FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

FDA finalizes guidance on patient-specific information-sharing by device makers

The guidance, originally published as a draft in June 2016, offers recommendations on device makers' responses to patient requests for data and addresses when the sharing of patient-specific data may be considered labeling.

The FDA finalized guidance offering recommendations on how device makers may respond to patient requests for patient-specific information, in recognition that patients are playing an increasingly active role in their healthcare and that such data may allow them to be more engaged with providers. Although patient-specific information from devices is often available via providers, patients may also contact manufacturers directly to request data. While not required by the Federal Food, Drug, and Cosmetic Act (FDCA), the guidance outlines best practices for when device makers decide to share such data.

The guidance applies to information unique to an individual or a patient's diagnosis and treatment derived from a legally marketed device. However, the guidance does not apply to a device maker's interpretation of data, unless it is an interpretation of data normally reported by the device to a patient or provider. Categories of patient-specific information may include data that providers input into the device to record the status of treatment, including patient-specific case logs, or information stored by the device, such as heart activity. The guidance doesn't impact existing regulations, such as the Health Insurance Portability and Accountability Act or privacy rules.

The guidance offers the following considerations:

- Patient-specific information will generally not be considered labeling and may be shared without premarket review, but if additional information or material — such as descriptions of intended use or

information about risks and benefits — is shared, it may be considered labeling and be subject to FDCA and FDA regulation.

- Any patient-specific information shared with patients should be comprehensive and contemporary. Device makers can format information to make it more usable to patients and should share all data available, including up to the most recent measurement.
- Device makers should direct patients to reach out to providers with any questions about the data.

Finalized guidance outlines process for dispute resolution with CDER, CBER

The guidance, originally published as a draft in 2015, describes the formal dispute resolution process to address issues between the FDA and sponsors pertaining to user fee product applications, such as NDA, ANDAs, INDs and BLAs. It outlines the information that should be provided when making a request and the timelines for officials to respond.

The FDA finalized guidance outlining procedures for the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) to take when resolving disputes with sponsors that can't be resolved at the division level. The guidance describes the formal dispute resolution (FDR) process for sponsors appealing a scientific or medical issue arising during the review of an application for a product covered by user fees. Per the guidance, an FDR may address regulatory action taken by the FDA pertaining to a user fee product application that has scientific or medical significance. This may include complete, partial or full clinical trial holds; a refuse to receive notification or request for breakthrough therapy designation; or a proprietary name review.

Prior to submitting an FDR request, sponsors should ask the review division or office that made the decision in question to reconsider the issue. For example, if a sponsor receives a clinical hold action or CR letter and has been granted a post-action meeting, an FDR request will not be accepted until the sponsor has participated in that meeting. If an FDR request is made, sponsors shouldn't engage in other regulatory or legal actions on the same matter. For example, if a sponsor receives a CR action and submits a request for an end-of-review meeting with the review division, an FDR request should not be submitted at the same time and will not be accepted.

No new information should be submitted as part of the request for FDR, as an appeal must be based on the same information used to make the initial decision in question. If a sponsor wishes to have the office consider new information that may impact the original decision, the information should be submitted to the sponsor's application for review by the division and the official who rendered the initial decision. The guidance points out that new analyses of previously assessed data are considered new information.

Once a sponsor has decided to submit a request for FDR, it may request a meeting with the deciding official to discuss the appeal issues. Throughout the FDR process, a sponsor may also request that a dispute be reviewed by an advisory committee. However, the guidance cautions that such a request should be made as early in the process as possible given that it can take a significant amount of time to schedule an advisory committee meeting.

When submitting an FDR request, a sponsor should provide information explaining the scientific or medical dispute, including a brief statement of each issue to be resolved and a statement identifying the division or office that issued the decision in question. The request should also state whether the sponsor is requesting a meeting with the deciding official or requesting an advisory committee review. A sponsor should also provide a list of documents submitted before the application that are essential to the resolution of the issue, as well as a statement that no

new information has been submitted to support the FDR request.

Once this information is received, the CDER Formal Dispute Resolution Project Manager or CBER ombudsman will conduct a preliminary review of the request to determine whether it meets procedural criteria and can be accepted. If accepted, the appeal will be forwarded to the appropriate management level and the sponsor will be sent an acknowledgment letter. The deciding official will then send a written decision to the sponsor granting or denying the appeal. If the official disagrees with the sponsor, a reason will be provided for the decision and the official may offer recommendations to achieve resolution and identify potential actions for sponsors to address outstanding concerns. Generally, the deciding official should respond or request additional information within 30 days.

FDA finalizes guidance on De Novo classification process, issues draft on acceptance criteria

Draft and finalized guidance establish the criteria for review of De Novo classification requests, as well as the designation process. The guidance documents make clear the process for requesting a De Novo classification and offer updates based on the Cures Act and MDUFA IV.

The FDA issued draft guidance on acceptance criteria for requests for De Novo classification and finalized guidance on the classification process. The guidance documents address provisions under Section 513(f)(2) of the FDCA, which created a process for De Novo classification in order to reduce unnecessary use of FDA and industry resources should devices with a reasonable assurance of safety and efficacy be subject to premarket approval. Under the section, device makers can request a De Novo classification for devices automatically classified as Class III because they represent a new type of device not previously classified by the agency.

The draft guidance discusses the information needed for a substantive review of a De Novo request and is meant to help make the review process more efficient, helping the FDA meet performance goals for timeliness under MDUFA IV. Though it doesn't modify the process through which devices are classified once accepted for review, the guidance adjusts the start of the FDA review clock for meeting MDUFA IV goals. It outlines the criteria the agency will assess in determining whether a request meets a minimum threshold of acceptability and includes an acceptance checklist, as well as a recommended content list. The guidance recommends that sponsors complete and include the acceptance checklist with their requests, identifying where supporting information for acceptance criteria can be found.

The acceptance review will ensure a request is administratively complete and that all the information needed for substantive review has been provided. A refuse to accept (RTA) designation may be issued if one or more of the items flagged as RTA items in the checklist are not provided. The guidance notes that not all criteria in the checklist may be pertinent to a particular device and directs agency staff to select "N/A" for elements that don't apply to the device in question. Using the checklist, items should be designated as "yes" or "N/A" in order for a request to be accepted for substantive review. For items designated as "no," the FDA will offer an explanation to describe the missing elements and a statement of additional information required to meet acceptance criteria. Upon receipt of a De Novo request, the FDA is expected to complete the acceptance review within 15 calendar days. The review clock begins when the Document Control Center receives the most recent De Novo request or additional information that resulted in an acceptance designation for the request, so long as the user fee has been paid and a validated eCopy has been presented. The clock does not start when a request is placed on eCopy or user fee hold or is designated RTA.

Separately, the finalized guidance offers recommendations for interactions between the FDA and

device makers related to the classification process and discusses the information needed when seeking a path to market using the De Novo process. The guidance clarifies that the FDA will review De Novo requests for devices that don't fall within a device type that has been classified under Section 513(a)(1) or within any existing classification regulation, so long as the requester has determined there is no predicate device or has received a not substantially equivalent (NSE) designation determination on a 510(k) submission. It also implements the Cures Act's removal of the requirement that requests be submitted within 30 days of receiving an NSE determination.

Requests must include a description of the device, along with detailed information and reasons for recommendation classification. The FDA will make a determination within 120 days of the request, and if the requester is able to show that the criteria of 513(a)(1)(A) or (B) are met, the request will be granted. If granted, a De Novo classification will permit the device to marketed immediately and will create a classification regulation for devices of that type, allowing the device to serve as predicate. Recommended content for requests includes:

- **Regulatory history:** Prior submissions and any response to previous feedback
- **Change summary:** If appropriate, details on any changes made to the device since a previous pre-submission or 510(k)
- **Classification summary:** A description of the search for legally marketed devices of the same type and a list of classification regulations, cleared 510(k)s, approved PMAs or product codes related to the subject device
- **Classification recommendation:** Recommended class (I or II) and a description of why the controls are sufficient to offer reasonable assurance of safety and efficacy
- **Risk and mitigation information:** A table demonstrating the proposed mitigation for each identified risk
- **Device labeling:** Labeling that clearly states the proposed intended use and indications for use, limitations, contraindications and so on

FDA takes steps to implement regenerative medicine policy framework for draft, final guidances

With a group of final and draft guidances, the FDA outlined its regulatory framework for regenerative medicine, implementing a risk- and science-based approach and making clear the agency's authorities and enforcement priorities.

The FDA published two final guidance documents and two draft guidances outlining its policy framework for the development and oversight of regenerative medicine products, building on the agency's established risk-based regulatory approach. Commissioner Scott Gottlieb said the field is at the precipice of a "paradigm change" in regenerative medicine, presenting unique challenges to the agency. He added that the framework is meant to balance the FDA's commitment to safety with mechanisms to drive innovation.

The two final guidance documents include:

- Guidance on the same surgical procedure exception under 21 CFR 1271.15(b), under which cell- and tissue-based products may be excepted from regulations if removed from and implanted into the same individual within the same surgical procedure and in the original form. The Q&A guidance makes clear that in order for products to meet the definition of "original form," the only processing steps permitted to an HCT/P are rinsing, cleansing, sizing and shaping. Even minimal manipulation may cause a product to no longer be in its original form, as required by the exception. In general, the guidance

indicates that an establishment that processes an autologous HCT/P before implantation will be subject to regulations and wouldn't qualify for the exception.

- Guidance addressing regulatory considerations for HCT/Ps, which outlines the FDA's interpretation of minimal manipulation and homologous use criteria. Under the FDA's tiered, risk-based regulatory approach, implemented in 2005, these criteria are part of the threshold for when an HCT/P is subject to premarket approval requirements. The finalized guidance offers a flowchart on the application of the criteria and Q&As on both definitions. It makes clear that the determination that an HCT/P is minimally manipulated is based on the effect manufacturing has on the original characteristics of the HCT/P as it exists in the donor, rather than on the intended use of the HCT/P in the recipient. It further clarifies that homologous use means the "repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor." The FDA said it plans to exercise discretion in enforcement for the first 36 months of the new policy for products that are subject to premarket review but that don't meet the requirements.

The two draft guidance documents include:

- Guidance outlining how the agency plans to evaluate devices used in regenerative medicine advanced therapies (RMATs), which outlines the FDA's current thinking regarding a range of concepts pertaining to the regulation of devices used in the recovery, isolation and delivery of RMATs. It outlines the agency's plans to streamline the application of regulatory requirements for combination devices and cell or tissue products, and discusses what intended uses or attributes may result in such a device being classified as Class III.

- Guidance on the expedited programs available for regenerative therapies for serious conditions, which addresses the designation of a product as RMAT under Section 506(g) of the FDCA, as added to the Cures Act. It discusses the programs available to regenerative therapies for serious conditions and offers insight into the provisions in the Cures Act for the accelerated approval pathway for RMATs.

For more information on any of these FDA regulatory and compliance updates, please contact Scott S. Liebman at sliebman@loeb.com.

Loeb & Loeb LLP's FDA Regulatory and Compliance Practice

Loeb & Loeb's FDA Regulatory and Compliance Practice comprises an interdisciplinary team of regulatory, corporate, capital markets, patent and litigation attorneys who advise clients on the full spectrum of legal and business issues related to the distribution and commercialization, including marketing and promotion, of FDA-regulated products. Focusing on the health and life sciences industries, including pharmaceuticals, biologics, medical devices, wellness products, dietary supplements and organics, the practice counsels clients on regulatory issues, compliance-related matters and risk management strategies; advises on laws and regulations related to product advertising and labeling; counsels on FDA exclusivity policies and related Hatch-Waxman issues; and provides representation in licensing transactions and regulatory enforcement actions.