Draft Guidance for Industry and Food and Drug Administration Staff - Providing Information about Pediatric Uses of Medical Devices Under Section 515A of the Federal Food, Drug, and Cosmetic Act

U.S. Food & Drug Administration

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov [1]. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Sheila Brown (for HDE-related questions) or Premarket Approval (PMA) Staff at 301-796-5640 and CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Preface

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Additional copies are available from the Internet. You may also send an e-mail request to dsmica@fda.hhs.gov [2] to receive an electronic copy of the guidance or send a fax request to 301-827-8149 to receive a hard copy. Please use the document number (1801) to identify the guidance you are requesting.

Additional copies of this guidance document are also available from the Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach and Development (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or by e-mail at

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http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm [3]

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Draft Guidance for Industry and Food and Drug Administration Staff - Providing Information about Pediatric Uses of Medical Devices Under Section 515A of the Federal Food, Drug, and Cosmetic Act

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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] [15] created Section 515A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360e). 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”;
- where to include the pediatric device use information within a submission;
- definitions of the pediatric patient population and of pediatric subpopulations;
- how to provide the pediatric device use information within the submission;
- some acceptable sources that could address the 515A pediatric use information requirement; and
- what FDA will do with the submitted pediatric device use information.

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 [EFFECTIVE DATE OF FINAL RULE], the effective date of the final rule.

A. any request for a humanitarian device exemption (HDE)[2] [16] 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.

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 information that is available in the public domain. All submitted pediatric device use information should be available through commonly used public resources for conducting biomedical, regulatory, and medical product research. FDA’s proposed rule to implement section 515A would codify this definition (proposed 21 CFR 814.3(q)). 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 patient population and pediatric subpopulations defined?

Section 520(m)(6)(E)(i) of the FD&C Act defines the 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). FDA’s proposed rule to implement section 515A would codify this definition (proposed 21 CFR 814.3(p)). Pediatric subpopulations are defined in Section 520(m)(6)(E)(ii) (and adopted by reference in Section 515A(c) of the FD&C Act) to be: Neonates, Infants, Children and Adolescents. Age ranges for these pediatric subpopulations are:

- Neonates: from birth through the first 28 days of life;[3] [17]
- 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 *[18]*. 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] [19]

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 the subpopulation of older adolescents, 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.

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) should be submitted to FDA. An acceptable data source should preferably have only data on U.S. subjects and 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 may 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 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* [20]. 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, this information may also be provided 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. The information submitted 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 briefly describe in narrative form the natural history of the disease or condition which the device is intended to treat, diagnose, or cure. If readily available, it would be helpful for you to also 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 sub population / 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., Duchenne's muscular dystrophy]	3,000	1,200	Adolescent 16-21	Widget Model M-111	http://www.cdc.gov/xxxxxx

[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.

* 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 provide the 515A pediatric device use information submissions 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 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 and 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.

[1] Food and Drug Administration Amendments Act of 2007 [21]

[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 *[22]*".

[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.

[4] *Id*.

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[2] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/mailto:dsmica@fda.hhs.gov
[3] http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm
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