FDA Regulatory and Compliance Monthly Recap

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FDA issues draft guidance to update policy on categorizing investigational device exemption devices to assist CMS coverage decisions

The draft guidance will amend the FDA's 20-year-old policy for categorizing devices as experimental or nonexperimental based on initial questions of efficacy and safety. The CMS uses these categorizations when making decisions regarding Medicare reimbursement.

The FDA published draft guidance to adjust its policy on categorizing investigational device exemption (IDE) devices to help the Centers for Medicare & Medicaid Services (CMS) make reimbursement decisions. In late 2015, the FDA's Center for Devices and Radiological Health (CDRH) and the CMS' Coverage and Analysis Group (CAG) signed a memorandum of understanding (MOU) to establish a more efficient process to categorize investigational medical devices in order to support the CMS' ability to make Medicare reimbursement decisions. The draft guidance is designed to implement the MOU, which came into effect June 2, 2016, by outlining the framework the FDA will follow for such decisions.

The MOU and draft guidance follow the CMS' modification in 2013 of the definitions for Category A and Category B devices. The categories, outlined in the Code of Federal Regulations (CFR) at 42 CFR 405.201, include:

- **Category A or experimental:** Devices for which the absolute risk has not been determined and for which it's unclear whether the device is safe and effective.
- **Category B or nonexperimental/investigational:** Devices for which incremental risk is the primary risk in question, meaning the device is known to be safe and effective.

The draft policy outlines the criteria the FDA will use to categorize devices when an IDE is approved or approved with conditions. A device will be considered Category A if it meets one of the following criteria:

- No premarket (PMA) approval, 510(k) clearance or *de novo* request has been granted, and initial safety and efficacy questions have not been resolved in nonclinical or clinical studies.
- The device has characteristics that differ from those of a legally marketed device, and the existing information on the marketed device does not resolve initial efficacy and safety questions.
- The device is being investigated for a new indication or new intended use for which information from a similar device related to the previous indication does not resolve initial efficacy and safety questions.

A device will be considered Category B if it meets one or more of the following criteria:

- No PMA approval, 510(k) clearance or *de novo* request has been granted, but existing data resolves initial safety and efficacy questions.
- The device has characteristics similar to a legally marketed device, and available information resolves initial safety and efficacy questions.
- The device is being studied for a new indication or use, but information from a previous indication resolves initial safety and efficacy questions.

The draft policy also indicates that a change in categorization may be warranted if evaluations provide sufficient data to resolve initial questions of safety and efficacy or if an IDE study receives a staged approval or staged approval with conditions. In such circumstances, the FDA will make a categorization decision upon study approval, study expansion or submission of a request to change the category.

FDA releases finalized guidance to clarify how to extrapolate clinical data to support pediatric medical devices labeling

The document is a revision of draft guidance initially published in May 2015. It explains the circumstances in which it may be appropriate to leverage existing clinical data to support pediatric device indications and labeling, with a view toward increasing the availability of such devices.

The FDA released finalized guidance titled "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices." The guidance outlines the approach the FDA uses to determine whether extrapolation is appropriate, and describes how data can be used to increase precision for pediatric inferences. It also provides a road map for leveraging existing clinical data when submitting premarket approval applications (PMAs) and *de novo* requests, as well as for use in supporting humanitarian device exemptions (HDEs).

The finalized document clarifies that for PMA, HDE or *de novo* premarket submissions, it may be appropriate to extrapolate existing clinical data when the course of the disease or effects of the device are sufficiently similar in adults and pediatric patients. However, information should be extrapolated only when the end points used in the adult data sources are relevant to the pediatric population, when the data quality is high and when existing data are determined to be scientifically valid evidence.

Comments submitted by industry on the draft version, according to the FDA, sought clarification of the concept of "borrowing strength." Thus, the finalized guidance explains that the quantitative information provided by existing adult data can be incorporated in one of two ways: The adult data can stand in as a substitute for pediatric data, or the adult data can be used to supplement pediatric data within a statistical model. This type of combination of data sources, the FDA writes, is known as borrowing strength,

and it can significantly boost the sample size of a prospective pediatric study.

The agency specifies that while the exact model used to borrow strength may vary depending on the case, the extent of leveraging depends on the similarity between borrowed data and any pediatric data that will be collected – regardless of the model used.

The guidance also notes that the types of existing data sources that may be considered for extrapolation include data from a variety of clinical investigations (e.g., randomized controlled trials, single-arm studies and studies from any individual treatment arm), historical clinical data, reference samples and published literature.

FDA issues final rule allowing for inclusion of stand-alone symbols on medical device and in vitro diagnostic labels

The final rule, in addition to allowing the optional use of symbols not accompanied by explanatory text ("stand-alone symbols"), permits the use of the symbol statements "Rx only" and "Px only" for prescription devices, provided they meet the rule's requirements.

Previously, the FDA prohibited companies from using stand-alone symbols on device and IVD labels and required that symbols on the labels be accompanied by explanatory text. Requests from the medical device industry led the agency to seek public comment in 2013 on a proposed rule that would allow stand-alone symbols to appear on device labels. In its final rule, titled "Use of Symbols in Labeling," the agency didn't bend on its requirement that all stand-alone symbols must be explained in a paper or electronic glossary included with the device – despite industry pressure for it to do so. Furthermore, the rule stipulates that the labeling on or within the device's packaging must include a prominent and conspicuous statement identifying the location of the glossary.

However, the final rule does differ from the proposed rule on one major front: It now allows manufacturers to include stand-alone symbols not recognized by the FDA, in addition to those developed by recognized standards development organizations. In those cases, companies can use their discretion as long as they determine a symbol is likely to be read and understood by an ordinary individual under customary conditions of purchase and use, in compliance with the Food, Drug and Cosmetic Act. The FDA also notes it still has authority to determine whether a symbol is noncompliant with the rule and to take enforcement action against violations.

The final rule will go into effect Sept. 13, 2016.

FDA draft guidance offers recommendations on how to ensure proper dissemination by manufacturers of patient-specific information derived from medical devices

The document clarifies that medical device manufacturers may share patient-specific data from a medical device with the patient using that specific device, and provides guidance on how to ensure the appropriate and responsible dissemination of such information.

The document, "Dissemination of Patient-Specific Information From Devices by Device Manufacturers," clarifies that the privacy protection provisions put in place under the Health Insurance Portability and Accountability Act (HIPAA) don't apply to manufacturers that wish to share medical device data with a patient being treated or diagnosed with that specific device. Further, medical device manufacturers may share such information without obtaining additional premarket review. However, the guidance specifies that any labeling provided to the patient by the manufacturer is subject to applicable requirements in the FD&C Act and FDA regulations.

The draft guidance defines patient-specific information as "any information unique to an individual patient or unique to that patient's treatment or diagnosis that, consistent with the intended use of a medical device, may be recorded, stored, processed, retrieved, and/or derived from that medical device."

The guidance states that generally, categories for patient-specific information may include but are not limited to:

- Data a health care provider inputs to record the status and ongoing treatment of an individual patient.
- Information stored by the device to record usage, alarms or outputs (e.g., pulse oximetry data, heart electrical activity and rhythms as monitored by a pacemaker).
- Patient-specific case logs entered into a medical device by a health care provider.

Since the information may be used to facilitate continuity of care, the FDA recommends that manufacturers ensure the information provided is interpretable and useful, and that they include relevant context to avoid any misinterpretation of the data by the patient.

Manufacturers should also include information on whom to contact for follow-up information, and advise patients to contact their health care providers should they have any follow-up questions related to their patient-specific information.

FDA issues draft guidance detailing benefit-risk approach when considering medical device availability, compliance and enforcement decisions

The draft guidance aims to shed light on appropriate responses to nonconforming product or regulatory compliance issues related to diagnostic and therapeutic medical devices, but does not apply to premarket review decisions. Once finalized, it is intended to provide a shared benefit-risk framework and to set forth overarching principles for FDA staff and stakeholders.

In this draft guidance document titled "Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions," the FDA highlights the benefit and risk factors it may take into consideration when prioritizing resources for compliance and enforcement efforts. The agency stresses the importance of carefully weighing risk-benefit profiles when determining the appropriate regulatory action, as failure to do so "could result in regulatory actions with unintended adverse effects (e.g., shortage of medically necessary devices)."

When determining the appropriate regulatory action, the following factors may be considered on a case-by-case basis when evaluating a device's **benefits**:

- Type of benefit(s) – including the medical device's impact on patient health and clinical management.
- Magnitude of benefit(s) – the degree to which patients experience the treatment benefit or the effectiveness of the medical device.
- Likelihood that the medical device will effectively treat or diagnose the patient's disease or condition.
- Duration of effects – how long the benefit can be expected to last for the patient.
- Patient preference on benefit – the value that patients place on use of the medical device.
- Benefit factors for health care professionals or caregivers – includes the benefit that health care professionals or caregivers experience by improving the way they care for patients, whether this directly improves patient outcomes or improves clinical practice.
- Medical necessity – whether the medical device provides benefits or addresses needs unmet by other medical devices or therapies.

The following factors are taken into account on a case-by-case basis when assessing a device's **risks**:

- Risk severity – This is categorized into three levels

and includes a duration component. The three levels are:

  - Medical device-related deaths and serious injuries.
  - Medical device-related nonserious adverse events.
  - Medical device-related events without reported harm.

- Likelihood of risk – The FDA considers three risk factors related to:
  - Likelihood of medical device nonconformity.
  - Likelihood of a harmful event given exposure to a nonconforming device.
  - Number of patients exposed.
- Nonconforming product risks.
- Duration of exposure to population.
- False-positive or false-negative result.
- Patient tolerance risk.
- Risk factors for health care professionals or caregivers.

Other factors that may be taken into account include uncertainty, mitigations, detectability, failure mode, scope of the device used, patient impact, preference for availability, nature of violations/nonconforming product and firm compliance history.

Additionally, the FDA says the draft guidance is meant to align the benefit-risk factors it applies in the above context with those it considers when evaluating marketing and IDE applications.

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.