NOT JUST FOR Adults ANYMORE

New Pediatric Considerations for Premarket Approval of Medical Devices in light of implementation of the Pediatric Medical Device Safety and Improvement Act of 2007

On September 27, 2007, President George W. Bush signed into law H.R. 3580, the Food and Drug Administration Amendments Act of 2007,[1] and in so doing, amended the Federal Food, Drug and Cosmetic Act ("the Act"). The law represented a significant addition to the Food and Drug Administration's ("FDA") authority. On April 1, 2010, the FDA promulgated a Direct Final Rule[2] implementing section 515A of the Act. Section 515A is also known as the Pediatric Medical Safety Device and Improvement Act of 2007.[3]

I. The Pediatric Medical Device Safety and Improvement Act of 2007

The Pediatric Medical Device Safety and Improvement Act of 2007 ("PMDSIA") was introduced by Senator Chris Dodd on March 8, 2007.[4] The purpose of the PMDSIA is to improve the process for the development of needed pediatric medical devices.[5] According to Senator Dodd, the PMDSIA provides a comprehensive approach to ensuring that children are not left behind as cutting-edge research and revolutionary technologies for medical devices advance:

As the parent of two young children, it is essential that products used in children's growing bodies, whether drugs or devices, are appropriately tested and designed specifically for their use . . . Because the pediatric market is so small and pediatric diseases relatively rare, there has been little incentive for medical device manufacturers to focus their attention on children. This legislation ensures that our nation's children are receiving the best possible medical treatment and care at a critical time in their development.[6]

A. Requirements of the PMDSIA

The PMDSIA requires applicants who submit certain medical device applications under section 515A(a) of the Act to include the following "readily available" information:

(1) a description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure; and

(2) the number of affected pediatric patients.[7]

The age ranges for each of the populations included in the term "pediatric subpopulation" are as follows: 1) newborn or neonate: from birth to 1 month of age; 2) infant: greater than 1 month to 2 years of age; 3) child: greater than 2 to 12 years of age; and 4) adolescent: greater than 12 to 21 years of age.[8] The FDA has concluded that the term "pediatric patient" in section 515A of the Act refers to patients who are 21 years of age or younger at the time of diagnosis or treatment.[9]

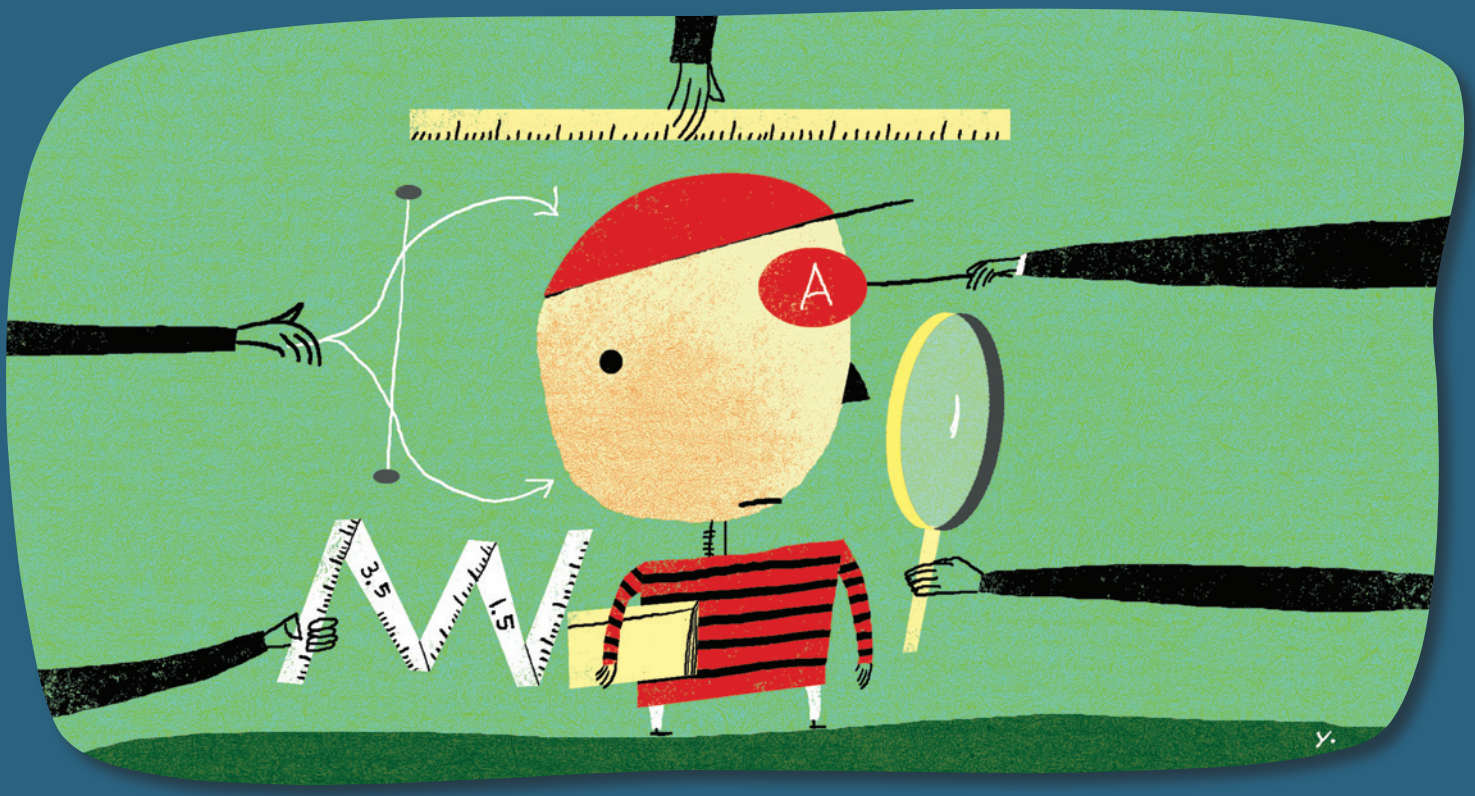
The PMDSIA requirements apply to the following applications when submitted on or after the effective date of the rule:

(1) any request for a humanitarian device exemption ("HDE") submitted under section 520(m) of the Act (21 U.S.C.A. §360j(m));

(2) any premarket approval application ("PMA") or supplemental PMA submitted under section 515 of the Act (21 U.S.C.A. §360e); and

(3) any product development protocol ("PDP") submitted under section 515 of the Act (21 U.S.C.A. §360e).[10]

A PMA supplement applicant may incorporate by reference previously submitted information satisfying these requirements. The applicant must submit addi-



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tional information that has become readily available to the applicant since the previous submission.[11]

The information submitted under the PMDSIA is designed to help the FDA track the following information that is required to be reported annually to Congress, in accordance with section 515A(a)(3) of the Act:

(1) the number of approved devices for which there is a pediatric subpopulation that suffers from the disease or condition that the device is intended to treat, diagnose or cure;

(2) the number of approved devices labeled for use in pediatric patients;

(3) the number of approved devices exempted from a review fee pursuant to section 738(a)(2)(B)(v) of the Act (21 U.S.C.A. §379j(a)(2)(B)(v)); and

(4) the review time for each device.[12]

According to Dr. Jeffrey Shuren, director of FDA's Center for Devices and Radiological Health, "[t]his requirement allows the agency to collect information that will help us better assess public health needs for medical devices that can be used for pediatric populations."[13]

In sum, the PMDSIA requires each applicant who submits an HDE, PMA, supplement to PMA, or PDP to: 1) describe, if "readily available," pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure; and 2) identify the number of affected pediatric patients.[14]

B. Consequences of Not Submitting "Readily Available" Information

The FDA may withhold approval of the application if the applicant fails to submit the required pediatric subpopulation information. If an applicant lacks the requisite information enumerated in the PMDSIA, the FDA has certain protocols to address the deficiency, which are dependent upon the degree of the violations.[15]

1. FDA May Issue Conditional "Approvable" Letter

The FDA will contact an applicant in the normal course of the FDA review to inform the applicant that the submission lacks the requisite information, and the FDA will ask the applicant to amend its application to provide the required information.[16] If the application has no other deficiencies and otherwise meets applicable statutory and regulatory requirements for approval, but still lacks the information required by section 515(A)(a) (21 U.S.C.A. §360e(a)(1)-(2)), the FDA will issue an "approvable" letter informing the applicant that the FDA will approve the application once the requisite data has been provided to FDA.[17]

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2. FDA May Issue "Not Approvable" or "Major Deficiency" Letter

If the application has other deficiencies or does not meet all applicable statutory and regulatory requirements for approval, the FDA will send a "not approvable" letter or "major deficiency" letter describing what the applicant must submit to the FDA before the FDA can approve the application.[18] These letters may cite the absence of the mandatory pediatric subpopulation information in the section listing minor deficiencies.[19]

II. Implementation of the Direct Final Rule

The Direct Final Rule for the PMDSIA is effective August 16, 2010. Comments on the Direct Final Rule must have been received by June 1, 2010 (comments on information collection requirements), and June 15, 2010 (comments on Direct Final Rule).[20] If the FDA receives no timely significant adverse comments, the FDA will confirm the August 16, 2010, effective date of the Direct Final Rule within 30 days after the comment period ends.[21]

Because the FDA believes that the Direct Final Rule is noncontroversial, it does not anticipate receiving any significant adverse comments.[22] In the event the FDA timely receives any significant adverse comment, though, the FDA will withdraw the Direct Final Rule in whole or in part within 30 days after the comment period ends.[23]

A significant adverse comment is defined as "a comment that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without change.[24] In determining the significance of an adverse comment, the FDA will consider whether the comment raises an issue serious enough to warrant a substantive response in accordance with the Administrative Procedure Act ("APA").[25] Frivolous comments, insubstantial comments, or comments outside the scope of the rule will not be considered significant unless the comment states why the additional change makes the rule effective.[26] Moreover, the rule may be severed and parts of the rule that are not the subject of a significant adverse comment may be adopted.[27]

The proposed amendments will not end, however, in the event of significant adverse comments. Consistent with the FDA's procedures on direct final rulemaking, the FDA, concurrent with the Direct Final Rule, also published a companion proposed rule that is identical in substance to the Direct Final Rule ("Proposed Rule").[28] The Proposed Rule provides the procedural framework to finalize the rule in the event that the Direct Final Rule is withdrawn because of

significant adverse comments.[29] The comment period for the Proposed Rule will run concurrently with the Direct Final Rule's comment period.[30] In that circumstance, any comments received will be considered comments on the proposed rule and will be considered in developing a final rule using the usual APA notice-and-comment procedures.[31]

III. Recommendations to Minimize the Possibility of Approval Delays

Although there is a chance that the FDA could withdraw the Direct Final Rule and delay implementation of the Proposed Rule, the FDA clearly does not anticipate any significant adverse comments that would warrant either withdrawal or delay. That being the case, steps should be taken now to gather the requisite pediatric subpopulation data for any devices companies plan on submitting for approval under the HDE, PMA/Supplemental PMA, or PDP processes. The necessary data may already be available from the underlying studies and research that have been done and may simply need to be put in the form required by FDA. If the data has not been tabulated, though, manufacturers should consider the most efficient and timely way to gather the data for purposes of submission. Because the FDA has not to date issued any guidance as to the scope of the term "readily available," manufacturers choosing to submit the device without the pediatric subpopulation data because the data may not be readily available could risk setting back the approval timeline for the device if the manufacturer's definition of "readily available" differs from that of the FDA. Clearly, companies should include tabulation of pediatric population data in the protocol for the development and manufacturing devices in the future so there will not be any snags at the approval process.

IV. Conclusion

On August 16, 2010, medical device manufacturers applying for FDA approval for their devices via: 1) a humanitarian device exemption; 2) premarket approval application; 3) supplemental premarket approval application; or 4) product development protocol will likely have to include information pertaining to pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure, as well as provide data pertaining to the number of affected pediatric patients. Although the FDA will allow applicants to incorporate by reference previously submitted information related to the referenced pediatric subpopulation, this information must be supplemented to include information that has become readily available to the applicant since the device's previous submission. Companies that fail to include the requisite information or properly supplement risk rejection of their respective applications until the FDA receives the data. Companies should, therefore, preemptively identify and produce the requested pediatric subpopulation data for devices the companies intend to submit for approval.

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[1] Codified at 21 U.S.C.A. §§350f, 353b, 355-1, 355d, 355e, 360a, 360e-1, 360n, 360bbb-5, 360bbb-6, 379d-1, 379d-2, 379h-1, 379h-2, 379j-1, 379dd, 379dd-1, 379dd-2, 399a, 2101 to 2110, and 42 U.S.C.A. §247d-5a.

[2] FDA Direct Final Rule, *Medical Devices; Pediatric Uses of Devices; Requirement for Submission of Information on Pediatric Subpopulations that Suffer From a Disease or Condition That a Device Is Intended to Treat, Diagnose or Cure*, 75 Fed. Reg. 16347 (April 1, 2010).

[3] 21 U.S.C.A. §360e-1.

[4] Senate Bill 830, The Pediatric Medical Device Safety and Improvement Act of 2007.

[5] *Id.*

[6] http://dodd.senate.gov/index.php?q=node/3802.

[7] 21 U.S.C.A. §360e(a)(1)–(2); *see also* 75 Fed. Reg. 16347 (April 1, 2010). The FDA does not define the term "readily available" in this context.

[8] 21 U.S.C.A. §360j(m)(6)(E)(ii); *see also, Premarket Assessment of Pediatric Medical Devices* (May 14, 2004) at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089740.htm.

[9] 75 Fed. Reg. 16347 (April 1, 2010).

[10] 21 U.S.C.A. §360e-1(b).

[11] 75 Fed. Reg. 16348 (April 1, 2010).

[12] 21 U.S.C.A. §360e-1(a) (3).

[13] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm206872.htm.

[14] *Id.*

[15] For information concerning FDA interactive review process, *see Guidance for Industry and FDA Staff: Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements at* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm.

[16] 75 Fed. Reg. 16348 (April 1, 2010).

[17] *Id.*

[18] *Id.*

[19] *Id.*

[20] 75 Fed. Reg. 16347 (April 1, 2010).

[21] *Id.*

[22] 75 Fed. Reg. 16366 (April 1, 2010).

[23] *Id.*

[24] 75 Fed. Reg. 16348 (April 1, 2010).

[25] *Id.*; *see* 5 U.S.C.A. §553 for relevant section from the Administrative Procedure Act.

[26] 75 Fed. Reg. 16348 (April 1, 2010).

[27] *Id.*

[28] FDA Proposed Rule, *Medical Devices; Pediatric Uses of Devices; Requirement for Submission of Information on Pediatric Subpopulations that Suffer From a Disease or Condition That a Device Is Intended to Treat, Diagnose or Cure*, 75 Fed. Reg. 16365 (April 1, 2010).

[29] 75 Fed. Reg. 16366 (April 1, 2010).

[30] *Id.*

[31] *Id.* ; *see* 5 U.S.C.A. §552a *et seq* for relevant section from the Administrative Procedure Act.

Written *by*
Michael Hewes