FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

FDA puts out guidance to require submissions in ICH's electronic format for certain pharmaceutical product applications within two years

The regulator issued guidance in accordance with the FDCA that outlines Electronic Common Technical Document (eCTD) specification requirements for submissions of new drug or biological products, requiring that all submissions be done electronically and in the ICH-developed format within the next two years.

The eCTD is an ICH format based on specifications developed by the initiative and its members, and the FDA's CDER and CBER have received eCTD format submissions since 2003. The format has also been the recommended format for electronic submissions to the CDER and CBER since 2008, with the majority of new electronic submissions being received in eCTD format.

Section 745A(a) of the FDCA states that two years after guidance specifying the electronic format for submissions is issued, submissions must be submitted electronically and in the format specified by the agency. The regulator is thus putting out the document to announce that submissions for NDAs, ANDAs and certain BLAs will need to be submitted electronically using the eCTD format beginning within the next two years, while IND application requirements will come into effect after three years.

The document, along with included technical specification documents, describes how to organize and submit content in electronic format using eCTD specifications listed in the FDA Data Standards Catalog.

The FDA's guidance document goes over electronic submission requirements, covering types of submissions, the implementation schedule and exemptions. Also explained are the eCTD specifications, presubmission considerations and submission structure, including

granularity, files and folders. The FDA goes on to specify file formats and versions, document life cycle, summary of clinical efficacy and safety, data sets and study information, and the transmission of electronic submissions. The document ends by going over FDA forms, restrictions on paper copy submissions and receipt dates.

OPDP warns Otsuka over improper marketing of antipsychotic drug Abilify

Otsuka received a warning letter after an FDA review of its pharmacology aid for its Abilify tablets showed the company made false or misleading claims about the drug as well as unsupported superiority claims.

According to the letter, promotional material for the company's Abilify — which is intended to treat bipolar disorder and major depressive disorder (MDD) — contains misleading claims and presentations about the drug, thus misbranding it.

The FDA wrote that the pharmacology aid deceptively implies a more significant degree of certainty about how the drug works in humans than is actually known. According to the letter, Otsuka suggests a "definitive understanding of Abilify's ability to modulate dopaminergic and serotonergic activity" even though this hasn't been established. Cited in the letter is the Clinical Pharmacology section of the PI for Abilify, which states "the mechanism of action of aripiprazole … is unknown." The OPDP also targets footnoted information that it says is not sufficient to clarify the misleading claims in the body of the aid and the references used by Otsuka to support its claims, stating they're insufficient.

The letter also faulted the company for the claims and presentations in its promotional material that misleadingly imply the drug offers advantages over other MDD or bipolar treatments despite the fact that this hasn't be shown. The OPDP states that the pharmacology aid contains comparative presentations suggesting Abilify has a clinical advantage because of its pharmacology, while there's no evidence to support that implication.

CDRH provides guidance on adaptive designs for clinical trials for medical devices in a bid to speed up decision-making

Keeping in line with its risk-based approach to regulation, the agency issued guidance on planning and implementing adaptive designs — as opposed to unchanged designs — for clinical studies in medical device development programs, saying these can reduce resource requirements and/or increase the chance of study success.

An adaptive design for a medical device clinical study allows for "prospectively planned modifications" based on study data that's being accumulated, without undermining the trial's integrity and validity. While modifications should be "prospectively planned" and described before a study is initiated, post-trial commencement study changes can be scientifically valid if the trial design decision-makers haven't had access to outcome results by treatment, the guidance explains. Adaptive study design planning is focused on anticipated modifications that could potentially be desirable based on the data accrued throughout the study. The FDA advises sponsors to expect and plan for changes based on a range of potential scenarios and to go over planning with the agency, noting unplanned modifications may not be approved by the agency.

The guidance lists several advantages of adaptive designs — compared to unchanged designs — noting that ultimately they may help accelerate device development decision-making, and thus enable more efficient resource investment in a study. It also provides guidance on how to determine whether an adaptive design is "feasible and advantageous," noting studies enrolling subjects quickly or complex studies with multiple endpoints and secondary endpoints for claims may not lend themselves to adaptation. However, studies with shorter endpoints

and longer recruitment times, as well as studies where the time to the primary endpoint evaluation is long and the accrual is longer, may benefit from adaptation. The FDA recommends that the choice of an adaptive design be considered during the planning of a pivotal study, using a number of realistic scenarios to make a determination.

The document — applicable to PMA applications, 510(k) submissions, *de novo* submissions, HDE applications and IDE submissions — also goes over principles for adaptation in the design of clinical studies, including controlling the chance of flawed conclusions and minimizing operation biases. The document also covers the use of unblended data, with group sequential designs, sample size adaptation and group sequential design with sample size reassessment as the most widely used, as well as special considerations. The FDA also lists regulatory considerations, recommending interactions and communication with the agency, and having a risk-based monitoring plan established. The guidance further describes best practices to protect study blinding, and the submission of an adaptive design's content to the FDA.

FDA to consider patient preference data during decision-making for devices under PMA, HDE or *de novo* review

The agency issued draft guidance on submitting patient preference information as part of PMA and HDE applications and de novo requests, as well as on incorporating the data in labeling, saying patient perspectives can be important to take into consideration when making benefit-risk determinations.

In Patient Preference Information – Submission, Review in PMAs, HDE Applications, and *De Novo* Requests, and Inclusion in Device Labeling, the FDA says it wants patients who use devices for medical treatment to share their experiences, saying the input would help the agency assess the benefit-risk profile of certain devices under PMA, HDE or *de novo* review.

The FDA defines patient preference information as assessments — qualitative or quantitative — of the "relative desirability or acceptability of attributes" that vary among "alternative diagnostic or therapeutic strategies." Device attributes include effectiveness, duration of effect and use, and other characteristics that may impact benefit-risk considerations.

While the submission of patient preference information is voluntary, the FDA says there are circumstances under which it may be useful, particularly when usage decisions are "preference-sensitive." This may be the case when there are multiple treatment options, but no option that is "clearly superior for all preferences." Devices with certain attributes may yield such circumstances, including ones with a direct patient interface, ones with novel technology and ones intended to directly affect the quality of life, for example.

The draft document goes a step further than the regulator's 2012 benefit-risk guidance, which says patients' tolerance for risk and perspective on benefits may be considered during device reviews — by providing guidance on patient preference data that may be considered. In issuing the guidance, the FDA is looking to:

- Encourage the voluntary submission of this information.
- Define qualities of patient preference studies.
- Provide recommendations for the collection of patient preference information.
- Provide recommendations for the inclusion of collected data in labeling for patient and health care professionals.

The FDA says patient preference information provides valid scientific evidence about patients' risk tolerance, also noting that patients' perspectives on benefits may inform its evaluation of a device's benefit-risk profile. In addition to explaining how the regulator might consider patient preference data throughout such evaluations, the guidance goes over how patient preference information can be used throughout the total product life cycle. The FDA lists examples, including using the data to inform device design and features during the discovery and ideation phase, and to inform redesign or device improvement as post-market patient-centered data accumulates.

The guidance document also explains study qualities the FDA will consider when deciding whether patient preference data constitutes valid scientific evidence, listing 11 recommended qualities, including representativeness of the sample and generalizability of results, patient-centeredness, minimal cognitive bias and study conduct.

Also covered in the guidance document were "additional considerations," which covered the maintenance of the integrity of patient preference data and conditions of approval, as well as submission of the information.

The agency also made recommendations for incorporating the patient preference information into device labeling, noting that for devices for which the regulator considered this type of information, labeling should describe study data.

FDA issues guidance on leveraging adult clinical data to support marketing approval and labeling of pediatric devices

The regulator is looking to remedy a lack of available scientific evidence to support pediatric device indications in PMA applications and HDEs by encouraging the extrapolation from existing clinical data, hoping the approach will streamline the requirements for establishing a pediatric intended use claim.

The FDA issued guidance aiming to increase the availability of pediatric devices by explaining when existing clinical data can be leveraged, describing how it will determine whether extrapolation is appropriate — and to what extent it can be used — and going over statistical methodology. Maintaining its risk-based approach, the FDA notes the criteria on which the regulator is basing its decision of whether to extrapolate are "considered separately for effectiveness and for safety."

The FDCA defines pediatric device patients as "persons aged 21 or younger at the time of their diagnosis or treatment." In 2004, the CDRH issued final guidance, Premarket Assessment of Pediatric Medical Devices, which states existing data can be used to support effectiveness and, on a limited basis, safety for PMAs when it is consistent with scientific principles. The FDAAA specifically authorized the use of adult data to show pediatric effectiveness.

In releasing Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices, the FDA says there are also cases where extrapolating for safety may be appropriate. Extrapolation can make use of existing clinical data that may be helpful in understanding device performance in pediatric patients, but the FDA notes that sponsors are limited to extrapolating from adult data only in situations where "the course of the disease or condition and the effects of the device are sufficiently similar in adults and pediatric patients."

The FDA will consider various types of existing data sources for extrapolation, including data from a variety of clinical investigations, historical clinical data, reference samples and published literature.

In its guidance, the regulator distinguishes full from partial extrapolation, and goes over when extrapolation is suitable to support effectiveness, safety or both — again noting that decisions relating to safety and effectiveness are made independently. The document also goes over the

extrapolation decision process, using a decision tree to illustrate how to determine whether extrapolation is appropriate. Statistical methodology is also covered in the guidance, which notes that Bayesian methods are "quite applicable for partial extrapolation from prior adult studies."

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

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