FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

FDA finalizes guidance on pediatric information in drugs, biologics labeling

The guidance describes what pediatric information should be included in the labeling of drugs and biologics and where it should be located to make it clear and accessible to health care providers. The FDA plans to issue separate guidance on pediatric use information for biosimilars licensed under section 351(k) of the Public Health Service Act.

The FDA finalized guidance to help drug and biologic sponsors determine what pediatric information to include in product labeling and to ensure that placement of the information is consistent. The guidance, which was initially published as a draft in 2018, addresses requirements under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). Generally, the FDA defines pediatric populations as those 16 years and younger. The agency recommends using phrases such as "pediatric patients X to Y years old" or "pediatric patients aged X years and older" to describe a specific age group or pediatric subpopulation in labeling. The guidance indicates, however, that use of another description may be considered on a case-by-case basis so long as there is a valid scientific reason for an alternative approach.

Per the guidance, data submitted in response to a written request under the BPCA as well as assessments in response to PREA study requirements need to be described in labeling, regardless of the findings. When studies are waived under the PREA because evidence indicates a treatment wouldn't be effective or may be unsafe in a particular pediatric age group, the safety concern needs to be described in the labeling. Pediatric use information is normally disclosed in the Pediatric Use subsection and is included in other labeling sections as appropriate. The guidance outlines which sections of labeling should include pediatric information and what information should be included based on four scenarios.

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1. **The evidence supports the safety and effectiveness of a drug for an indication in pediatric patients.** Approved pediatric information should be included in the following:

   - Indications and Usage section. If a drug is indicated for the entire pediatric population, the term "pediatric patients" or "pediatric patient" should be included in the indication statement; however, if a drug's pediatric indication is limited to a specific age group, the indication statement should specify those ages.

   - Dosage and Administration section. This section should include recommended dosage in pediatric patients as well as preparation and administration instructions related to pediatric use.

   - Adverse Events section. The labeling should provide details of pediatric adverse reaction data from clinical or postmarketing trials.

   - Pediatric Use subsection. This subsection should include a pediatric use statement or reasonable alternative, such as "The safety and effectiveness of DRUG X (for Indication Y) have been established in pediatric patients aged 6 years and older." When a drug is approved for pediatric use based on studies in adults and supporting pediatric information, the basis of approval should be described after the pediatric use statement. The Pediatric Use subsection should also provide information regarding any specific risks or safety concerns in pediatric patients, limitations on the pediatric indication and any differences between pediatric and adult populations.

   - Clinical Pharmacology section. This section should include detailed descriptions of pediatric pharmacokinetic, pharmacodynamic and/or pharmacogenomic study data, including dose response information.

   - Clinical Studies section. The labeling should describe studies that provide substantial evidence of effectiveness for use in pediatric patients.

2. **The evidence doesn't support the safety and effectiveness of a drug for an indication in pediatric patients because studies were negative or inconclusive.** In such cases, any pertinent pediatric information related to the unapproved use that is included in labeling should be placed in the Pediatric Use subsection with a brief summary of the negative or inconclusive studies. An appropriate pediatric use statement should be included before the summary of available evidence, such as "The safety and effectiveness of DRUG X have not been established in pediatric patients (for Indication Y)." Any risk or safety concerns should be described.

3. **There is no evidence to support the safety and effectiveness of an indication in pediatric patients because studies have not been completed, have been waived under PREA or are ongoing.** In these instances, an appropriate pediatric use statement must be placed in the Pediatric Use subsection to make clear that the safety and effectiveness in pediatric patients haven't been established, such as "The safety and effectiveness of DRUG X have not been established in pediatric patients."

4. **The available evidence indicates the drug is contraindicated for use in pediatric patients.** In these cases, the contraindication and reason for the contraindication should be stated in the Pediatric Use subsection and in the Contraindications section. If the contraindication applies to all pediatric patients, the contraindication statement should be used as an alternative pediatric use statement in the Pediatric Use subsection. On the other hand, if the contraindication applies only to a specific age group, an additional pediatric use statement should be added to describe the evidence or lack thereof to support the remaining age groups.

CBER finalizes guidance on use of standards in regulatory submissions

The guidance provides a Q&A on what a standard is, how voluntary standards are developed and what the CBER's policy on accepting standards used in regulatory submissions is. The guidance doesn't endorse the activities of specific standards development organizations or recommend specific standards for use in regulatory submissions. Rather, it describes how using voluntary consensus standards can facilitate development.

In recognition that the use of standards can facilitate a more efficient evaluation of regulatory submissions, the FDA's Center for Biologics Evaluation and Research (CBER) finalized guidance on the use of standards in product development and the review process. The Q&A guidance addresses the use of standards in regulatory submissions such as investigational new drug applications (INDs), biologics license applications (BLAs), new drug applications (NDAs), investigational device exemptions (IDEs), premarket approval applications, and premarket notifications, supplements and amendments.

Per the guidance, voluntary consensus standards are "standards developed or adopted by a domestic or international voluntary consensus standards body," which develops standards using due process, with an opportunity for appeal, and the following attributes:

- Openness. Interested parties are provided meaningful opportunities to participate, and the processes for standard development are transparent.
- Balance. There is meaningful involvement from an array of parties, with no single interest dominating the decision-making.
- Consensus. Consensus is defined as general agreement but not necessarily unanimity, and objects are considered using fair, impartial, open and transparent processes.

The guidance notes that while the CBER often participates in the development of voluntary standards, such participation does not constitute endorsement of a standard. Rather, the CBER participates in standards development organizations (SDOs) to familiarize itself with standards as they are developed. This participation helps to ensure standards don't conflict with FDA regulations or policies and increases the likelihood that standards will be suitable for use in regulatory submissions.

The guidance states that the CBER plans to preferentially use internationally harmonized standards when such standards are the most appropriate for a specific purpose and don't conflict with U.S. law. It recommends that sponsors confirm that the standard was used as published or describe how they deviate from the assay described in the standard. The guidance directs sponsors to discuss a proposed use of a standard with the CBER before implementing it to ensure the standard is appropriate for the intended regulatory purpose.

Per the guidance, sponsors should provide a complete reference for the standard when using it in a regulatory submission. Sponsors may use appropriate written or documentary standards that describe a process or assay to assess manufacturing or intermediate or final products, or they may use physical standards or reference material in the development and testing of their product. Sponsors should provide information on the reference standards or material used in a regulatory submission. The guidance recommends that sponsors provide the source, lot number, expiration date, and certificates of analyses and evidence—both internal and external—of identity and purity for each reference standard. Compendial standards may also be used to support a regulatory submission if the CBER determines it is appropriate. Data standards, such as structured product labeling, may also be used to make the regulatory review process more efficient.

When assessing compliance to regulatory requirements, the guidance indicates that the CBER may in some instances take into consideration accreditation standards from organizations such as AABB (transfusion medicine and cellular therapies) and the Foundation for the Accreditation of Cellular Therapy (cellular therapy). The guidance adds that the World Health Organization (WHO) doesn't meet the CBER's definition of an SDO, but that the standards it develops "have a role in the development, manufacturing, and use of certain medical products."

Draft guidance establishes uniform standards, processes for medical device inspections

The guidance establishes uniform processes and standards for inspections of both domestic and foreign medical device firms. The FDA said consistency in investigators' approaches may help firms prepare for inspections and establish baseline communication and timing expectations.

The FDA published draft guidance as part of its mandate under the FDA Reauthorization Act of 2017 (FDARA) to establish uniform processes and standards for inspections, other than for-cause, of foreign and domestic medical device firms. Section 702(b)(1) of the FDARA added section 704(h)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), which directs the FDA to adopt uniform processes and standards describing how the agency should pre-announce inspections, provide a reasonable estimated timeline for inspections and ensure regular communication with device makers.

As mandated by the FDARA, the FDA reviewed the processes and standards related to medical device inspections and identified uniform processes and standards. The guidance establishes the following processes and standards:

- **Pre-announcement notice and communication.** An FDA inspector will notify establishments by telephone prior to surveillance or preapproval inspections, though the FDA retains the authority to conduct unannounced, for-cause inspections. For domestic firms, the announcement will be no less than five calendar days before the inspection. Due to requirements of particular country clearances, the announcement may be more than five days before inspection of foreign firms. Per the guidance, notifications should generally include information regarding the type and nature of the inspection. When possible, the FDA should provide device makers advance notice of records that may be requested by inspectors.

- **Standard inspection time frame.** Typically, a reasonable time frame for an inspection ranges from three to six days. The guidance indicates that the FDA will share estimated durations for each inspection at the time of pre-announcement. The duration of inspection may change depending on factors such as the complexity of operations, availability of knowledgeable staff and nature of observed issues. The guidance cautions that inspections may need to be extended for a number of reasons, such as follow-up on postmarket safety information. However, unless an investigator identifies a reason for additional time and communicates it verbally to the device maker, inspections should take place within a standard time frame and take place over consecutive business days.

- **Communication during inspections.** When able, inspectors should "make every reasonable effort" to discuss with the firm's management all observations as they are observed or on a daily basis. Such communications may be recorded by the FDA or the firm, so long as there is advance notice and mutual consent.

FDA finalizes rule to update, eliminate certain biologic inspection requirements as part of 'one-in, two-out' executive order

The rule updates biologics regulations related to time of inspection requirements and eliminates certain inspector requirements. It eliminates outdated requirements as part of the 'one-in, two-out' executive order and is meant to facilitate a risk-based inspection approach and provide flexibility.

The FDA finalized a rule amending biologics regulations to facilitate a risk-based inspection frequency. The rule updates the time of inspection requirements under section 600.21 and eliminates the duties of inspector requirements under section 600.22 but does not alter the inspection requirements and requirements for investigator duties under sections 704 and 510(h) of the Federal Food, Drug, and Cosmetic Act (FDCA) or section 315(c) of the Public Health Service Act.

The rule removes the biennial inspection requirement for facilities registered either as drug establishments or device establishments. Per the FDA, the requirement is being removed because the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) implemented a requirement that the FDA inspect establishments using a risk-based schedule rather than biennially. In addition, the FDA Reauthorization Act of 2017 (FDARA) replaced the biennial inspection schedule for device establishments under the FDCA with a risk-based schedule, making the requirement under section 600.21 for biennial inspections inconsistent with the FDCA.

The rule also eliminates requirements regarding inspectional notice and the timing of pre-licensure reinspections of biological establishments, as the FDA determined they are outdated and unneeded. The agency also determined that section 600.22, which establishes specific duties for inspectors, is unnecessary because the requirements are duplicative of statutory requirements under section 704 of the FDCA. The FDA notes that removal of these regulations does not alter the established process for risk-based inspection planning.

The rule was initially withdrawn due to "significant adverse comments." In response, the FDA argued that a risk-based approach would not have negative health consequences because while some establishments may not be inspected every two years, these will be the ones deemed lower risk. The FDA explains that resources saved by performing less-frequent inspections of lower-risk establishments can be directed toward inspections of higher-risk facilities. It also argues that concerns about the risk-based approach will be addressed through its review of known safety risks of drug and device establishments and its ability to inspect as needed.

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