, and orphan drug exclusivity. The *Orange Book* and its supplements are available on the Internet at http://www.accessdata.fda.gov/ob. FDA publishes new and cumulative changes to the *Orange Book* at http://www.fda.gov/cder/orange/docket.pdf. FDA will also include information at the website http://www.fda.gov/cder/pediatric on approved active moieties and approved drug products that have received pediatric exclusivity.

B. Other Pediatric Exclusivity Information

FDA maintains a website containing extensive information about pediatric exclusivity at http://www.fda.gov/cder/pediatric. FDA has posted on this website policies and guidances, relevant regulations, some Written Request templates, statistics regarding numbers of Written Requests, transcripts from pediatric meetings and conferences, and press releases. FDA will update this site regularly.

XII. HOW WILL FDA TREAT INFORMATION SUBMITTED IN SUPPORT OF A REQUEST FOR PEDIATRIC EXCLUSIVITY?

~~If FDA finds that a significant number of applications are obtaining pediatric exclusivity without the useful information derived from the studies being announced through labeling changes, FDA will consider appropriate methods for making the information publicly available to benefit the pediatric~~ population.

XIII. WILL I QUALIFY FOR PEDIATRIC EXCLUSIVITY IF I COMPLETE PEDIATRIC STUDIES REQUIRED BY 21 CFR 201.23, 314.55, OR 601.27?

On December 2, 1998, FDA published a final rule in the *Federal Register* that requires sponsors to conduct pediatric studies of certain new and marketed drug and biological products (63 FR 66632). The final rule became effective on April 1, 1999, and is codified primarily at 21 CFR 201.23, 314.55, and 601.27.

A sponsor who submits pediatric studies required under the rule may receive a 6-month extension of exclusivity or patent protection if such studies meet the completeness, timeliness, and other requirements of section 505A (section 505A(i) of the Act). One of the requirements of section 505A is that the pediatric study must be responsive to a Written Request from FDA for the study. To obtain a Written Request, a sponsor should submit a proposed pediatric study request to FDA that contains the information described in this guidance. A sponsor should submit a proposed pediatric study request as soon as possible if FDA has said in the end-of-phase 1 or end-of-phase 2 meeting that it is FDA's best

judgment at that time that it does not intend to waive the study requirement. FDA may issue a Written Request that includes studies required under the rule in accordance with the procedures in this guidance.

A. Comparison of Scope of Studies

FDA does not necessarily ask a sponsor to complete the same studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule. [redacted], FDA issues a Written Request for studies [redacted] (either approved or unapproved) [redacted] (see section IV.B). [redacted], FDA is requiring applicants to conduct a pediatric assessment [redacted] n. Under the rule, FDA also has the authority to require pediatric studies on an approved drug product if there is *substantial use* in the pediatric population **or** the product would provide a *meaningful therapeutic benefit* **and** the absence of adequate labeling could pose significant risk (see 21 CFR 201.23(a)).

B. Qualifying for Pediatric Exclusivity v. Fulfilling the Requirements of the Rule

A sponsor could conduct a study that is adequate to meet the requirements of the pediatric rule but that does not meet the terms of a Written Request. That sponsor would not earn pediatric exclusivity. If a sponsor submits a study that is inadequate to satisfy the pediatric rule, the sponsor will have to complete further studies unless FDA waives the requirement.

FDA may provide additional information in guidance on the pediatric rule.

XIV. WHAT HAPPENS AFTER JANUARY 1, 2002?

The pediatric exclusivity statute contains a *sunset* date of January 1, 2002 (section 505A(j)). This sunset provision has the effects described below.

FDA can review studies submitted on or after January 1, 2002, and can grant pediatric exclusivity for those studies if:

1. the studies are submitted in response to a Written Request issued on or before January 1, 2002, and
2. the Written Request is for a drug (active moiety) for which an application was submitted on or before January 1, 2002.

FDA can issue a Written Request for a drug (active moiety) after January 1, 2002, only if:

1. an application for the drug is submitted on or before January 1, 2002; and
2. the drug was in commercial distribution on November 21, 1997; and
3. the drug is on the List on January 1, 2002; and
4. FDA finds 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 the pediatric population (section 505A(j)).

FDA cannot issue a Written Request for a drug (active moiety) after January 1, 2002, if the first application for the drug is submitted after January 1, 2002.

ATTACHMENT A - SECTION 111 OF THE MODERNIZATION ACT

21 USC 355a (1997)

§ 355a. Pediatric studies of drugs

(a) MARKET EXCLUSIVITY FOR NEW DRUGS. If, prior to approval of an application that is submitted under section 505(b)(1), the Secretary determines that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the Secretary makes a written request for pediatric studies (which shall include a timeframe for completing such studies), and such studies are completed within any such timeframe and the reports thereof submitted in accordance with subsection (d)(2) or accepted in accordance with subsection (d)(3)--

(1) (A) (i) the period referred to in subsection (c)(3)(D)(ii) of section 505, and in subsection (j)(4)(D)(ii) of such section, is deemed to be five years and six months rather than five years, and the references in subsections (c)(3)(D)(ii) and (j)(4)(D)(ii) of such section to four years, to forty-eight months, and to seven and one-half years are deemed to be four and one-half years, fifty-four months, and eight years, respectively; or

(ii) the period referred to in clauses (iii) and (iv) of subsection (c)(3)(D) of such section, and in clauses (iii) and (iv) of subsection (j)(4)(D) of such section, is deemed to be three years and six months rather than three years; and

(B) if the drug is designated under section 526 for a rare disease or condition, the period referred to in section 527(a) is deemed to be seven years and six months rather than seven years; and

(2) (A) if the drug is the subject of--

(i) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(ii) or (j)(2)(A)(vii)(II) of section 505 and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or

(ii) a listed patent for which a certification has been submitted under subsections (b)(2)(A)(iii) or (j)(2)(A)(vii)(III) of section 505,

the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

(B) if the drug is the subject of a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505, 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 section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(b) SECRETARY TO DEVELOP LIST OF DRUGS FOR WHICH ADDITIONAL PEDIATRIC INFORMATION MAY BE BENEFICIAL. Not later than 180 days after the date of enactment of the Food and Drug Administration Modernization Act of 1997, the Secretary, 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. The Secretary shall annually update the list.

(c) MARKET EXCLUSIVITY FOR ALREADY-MARKETED DRUGS. If the Secretary makes a written request to the holder of an approved application under section 505(b)(1) for pediatric studies (which shall include a timeframe for completing such studies) concerning a drug identified in the list described in subsection (b), the holder agrees to the request, the studies are completed within any such timeframe, and the reports thereof are submitted in accordance with subsection (d)(2) or accepted in accordance with subsection
(d)(3)--

(1) (A) (i) the period referred to in subsection (c)(3)(D)(ii) of section 505, and in subsection (j)(4)(D)(ii) of such section, is deemed to be five years and six months rather than five years, and the references in subsections (c)(3)(D)(ii) and (j)(4)(D)(ii) of such section to four years, to forty-eight months, and to seven and one-half years are deemed to be four and one-half years, fifty-four months, and eight years, respectively; or

(ii) the period referred to in clauses (iii) and (iv) of subsection (c)(3)(D) of such section, and in clauses (iii) and (iv) of subsection (j)(4)(D) of such section, is deemed to be three years and six months rather than three years; and

(B) if the drug is designated under section 526 for a rare disease or condition, the period referred to in section 527(a) is deemed to be seven years and six months rather than seven years; and

(2) (A) if the drug is the subject of--

(i) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(ii) or (j)(2)(A)(vii)(II) of section 505 and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or

(ii) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iii) or (j)(2)(A)(vii)(III) of section 505,

the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

(B) if the drug is the subject of a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505, 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 section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(d) CONDUCT OF PEDIATRIC STUDIES.

(1) Agreement for studies. The Secretary may, pursuant to a written request from the Secretary under subsection (a) or (c), after consultation with--

(A) the sponsor of an application for an investigational new drug under section 505(i);

(B) the sponsor of an application for a new drug under section 505(b)(1); or

(C) the holder of an approved application for a drug under section 505(b)(1),

agree with the sponsor or holder for the conduct of pediatric studies for such drug. Such agreement shall be in writing and shall include a timeframe for such studies.

(2) Written protocols to meet the studies requirement. If the sponsor or holder and the Secretary agree upon written protocols for the studies, the studies requirement of subsection (a) or (c) is satisfied upon the completion of the studies and submission of the reports thereof in accordance with the original written request and the written agreement referred to in paragraph (1). Not later than 60 days after the submission of the report of the studies, the Secretary shall determine if such studies were or were not conducted in accordance with the original written request and the written agreement and reported in accordance with the requirements of the Secretary for filing and so notify the sponsor or holder.

(3) Other methods to meet the studies requirement. If the sponsor or holder and the Secretary have not agreed in writing on the protocols for the studies, the studies requirement of subsection (a) or (c) is satisfied when such studies have been completed and the reports accepted by the Secretary. Not later than 90 days after the submission of the reports of the studies, the Secretary shall accept or reject such reports and so notify the sponsor or holder. The Secretary's only responsibility in accepting or rejecting the reports shall be to determine, within the 90 days, whether the studies fairly respond to the written request, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with the requirements of the Secretary for filing.

(e) DELAY OF EFFECTIVE DATE FOR CERTAIN APPLICATION. If the Secretary determines that the acceptance or approval of an application under section 505(b)(2) or 505(j) for a new drug may occur after submission of reports of pediatric studies under this section, which were submitted prior to the expiration of the patent (including any patent extension) or the applicable period under clauses (ii) through (iv) of section 505(c)(3)(D) or clauses (ii) through (iv) of section 505(j)(4)(D), but before the Secretary has determined whether the requirements of subsection (d) have been satisfied, the Secretary shall delay the acceptance or approval under section 505(b)(2) or 505(j) until the determination under subsection (d) is made, but any such delay shall not exceed 90 days. In the event that requirements of this section are satisfied, the applicable six-month period under subsection (a) or (c) shall be deemed to have been running during the period of delay.

(f) NOTICE OF DETERMINATIONS ON STUDIES REQUIREMENT. The Secretary shall publish a notice of any determination that the requirements of subsection (d) have been met and that submissions and approvals under subsection (b)(2) or (j) of section 505 for a drug will be subject to the provisions of this section.

(g) DEFINITIONS. As used in this section, the term "pediatric studies" or "studies" means 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.

(h) LIMITATIONS. A drug to which the six-month period under subsection (a) or (b) has already been applied--

(1) may receive an additional six-month period under subsection (c)(1)(A)(ii) for a supplemental application if all other requirements under this section are satisfied, except that such a drug may not receive any additional such period under subsection (c)(2); and

(2) may not receive any additional such period under subsection (c)(1)(B).

(i) RELATIONSHIP TO REGULATIONS. Notwithstanding any other provision of law, if any pediatric study is required pursuant to regulations promulgated by the Secretary and such study meets the completeness, timeliness, and other requirements of this section, such study shall be deemed to satisfy the requirement for market exclusivity pursuant to this section.

(j) SUNSET. A drug may not receive any six-month period under subsection (a) or (c) unless the application for the drug under section 505(b)(1) is submitted on or before January 1, 2002. After January 1, 2002, a drug shall receive a six-month period under subsection (c) if--

(1) the drug was in commercial distribution as of the date of enactment of the Food and Drug Administration Modernization Act of 1997;

(2) the drug was included by the Secretary on the list under subsection (b) as of January 1, 2002;

(3) the Secretary 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 requirements of this section are met.

(k) REPORT. The Secretary shall conduct a study and report to Congress not later than January 1, 2001, based on the experience under the program established under this section. The study and report shall examine all relevant issues, including--

(1) the effectiveness of the program in improving information about important pediatric uses for approved drugs;

(2) the adequacy of the incentive provided under this section;

(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 on lower income patients; and

(4) any suggestions for modification that the Secretary determines to be appropriate.

HISTORY: (June 25, 1938, ch 675, Ch V, § 505A, as added Nov. 21, 1997, P.L. 105-115, Title I, Subtitle B, § 111, 111 Stat. 2305.)