FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

FDA issues guidance documents on how it considers balancing premarket and postmarket data collection during PMA reviews in a bid to accelerate the approval of new breakthrough devices

The regulator explains how it determines when it's appropriate to increase reliance on postmarket collection to reduce the extent of premarket collection to support premarket approval, in a document integral to the CDRH's risk-based approach to regulation and the FDA's broader fulfillment of the "least burdensome provision" of the FDCA. The guidance correlates with the Expedited Access Pathway program, for which the FDA provides guidance in a separate document.

In its guidance document clarifying its policy on balancing premarket and postmarket data collection during PMA reviews, the FDA writes that a "right balance" — specifically, offsetting the reduction of premarket data collection with an increased reliance on postmarket collection — will help speed up patient access to new devices. The guidance is aimed at helping sponsors determine when this is appropriate.

A "least burdensome provision" in the FDCA, as explained in the regulator's 2002 Least Burdensome Guidance, requires that the role of postmarket information be taken into account when determining how much data should be gathered in the premarket setting to support premarket approval; and further, reliance on postmarket controls should be considered as a way to decrease the extent of premarket data collection for PMAs. In its 2012 Benefit-Risk Guidance, the FDA describes what it considers when making benefit-risk determinations during premarket reviews for certain devices, specifying that the degree of certainty of probable benefits and risks of a device is one of the considered factors. The regulator considers postmarket data part of this benefit-risk framework.

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The "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval" guidance explains that the FDA may allow the of use post-approval studies rather than premarket ones when there's an acceptable degree of uncertainty related to risks and benefits in terms of the overall benefit-risk profile of the device at the time of premarket approval. Several examples of this are listed, including when mature technology is involved, in which case benefits and risks are well-characterized by a robust history of testing and clinical use, and migration when the documentation of design controls, risk analyses and prior performance studies on already-marketed devices can provide sufficient knowledge, among others.

The document also covers conditions of approval, which may include postmarket or labeling requirements. When post-approval data collection is appropriate, post-approval studies or surveillance may be required as an approval condition. The FDA may also impose labeling requirements as a PMA approval condition, as well as continuing periodic reporting on the safety, effectiveness and reliability of a device post-approval. The FDA also warns that certain postmarket actions may be appropriate as a result of approval conditions, including submissions of a PMA supplement, safety communications, panel meetings, administrative and enforcement actions, and panel meetings.

Separately, the FDA issued the Expedited Access for Device Guidance. As part of the Expedited Access Pathway program, which the document explains, and in a bid to make earlier patient access easier for devices demonstrating the potential to address unmet medical needs, the FDA may accept greater uncertainty related to the benefit-risk profile of a device at the time of approval — which it will counterbalance with postmarket data.

The EAP program borrows features from the CDRH'S Innovation Pathway, but is a separate and distinct initiative tailored to devices. One of the key features influenced by the Innovation Pathway is the Data Development Plan, which outlines premarket and postmarket data that will be collected in support of device approval.

The program is voluntary, must be requested by the device's sponsor and requires approval from the FDA. To be eligible for the EAP program, a device must be intended for the treatment or diagnosis of a life-threatening or irreversibly debilitating disease. It must also satisfy at least one of the following criteria: there is no alternate treatment or means of diagnosis for the condition/disease; it signifies a technological breakthrough that would provide an advantage over existing marketed technologies; it offers an advantage over other existing marketed alternatives; or the device's availability is in the best interests of patients.

When applying for EAP designation, the sponsor is required to include a description of the data collection plan, including the study plan and design. It should also include an explanation and justification for the proposed balance of premarket and postmarket data collection. Finally, it should include a timeline for the development and marketing of the device as well as the postmarket data collection. The FDA will respond to the sponsor within 30 days with its decision and, if necessary, the FDA may require the sponsor to submit additional information.

Guidance explains how the FDA will define and process submissions for changes to risk management plans

The regulator issued guidance on changes to approved risk evaluation and mitigation strategies (REMS), distinguishing "modifications" from "revisions," and explaining how these should be submitted and how the FDA will review and act on them.

As noted in the FDA's guidance, certain drugs require a risk management plan that uses measures beyond the PI to make certain that benefits outweigh risks.

As reported by Law360, this document — which provides guidance on the submission of changes to these plans — was prompted by the 2012 user fee law that contained provisions meant to streamline amendments to REMS. The FDA committed to REMS reforms under the user fee law, and in September put out a report updating its progress on the matter and promising specific actions in several areas, including patient comprehension, physician education, REMS standardization and access to REMS policies.

In its guidance, the FDA says REMS changes will be categorized by the degree of their possible impact on the risk message and other REMS requirements, and that they will fall into one of two categories: "revisions" or "modifications." The FDA specified that a risk message is potentially affected when a change increases, reduces or modifies its focus or addresses a new serious risk, while a REMS requirement can be affected when a change increases, minimizes or changes the plan's goals, elements and tools, and/or actions required for compliance.

Revisions are limited to editorial changes, corrections of typographical errors or application holder name or address changes — all of which don't have any effect on the risk message and other REMS requirements. The FDA also noted that amendments to the REMS document and/or appended material don't have an impact on the risk message or requirements of the REMS. Included in the guidance document is a list of changes that will be deemed revisions, with the FDA specifying that any change not included in the list will be considered a modification. Revisions should be submitted as "REMS Revisions" and documented in the next annual report.

Modifications are split into two categories: minor and major. Minor modifications may nominally impact the risk message or REMS requirements and should be submitted as a CBE-30 supplement, while major modifications can significantly affect the risk message or REMS requirements and should be submitted as a PAS. The document lists examples of minor and major modifications, with the FDA clarifying that the examples are only representative. Examples of minor modifications include nominal amendments to REMS requirements or associated processes, such as the expansion of the enrollment process, or changes that nominally affect the risk message, such as changes in graphics. Examples of major modifications include any amendment relating to a REMS goal; changes to an element of the plans, such as the removal of the Medication Guide; amendments to a REMS tool, such as the removal of a prescriber educational tool; or changes due to safety labeling modifications.

The guidance document also covers procedures related to REMS changes. The FDA goes over general considerations, detailing information that should be included in submissions, recommended formats and methods of submissions. Submission procedures for each type of change are also covered.

FDA to conduct study to determine whether medical device labeling should be standardized

The study will look into whether a standard format of labeling would be beneficial to healthcare providers, as the regulator worries current labeling is too complicated and difficult to navigate.

While medical device makers are required to label their products with certain information, they have a lot more flexibility when it comes to the format and layout of that information, as pointed out by RAPS. These format and layout inconsistencies make it challenging to gather and compare medical device labeling information, resulting in the absence of a single repository for labels.

The study, announced in a Federal Register notice, is the third part of a three-part study. The FDA conducted focus groups of healthcare practitioners, asking them what they want in labeling, where they find labeling, what the most important sections of labeling are and whether they even look at labeling. Responses indicated health care professionals don't

look at labeling because it's complicated and they typically can't find the information they seek in one section. The practitioners said they would like an abbreviated version of labeling — so they could find information more easily — and a standard content of labeling. The focus group respondents also indicated they would like to find the information electronically and in one place.

Based on the previous phases of the study, the FDA is looking to test a standard content of labeling against an existing piece of the same labeling to determine whether health care practitioners can find what they need in a more consistent and easy way.

To achieve this, the FDA's study will compare existing device labeling from approximately six different types of medical devices with a standard content and format of the same labeling, which FDA researchers are crafting using existing labeling as their source of the information.

The regulator wants to assess the usability and usefulness of a draft standard content and format of device labeling to see whether health care practitioners find the format and content of device labeling clearer, more understandable, useful and user-friendly. Findings will inform the FDA's planned regulatory approach to standardizing medical device labeling.

It's worth noting that the FDA specified in a response to a comment that the study is "a cognitive testing of a standard content of labeling" and that the study doesn't address standard of care-related questions. Seemingly alluding to off-label use, the regulator responded to a comment stating that the agency should question whether physicians are required by the standard of care to read user instructions by writing that it doesn't "regulate the practice of medicine," but rather "labeling that accompanies a device."

OPDP to study the impact of comparative pricing information in DTC and professional prescription ads

The agency will investigate how prescription drug product perceptions are impacted by the inclusion of price comparison information and supplementary contextual information in advertising geared at consumers and health care professionals, amid concern that the impression remains that price is the main factor to consider.

As noted in the FDA's Federal Register notice announcing the study, in prescription drug advertising, drugmakers are allowed to include "truthful, non-misleading information about the price of their products in promotion" — which extends to price comparison information. However, when drugmakers include information about the price of a competing product to make advantageous claims, they should also include the context that the drugs being compared may not be comparable efficacy- and safety-wise and that the presented prices don't necessarily reflect the actual prices paid by consumers, pharmacies or third-party payers. However there's concern that the inclusion of contextual information about efficacy or safety doesn't do enough to correct the impression that the products are interchangeable and that price is the primary factor to take into consideration.

The OPDP said its "greatest interest" related to this study is to investigate whether the inclusion or absence of price comparison information and contextual information has an impact on outcomes such as perceptions of comparative safety and efficacy, impressions of the comparator product, and intentions to seek additional information about the advertised product.

Participants in the study will be consumers self-identifying as being diagnosed with diabetes and physicians who are general practitioners and specialists. In its responses to comments, the

regulator specified that it's using a fictional product for the study, though the comparator is a real product. The study will measure participants' experience with medication for diabetes, prior exposure to advertising for the comparator and prior experience taking the comparator. The OPDP also said that while it would be informative to broaden the study to examine a variety of cost information, a lack a resources makes this impossible, and so the price comparison will be for the same indication on a yearly basis.

FDA rejects Otsuka's assertions of orphan exclusivity for Abilify, allowing generics to proceed

The impact of the FDA's decision is that several companies will be allowed to enter the market with generic aripiprazole, although the generics must carve out the use of the drug for treating pediatric Tourette's Disorder from their labeling and marketing while the exclusivity period for that pediatric use remains in effect.

Otsuka maintained that the FDA's approval of Abilify (aripiprazole) for pediatric Tourette's Disorder precluded the approval of a generic for any uses while the exclusivity period for that specific use remained in effect. In an April 28, 2015, letter, however, the FDA rejected Otsuka's contention. Instead, the FDA insisted that amendments to the Federal Drug and Cosmetics Act allow the Administration to approve applications for generics once the original exclusivity period of a drug expires. Moreover, even if a pharmaceutical company has been granted orphan drug exclusivity for certain uses — including pediatric uses — that exclusivity does not prevent the FDA from approving generic versions of the drug for its original uses. The FDA letter asserted that its administration harmonizes exclusivity provisions under the Hatch-Waxman Amendments and the Orphan Drug Act. Reading those provisions together, the FDA took the position that granting approval for a specific new use under the Orphan Drug Act does not necessarily extend a patent holder's period of exclusivity for the drug's originally approved uses.

In this case, Otsuka enjoyed a five-year exclusivity period for Abilify after the drug was first approved for schizophrenia, during which time Otsuka also sought and received approval to market the drug for pediatric Tourette's Disorder. This new use entitled the manufacturer to three years of Hatch-Waxman exclusivity and seven years of orphan drug exclusivity for the specific use of the drug in the treatment of Tourette's Disorder. When the original exclusivity term for Abilify was expiring, Otsuka sought a decision from the FDA preventing other companies from marketing a generic on the basis that Abilify was still entitled to exclusivity under the Orphan Drug Act and, because the FDA could not permit the omission — or carving out — of pediatric use information on labeling for uses protected by orphan drug exclusivity, the FDA was precluded from approving the marketing of a generic version of Abilify until Otsuka's orphan drug exclusivity period expires.

The FDA, however, rejected Otsuka's interpretation of the Orphan Drug Act, explaining that it has long permitted labeling carve-outs to remove indications protected by unexpired orphan drug exclusivity in circumstances where omission of the label information specific to the orphan indication would not make the generic less safe and effective for the original approved indication. The Administration noted that, in certain situations, it has determined that generic labeling needed to retain pediatric information related to an indication protected by exclusivity where carving it out would present a safety risk to pediatric patients using the drug for its approved (non-protected adult) indication. According to the letter, pediatric information is only required when the use for which pediatric information is being omitted is the same one that is approved for adult use — which was not the case with Abilify. The FDA determined as a factual matter that it was not necessary to retain in the generic drug labeling any information related to

the drug's protected Tourette's Disorder use, and that the generic with the protected information carved out "remains safe and effective for all of the remaining non-protected conditions of use." The FDA also concluded that there was no information remaining in the labeling describing the use of the generic in adults that would lead to an unsupported use of the generic in pediatric patients with Tourette's Disorder.

According to the letter, the conclusion would remain the same even if the Tourette's Disorder indication were protected only by orphan drug exclusivity. Abilify's labeling contains no information about the use of the drug for Tourette's Disorder in adults. If the pediatric information related to Tourette's Disorder is carved out for generic labeling purposes, the remaining labeling would not include any information on use of the drug to treat Tourette's Disorder in adults, because this information is not included on Abilify's labeling.

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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