FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

FDA publishes draft guidance describing pathways for combination product review

The guidance outlines the principles for premarket review of combination products and discusses how to determine which type of premarket submission is appropriate. It indicates that a single application is typically suitable for a combination product, with the primary mode of determinizing which type should be submitted.

As part of its efforts to implement the 21st Century Cures Act, the FDA issued draft guidance describing the principles for premarket review of combination products. Section 3038 of the Cures Act amended the Federal Food, Drug, and Cosmetic Act 26 (FDCA) to improve the predictability and consistency of premarket review of combination products by ensuring that FDA components coordinate. The draft guidance reflects the FDA's effort to implement those amendments and ensure transparency and consistency in the regulatory process.

Per the guidance, combination products will be assigned to a lead FDA center, which will be the primary point of contact between the agency and sponsor, based on the primary mode of action (PMOA). If the PMOA of a combination is related to the biological component, for instance, the center responsible for premarket review of such a biological would have primary responsibility for oversight of the combination. The guidance notes that sponsors may submit a request for designation (RFD) if they want a binding classification assignment or a "Pre-RFD" if they want informal feedback on the classification of a product. To facilitate agency coordination, meetings between the FDA and sponsors will include review staff from each center, as appropriate, for the purpose of the meeting.

The guidance explains that drugs, devices and biological products don't lose their "distinct regulatory identity" when part of a combination. Therefore, premarket requirements for combination products are based on the statutory and regulatory requirements applicable to constituent

parts, though a single application will generally be appropriate. The guidance indicates that the marketing application type should align with the PMOA of the combination. For instance, a new drug application may be used for a drug-led combination. In certain instances, however, the guidance notes a single application may not be appropriate or an application type associated with nonlead constituent parts may be needed. The applications should provide for a "substantially similar evaluation" compared with what would be applied if each constituent part were reviewed separately. Irrespective of which center is the lead and which application type is appropriate, the FDA will apply a risk-based approach to address regulatory questions.

The guidance cautions that the data and information needed to address questions of safety and efficacy for nonlead constituents may differ from that needed to obtain marketing authorization if that part were a stand-alone product rather than part of a combination. The premarket review of a combination product may be accelerated in cases in which a sponsor is legally permitted to rely on the FDA's previous findings of safety and efficacy or substantial equivalence for an approved or cleared constituent part, or in cases in which a sponsor has a right of reference for another sponsor's data. For instance, in a device application for a device-led combination, the FDA's previous findings of safety and efficacy for drug constituent parts may be referenced when scientifically appropriate.

The FDA said it would be issuing additional guidance on specific premarket considerations for combination products. Commissioner Scott Gottlieb said the goal was to implement an efficient framework that ensures timely and effective product review, adding that cross-center collaboration will be critical.

FDA finalizes guidance outlining guiding principles for application of least burdensome provisions for medical devices

The guidance describes the guiding principles and applications of the least burdensome provisions for medical devices. The guidance was updated to reflect statutory changes and to promote new initiatives within the FDA, such as the use of FDA-recognized voluntary consensus standards and FDA feedback on inspectional observations from device-manufacturing facilities.

The FDA finalized guidance, initially published as a draft in 2017, describing the guiding principles and recommended approach to implementing least burdensome principles for medical devices. The guidance reflects updates to the least burdensome provisions under legislation such as the Food and Drug Administration Safety and Innovation Act of 2012 and the 21st Century Cures Act, and it makes clear that the statutory definition of a medical device includes device constituent parts in combination products. It defines least burdensome as "the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time."

The least burdensome provisions apply to all products that meet the statutory definition of a device and apply to all activities related to the regulation of medical devices throughout the entire product life cycle from pre- to postmarket, including premarket submissions such as premarket approval applications and 510(k)s, panel reviews and recommendations, information or interactive inquiries about device development, and compliance-related integrations. However, the least burdensome principles don't alter the applicable regulatory and statutory standards or requirements, such as content requirements for premarket submissions.

The guidance delineates seven guiding principles to apply a least burdensome approach:

1. The agency will ask for the minimum information needed to sufficiently address a regulatory question or issue.

2. Industry members should provide material to the FDA that is the least burdensome for the agency to review, ensuring that information is well-organized,

clear and concise and that no information is provided that is unrelated to regulatory decision-making.

3. The most efficient means available will be used to resolve regulatory questions and issues, including by leveraging "all reasonable means" to accelerate processes and policies and make decisions within established timelines such as MDUFA and by taking tailored approaches to address specific questions and issues.

4. The right information should be made available at the right time to address the right questions, including by considering the use of postmarket data to reduce premarket data collection when appropriate and practicable.

5. Regulatory approaches need to be designed to fit the technology by considering unique innovation cycles, evidence-generation needs and timely patient access.

6. The agency anticipates using data from other countries and decisions made by other regulatory authorities when appropriate and feasible.

7. The FDA intends to apply the least burdensome principles to international device convergence and harmonization efforts – such as participation in the International Medical Device Regulators Forum – by actively engaging in the development, recognition and use of voluntary consensus standards issued by international organizations.

The guidance provides examples to illustrate how the least burdensome principles can be applied in practice. For instance, real-world evidence generated from a registry may be used to support expanded indications for a product, or nonclinical data may be considered as a replacement for clinical data when appropriate. The guidance recommends the consideration of alternative approaches to optimize time and resources – for instance, by considering alternative and limited indications-for-use labeling to support marketing authorization for a device that otherwise would receive a "not substantially equivalent" determination. As an example of the application of least burdensome principles to streamline administrative burdens, the guidance points to the use of bundled marketing submissions or dual 510(k)/Clinical Laboratory Improvement Amendments (CLIA) Waiver submissions. It also directs sponsors to consider using qualified medical device development tools to reduce development costs and review times. The guidance emphasizes a total product life cycle approach, with a focus on balancing premarket and postmarket information needs and assessing the right time for obtaining information. In terms of compliance, an example of least burdensome provisions is the FDA's program for device makers to request nonbinding feedback on inspectional observations.

CDER proposes program to informally recognize voluntary quality consensus standards

The program would allow industry stakeholders to recommend pharmaceutical quality standards for potential recognition by the FDA. The program applies to informally recognized standards and is separate from the FDA's formal recognized standards program. It is meant to promote the development and use of consensus standards for emerging technologies such as continuous manufacturing, which may accelerate drug development and review.

The FDA's Center for Drug Evaluation and Research (CDER) issued draft guidance outlining a proposed program to develop a public listing of informally recognized voluntary pharmaceutical quality consensus standards. Under the proposed program, external stakeholders and CDER staff would be allowed to propose voluntary consensus standards, defined as "a standard that is developed or adopted by domestic and international voluntary consensus standards bodies," for informal recognition by the FDA in order to accelerate the assessment of marketing applications.

FDA Commissioner Scott Gottlieb said recognition of a standard may help limit regulatory uncertainty. The FDA will streamline the review of applications referencing recognized standards, but Gottlieb cautions that the program doesn't alter the requirements of the FDCA.

The program would allow stakeholders to submit a candidate consensus standard, along with pertinent information such as the scope and purpose of the standards, after which the CDER would determine whether to informally recognize it – either in part or in whole – and would then list the standard in a publicly searchable database. Per the guidance, the CDER will consider standards developed by voluntary consensus standards bodies that adhere to five key elements:

1. Openness – The procedures or process for standards development are transparent and open, with interested parties given "meaningful opportunities" to engage in development in a nondiscriminatory manner.

2. Balance – An array of stakeholders are given the opportunity to take part in standards development, with no single interest group controlling the decision-making.

3. Due process – The development process for the voluntary consensus standards body includes a due process provision under which standards development policies and procedures are documented and publicly available and all stakeholders are provided notice of development activities with enough time to engage in development (e.g., by preparing objections).

4. Appeals process – An appeals provision is included in the standards development process to allow the body to impartially deal with procedural appeals.

5. Consensus – Comments and objections are considered using "fair, impartial, open, and transparent processes" during the development of consensus, which is defined as a "general agreement, but not necessarily unanimity."

The CDER's Pharmaceutical Quality Standards Working Group (PQSWG) plans to develop an internal process for informally recognizing standards after reviewing comments on the program, which will be made public in the Manual of Policies and Procedures. The PQSWG will follow general procedures such as assessing all requests for informal recognition of voluntary consensus standards and confirming that standards will not conflict with existing statutes, regulations or policies. If a proposed standard meets the qualifying criteria, the group may recommend the formation of a subgroup of experts to review the standard or may recommend an FDA laboratory assess the proposed standard. Subject matter experts and the PQSWG will work together to create an information sheet describing the information recognition of the standard and any pertinent information about the standard. Gottlieb said that once the FDA recognizes a standard, applications won't typically have to validate the approach outlined in the standard, focusing instead on appropriate use of the method and the acceptance criteria.

FDA publishes draft guidance establishing process for device makers to request nonbinding feedback on inspectional observations

The guidance describes the process through which device makers can ask the agency for nonbinding feedback on certain kinds of inspectional observations issued on a Form 483 during either pre- or postmarket inspections. It was issued per a requirement under the FDA Reauthorization Act of 2017, as companies previously could request feedback only for proposed corrective actions.

The FDA issued draft guidance outlining a process through which the "owner, operator or agent in charge of a device establishment" can ask for nonbinding feedback from the FDA on proposed actions to address inspectional observations documented on a Form 483. Per the guidance, timely nonbinding feedback can help device makers ascertain whether their planned actions

sufficiently address inspection observations, potentially mitigating unnecessary investment in solutions that may not be satisfactory. Under Section 704(h)(2) of the FDCA, which was added in 2017, the FDA was directed to provide nonbinding feedback within 45 days after receiving a request for feedback on actions in response to observations that involve a public health priority, implicate systemic or major actions, or relate to emerging safety issues.

Per the guidance, requests should be made in a timely manner, defined as being submitted no later than 15 business days after the FDA issued a Form 483. If the request for feedback coincides with a response to a Form 483, the FDA recommends the response and request be included in the same submission but as two distinct documents. Requests should include:

- A statement header indicating it is a request for nonbinding feedback following an inspection;
- Contact information for the person submitting the request;
- The name, address and FDA Establishment Identification (FEI) number of the establishment, along with the date of the inspection; and
- A justification for why the request meets the statutory eligibility for feedback. Situations in which a request meets requirements include:
  - The observations request resolution because they have resulted in – or may result in – the release of a violative product that may cause serious injury or death;
  - The observations suggest the quality system or subsystems are deficient and have resulted in – or are likely to result in – the manufacture of nonconforming, violative and/or defective finished devices; or
  - The observations pertain to emerging safety issues that may result in the release of devices that are likely to cause death or serious injury.

The guidance directs requests to describe, in detail, how each individual observation meets one or more of the eligibility criteria. The FDA is required to provide feedback on observations for which the justification satisfies at least one of the statutory eligibility criteria. The requests should explicitly state the inspectional observations the requester is seeking feedback on, followed by proposed actions in response to those observations.

Once the FDA has received a timely request and has verified the request is made by the "owner, operator, or agent in charge of the device establishment" or a designated representative, it will ascertain whether the justification is sufficient and either provide feedback or notify the requester that the request isn't eligible for feedback within 45 days. The feedback will identify whether the proposed actions appear to be adequate, partially adequate or inadequate if implemented effectively. If the agency determines the actions are partially adequate or inadequate, it will explain why and provide a recommendation on what may be needed for the actions to be considered adequate.