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Providing Information about Pediatric Uses of Medical Devices

Guidance for Industry and Food and Drug Administration Staff

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Center for Biological Evaluation and Research

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See additional PRA statement in Section III of this guidance.

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Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852-1740. Identify all comments with the docket number FDA-2013-D-0117. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Providing Information about Pediatric Uses of Medical Devices

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

Section 302 of Title III of the Food and Drug Administration Amendments Act of 2007 (FDAAA),[1] created Section 515A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360e-1). Section 515A requires submitters to FDA of premarket approval applications (PMAs), supplements to PMAs, humanitarian device exemptions (HDEs), and product development protocols (PDPs) for new devices to include readily available information about pediatric subpopulations that suffer from a disease or condition that the device is intended to treat, diagnose, or cure.

This guidance document describes how to compile and submit the readily available pediatric use information required under Section 515A of the FD&C Act. Topics covered include:

- the types of premarket submissions that must include the pediatric device use information;
- a description of the specific pediatric device use information required to comply with Section 515A of the FD&C Act;
- what is meant by "readily available information";
- definitions of the pediatric patient population and of pediatric subpopulations;
- some acceptable sources that could address the 515A pediatric use information requirement;

[1] Food and Drug Administration Amendments Act of 2007 - http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/foodanddrugadministrationamendmentsactof2007/default.htm

- where to include the pediatric device use information within a submission;
- how to provide the pediatric device use information within the submission;
- what FDA will do with the submitted pediatric device use information; and
- why FDA does not consider the submitted pediatric device use information to be sufficient to establish a new pediatric indication.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Frequently Asked Questions Concerning Pediatric Tracking

1. What types of premarket submissions must include pediatric device use information under section 515A?

In accordance with the FD&C Act, the requirement to submit pediatric device use information applies to the following applications when submitted on or after April 10, 2014, the effective date of the final rule.

A. any request for a humanitarian device exemption (HDE)[2] submitted under Section 520(m) of the FD&C Act;
B. any premarket approval application (PMA) or supplement to a PMA submitted under Section 515 of the FD&C Act; and
C. any product development protocol (PDP) submitted under Section 515 of the FD&C Act.

Please note that FDA does not interpret 30-day notices submitted pursuant to 21 CFR 814.39(f) to be PMA supplements as described above. Section 515(d)(6)(A) of the FD&C Act distinguishes between manufacturing changes, which require the submission of a written notice, and other changes that affect safety and effectiveness and require the submission of a "supplemental application." Because of this statutory distinction, 30-day notices are not considered PMA supplements for purposes of the rule and, therefore, are not required to include readily-available pediatric information.

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[2] For additional information, refer to "*Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and FDA Staff: Humanitarian Device Exemption (HDE) Regulation: Questions and Answers*",available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110203.pdf

2. What pediatric device use information is required to comply with section 515A of the FD&C Act?

Section 515A of the FD&C Act requires that each new HDE, PMA, PMA supplement and PDP include a description, based on readily available information (see Section II, question 3), of:

- any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure; and
- the number of affected pediatric patients, as a whole and within each pediatric subpopulation.

3. What is meant by "readily available" information?

For purposes of Section 515A of the FD&C Act, "readily available information" is defined as information in the public domain through commonly used public resources for conducting biomedical, regulatory, and medical product research. See FDA's final rule at 21 CFR 814.3(t) (79 FR 1740, January 10, 2014). Examples of scientific research resources include, but are not limited to bibliographic databases of life sciences and biomedical information (such as MEDLINE and PubMed) and online scientific and medical publishers (such as the Public Library of Science (PLoS) and the Cochrane Library).

Submitted 515A pediatric device use information for approved submissions will routinely be made available to the public (for example, as part of the annual report to the United States Congress on pediatric uses of medical devices required in Section 515A(a)(3) of the FD&C Act). Therefore, the submitted 515A pediatric device use information should exclude proprietary, trade secret, and commercial confidential information about the device.

4. How are the pediatric patients and pediatric subpopulations defined?

FDA's final rule at 21 CFR 814.3(s) (79 FR 1740, January 10, 2014) defines "pediatric patients" as persons who are age 21 years or younger at the time of their diagnosis or treatment (that is, from birth through the twenty-first year of life, up to but not including the twenty-second birthday). Section 515A(c) defines "pediatric subpopulations by reference to section 520(m)(6)(E)(ii). Those subpopulations are: Neonates, Infants, Children and Adolescents. Although these subpopulations are specified in the final rule, the age ranges for each subpopulation are not. The recommended age ranges for these pediatric subpopulations are:

- Neonates: from birth through the first 28 days of life;[3]

[3] See *Pediatrics* 2011; 128:177-181; American Academy of Pediatrics; American College of Obstetrics and Gynecology: Appendix D: standard terminology for reporting reproductive health statistics. In: *Guidelines for Perinatal Care.* 6th ed. Elk Grove Village, Il: American Academy of Pediatrics; 2007: 389-404.

- Infants: 29 days of age to less than two years of age;
- Children: Two years of age to less than 12 years of age; and
- Adolescents: 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday).

Except for neonates and infants, the age ranges provided above are consistent with those in the current CDRH Guidance, *Premarket Assessment of Pediatric Medical Devices*, available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089740.htm. In this draft guidance, the upper age boundary for neonates (through the first 28 days of life) and the lower age boundary for infants (29 days) are defined in days rather than months, consistent with national statistical standards for reporting neonatal and infant mortality according to post-natal age. [4]

During its scientific and regulatory review of PMA and HDE applications, FDA considers whether the device and its proposed indications for use warrant specific considerations for older adolescents within the subpopulation, those who are 18 through 21 years of age. FDA is aware that for certain diseases and conditions, patients who are 18 through 21 years of age are not affected differently than adults; however, for other diseases and conditions, there may be special considerations for this subgroup. If readily available, you should include information about any special considerations for older adolescents as part of your description of the subpopulation. In cases where older adolescents suffer from the disease or condition at a similar prevalence and are not affected differently than adults in response to treatment or diagnosis with a device, you should only submit the pediatric device use information described in Section II.7 of this guidance.

5. What are some acceptable sources that could address the 515A pediatric use information requirement?

All readily available information from acceptable data sources (U.S. and non-U.S) concerning U.S. subjects must be submitted to FDA. An acceptable data source should include information on the number of pediatric patients that suffer from the disease or condition and basic demographic data. This data source should be representative of the population at large and allow the applicant to generate population based estimates of disease prevalence.

In the absence of readily available information on U.S. subjects, or where the estimate of the number of pediatric patients that suffer from the disease or condition is believed to be unreliable, relevant information should be obtained from data on non-U.S. subjects. However, the data source should be evaluated and a discussion provided regarding the applicability of the non-U.S. data to the U.S. patient population. Factors such as the overall prevalence of the disease or

[4] *Id.*

condition (in both adult and pediatric patients), geographic differences in medical practice, and environmental conditions may impact the applicability of data on non-U.S. patients.

A. Reliable sources of readily available information in the public domain include, for example:

- Original research reports published in peer-reviewed medical and scientific journals;
- Federal, state or local government sources of vital statistics and disease frequency data (e.g., Center for Disease Control (CDC) National Center for Health Statistics surveys, Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP);
- Systematic research syntheses such as those available on the Cochrane Database of Systematic Reviews;
- Complete previous research study results available on clinicaltrials.gov;
- Premarket pivotal trial data (if data are publicly available);
- Professional society registry data;
- Administrative and clinical databases (e.g., Hospital Discharge Data); and
- Large surveys (e.g., National Emergency Injury Surveillance System, National Survey of Children's Health)

B. Unacceptable data sources

Examples of unacceptable data sources include the following:

- Internal marketing tracking;
- Sales records;
- Research and development reports;
- Consultation with pediatric experts; and
- Unpublished presentations or abstracts from major professional meetings.

To clarify, readily available information does not include data that can be collected only by conducting a new clinical study. This does not preclude the need for clinical data necessary to support a pediatric indication for the device.

You should demonstrate in your application and/or supplement that you have made a reasonable effort to provide the information required by Section 515A(a)(2) of the Act. We recommend that you include documentation of the type of search you performed and how it was performed, as well as a tabular summary of the search engines and search words used, and the criteria you used to determine which sources to discard and which to retain.

6. Where in the submission should the applicant provide the pediatric use information?

The applicant should provide the required pediatric device use information in a separate section of their device application, supplement, or PDP that is titled "515A Pediatric Device Use Information."

Many PMA applications begin with the submission of one or more PMA modules; see *Premarket Approval Application Modular Review — Guidance for Industry and FDA Staff*, available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089764.htm. Applicants who choose to use the modular approach should submit the information required by Section 515A of the FD&C Act in the final PMA module (i.e., the module that includes final clinical data, proposed labeling, and the Summary of Safety and Effectiveness Data). Upon receipt of this final PMA module, FDA will assign a PMA number to the complete application.

7. How should the pediatric device use information be provided in the device submission?

The device submission must provide the pediatric use information, if readily available, for diseases or conditions that the device is intended to treat, diagnose or cure, or for which the submitter is seeking approval. The submission should include an estimate of the number of pediatric patients with the disease or condition that the device is intended to treat, diagnose, or cure that is based on actual population counts or on population-based estimates that are derived from statistically valid population surveys. In addition, applicants may voluntarily provide this information for uses of the device outside the approved or proposed indication if such uses are described or acknowledged in acceptable sources of readily available information. Submission of this latter information will allow FDA to identify pediatric uses outside their approved or proposed indication for use in order to determine areas where further pediatric device development could be useful.

The pediatric use information submission consists of these major elements: (1) a description of the uses of the device (proposed indication for the device) and (2) an estimate of the number of affected pediatric patients in the United States that suffer from the disease or condition that the device is intended to treat, diagnose or cure (including an estimate of the affected pediatric patient population size as a whole and according to the pediatric subpopulations defined above in Section II, question 4).

To put the pediatric use information into context, your submission should summarize, in narrative form, the natural history of the disease or condition which the device is intended to treat, diagnose, or cure. If readily available, applicants may voluntarily explain whether adult and pediatric populations are affected similarly (e.g., course of disease, detectable symptoms, how the device is used) and, if they are not, how each subpopulation is affected.

If the device has already been approved for use in a particular subpopulation, and you are seeking approval of the device for use in an additional subpopulation, you should indicate this in your submission. Section II, question 5 provides more detail about the scope and acceptable sources of readily available information to include in the pediatric use information section of the application, supplement or protocol.

Each supplement to a PMA must also provide any newly available information about pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure. When no new pediatric information about the device is readily available, the applicant may meet their pediatric reporting requirement by stating there is no new information and providing a reference to their most recent submission containing complete pediatric device use information.

To facilitate FDA review of the information, we suggest that you submit the information requested in Section II, question 2 in tabular format in your submission, as suggested in the example below. If you were not able to obtain any readily-available information, please include a brief summary of how you sought the information.

Your pediatric information table should include the indication for use, the incidence and prevalence of the disease or condition the device is intended to diagnose, treat, or cure in the pediatric population and subpopulations, the specific device or device component that could be used or is expected to be used in that population or subpopulation, if applicable (see Section II, question 4), and where the data was obtained (e.g., literature, previous submissions to FDA, FDA master file, American Academy of Pediatrics (AAP) database online, CDC database of diseases).

Immediately following the table you should include a key to any abbreviations or acronyms used in your table, as well as definitions of terms, if appropriate. When citing numbers, you should include the units of scale and references for your information.

Example of Pediatric Summary Table (to be provided separately according to each use or indication)

Indication	Pediatric Incidence [1]	Pediatric Prevalence[2]	Pediatric subpopulation / age range	Specific device/ Component	Source*
This device is indicated for use as an adjunct to medical therapy in the management of pediatric and adult patients with the following clinical conditions: Congestive heart failure related to [rare congenital disease, e.g.,	3,000	1,200	Adolescent 16-21	Widget Model M-111	http://www.cdc.gov/xxxxxx

Duchenne's muscular dystrophy]					

1 Incidence is defined as the number of new pediatric subjects that suffer from the disease or condition that the device is intended to treat, diagnose, or cure every year.
2 Prevalence is defined as the number of all pediatric subjects that suffer from the disease or condition that the device is intended to treat, diagnose, or cure at the time of the report submission.
3 If the pediatric subjects in the source material are not stratified into the recommended subpopulations as defined in question 4 above, still provide the available information and state that the subjects were not stratified in this way. If the subjects are stratified into different subpopulations, please note that this is the case and provide the information for the subpopulations reported.

* See Section II, question 5 for examples

8. What will FDA do with the 515A pediatric device use information?

Section 515A(a)(3) of the FD&C Act requires the Secretary of Health and Human Services to submit to the Committee on Health, Education, Labor and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives an annual report that includes, among other information, the number of devices approved in the year preceding the year in which the report is submitted, for which there is a pediatric subpopulation that suffers from the disease or condition that the device is intended to treat, diagnose, or cure. FDA will use the 515A pediatric device use information included in regulatory submissions to identify devices that should be included in this annual report to Congress.

In addition, information about pediatric populations that suffer from the disease or condition may warrant limitations or even warnings or contraindications against use in pediatric populations if available evidence suggests there is a potential for harm from off-label use in such populations.

Ultimately, FDA would like to use this data to determine unmet pediatric needs in medical device development. Once unmet needs are identified, FDA will be better able to coordinate efforts of stakeholders, device manufacturers and FDA staff to promote new device development and proper labeling of existing medical devices for pediatric use.

9. Does FDA consider the submitted pediatric device use information to be sufficient to establish a new pediatric indication?

Providing only the information described in this guidance to address Section 515A(a)(2) of the FD&C Act is not sufficient to establish the safety and effectiveness of a device for a new pediatric indication. Additional data would generally be needed to support a new pediatric indication. If you believe data developed in adult populations can be successfully extrapolated to support an indication for pediatric populations, we strongly recommend you speak to FDA. In addition, the information provided in this guidance is not intended to supplant any device-specific guidance. For more information on data needed to support a new pediatric indication, the applicant should contact the appropriate review division.

III. Paperwork Reduction Act of 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA) of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated to average 0.5 hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

FDA PRA Staff,
Office of Operations,
Food and Drug Administration,
PRAStaff@fda.hhs.gov

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0231 (To find the current expiration date, search for this OMB control number available at https://www.reginfo.gov).