FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

FDA finalizes guidance on medical product communication amid push toward value-based purchasing

In line with the HHS blueprint to lower drug prices and link payments for drugs to their value, the FDA finalized guidance to provide drug makers with recommendations for open communication with payors, including about unapproved uses and information consistent with labeling.

As part of what the FDA commissioner called efforts to support the shift to value-based payment arrangements and encourage competitive contracting, the agency finalized two guidance documents on medical device communication – one addressing communications with payors and the second addressing communication of information consistent with FDA-required labeling.

The guidance on communications with payors, which includes formulary committees and similar entities with expertise in healthcare economic analysis, addresses the communication of healthcare economic information (HCEI) for prescription drugs and medical devices as well as information about products not yet approved or about unapproved uses of approved products. HCEI is defined as any analysis that identifies, measures or describes economic consequences, such as monetary costs or resource utilization, of the use of a drug. The guidance recognizes that payors seek information on the effectiveness, safety and cost-effectives of products to support product selection, formulary management and reimbursement decisions, which may differ from the information reviewed by the FDA when making approval or clearance decisions. However, it notes that information provided by firms to payors needs to be truthful and non-misleading, and provided with appropriate background and contextual information.

The guidance explains that HCEI may be presented in an array of ways, including in an evidence dossier, as a reprint of a publication from a peer-reviewed journal, as a budget-impact model or as a payor brochure. The

guidance applies to dissemination of such information to entities with expertise in healthcare economics carrying out responsibilities for the selection of drugs for coverage or reimbursement, but does not apply to consumers or healthcare providers making individual prescribing decisions. Per the guidance, if HCEI is provided to the appropriate audience, is related to an approved indication and is based on competent and reliable scientific evidence (CARSE), it will not be considered false or misleading. In addition, HCEI provided in a manner consistent with the guidance will not be considered evidence of a new intended use. The guidance cautions that HCEI that includes material differences from FDA-approved labeling needs to present "a conspicuous and prominent statement describing any material differences between the healthcare economic information and the labeling approved for the drug."

For unapproved uses of approved products or unapproved products, the guidance notes that the FDA will not object to information that is "unbiased, factual, accurate, and non-misleading." The agency will not use such communication as evidence of intended use, nor does it intend to enforce postmarketing submission requirements to such material, which may include factual presentations of results from clinical studies, product pricing information, anticipated approval time lines or patient utilization projections. When providing such information, the guidance recommends that firms include a clear statement that the product or use isn't approved or cleared and safety and effectiveness hasn't been established, along with information on the stage of development and descriptions of material aspects of study design and methodology for study results presented.

The guidance on communications with FDA-required labeling provides recommendations on sharing information about the approved or cleared use of a product that may not be captured in FDA-required labeling. Labeling is subject to content requirements and limitations and doesn't address everything known about a product for its approved or cleared uses. Given that, the guidance makes clear that information shared by firms that isn't contained in labeling, but is consistent with the labeling, will not be used to establish a new intended use. However, communications consistent with labeling but that are false or misleading will be subject to enforcement. Per the guidance, the agency will use three factors for determining whether communications are consistent with labeling: 1) how the information compares to the conditions of use listed in the labeling (i.e., indication, patient population, limitations and directions for use, and dosing and administration); 2) whether the presentation in the communication increases the potential for harm; and 3) whether the directions for use in the labeling allow for safe and effective use under the conditions presented in the communication. The guidance cautions that communications that lack appropriate evidentiary support are likely to be false or misleading. Given that, firms should rely on data, studies or analyses that are scientifically appropriate and statistically sound to support communications.

FDA issues draft guidance on formal meetings between BsUFA product developers

The guidance describes the process for requesting, preparing, scheduling and conducting formal meetings with the agency. It outlines the types of meetings that may be requested and discusses what should be included in meeting requests and packages.

The FDA issued draft guidance on formal meetings concerning the development and review of biosimilars or interchangeable biological products regulated by the CDER or CBER. The guidance describes five types of formal meetings:

1. Biosimilar Initial Advisory – An initial assessment regarding the feasibility of licensure under Section 351(k) of the PHS Act for a particular product, with general advice on expected content for the development program. While this type of meeting

doesn't include substantive review of summary data or full trial reports, preliminary comparative analytical similarity data should be provided in the meeting package, so the agency can make a preliminary determination about licensure. In addition, a general overview of the development program, including information about planned studies, should be provided.

2. Biosimilar Biological Product Development (BPD) Type 1 – A necessary meeting for an otherwise stalled development program to move forward or to address an important safety issue. These may include meetings about clinical holds, dispute resolution meetings or post-action meetings following an FDA regulatory action other than approval.

3. BPD Type 2 – A meeting to secure targeted advice from the FDA on a specific issue or question about an ongoing development program. This type of meeting may include a substantive review of summary data, but not a review of full study reports.

4. BPD Type 3 – An in-depth review and advice meeting about an ongoing development program, which may include a substantive review of full study reports or an extensive data package. Under this type of meeting, a request may solicit FDA advice about the similarity between a proposed biosimilar or interchangeable product and the reference product based on a comprehensive data package. Requesters may also ask for advice on the need for additional studies. The FDA recommends that requesters provide an update on the development plan on the proposed product based on the data reported in the full study reports, including proposals for any planned additional studies.

5. BPD Type 4 – A presubmission meeting to address the format and content of a complete application for an original biosimilar or interchangeable product application or supplement. These meetings may be used to address the identification of studies used to support a demonstration of biosimilarity or interchangeability, and to discuss potential review issues and the best approach to present data in marketing applications.

Table 2: FDA Meeting Scheduling Time Frames

Meeting Type	Meeting Scheduling (calendar days from receipt of meeting request and meeting package)
BIA	75 days
BPD 1	30 days
BPD 2	90 days
BPD 3	120 days
BPD 4	60 days

Source: FDA

To request meetings, a written request should be submitted to the FDA containing the meeting type requested, the proposed format, a statement describing the purpose of the meeting and a brief background of underlying issues, as well as a list of objectives or outcomes and a proposed agenda. The guidance also recommends that meeting requests provide a list of questions with a brief explanation of the content and purpose of each question, a list of requested FDA attendees and planned sponsor attendees, and suggested dates and times. The guidance notes that the list of questions is the most critical component to understanding the information or input sought, and should be limited to those that can be reasonably answered in the allotted meeting time. The guidance sets a time line for response to meeting requests ranging from 14 to 21 days, as well as time frames for meeting schedules.

The guidance outlines suggested content for meeting packages, noting that sponsors should provide information pertinent to the product, stage of development and meeting type requested, along with supplementary information that may be needed to develop responses to the issues raised. The guidance notes that if a development plan veers from current guidance or practice, the deviation should be noted

and explained. In addition, known or anticipated design and evidence issues should be addressed. Per the guidance, meetings will be chaired by an FDA staff member and minutes will be issued within 30 days of the meeting. Meeting minutes will outline the important agreements, disagreements or issues for further discussion, as well as action items from the meeting. Per the guidance, the agency may communicate additional information in the final minutes not explicitly communicated during the meeting.

FDA issues draft guidance updating Q-Submission program for device makers

The guidance reflects the FDA's commitment under MDUFA IV to establish a performance goal for the timing of FDA feedback on Pre-Submissions, and outlines the Q-submission process from content submission to submission tracking and meetings. It applies to an array of device-related submissions, including planned premarket applications and 510(k) submissions.

The FDA published draft guidance outlining the mechanisms through which industry may ask for feedback from or a meeting with the FDA over a planned medical device application as part of the Q-Submission (Q-Sub) program, reflecting changes under MDUFA IV. The Q-Sub program includes Pre-Submissions (Pre-Subs), which include a formal written request for FDA feedback prior to an intended submission of a premarket submission, as well as additional opportunities to engage with the agency.

Per the guidance, a request for a Pre-Sub should include specific questions about review issues pertinent to the planned application, such as questions about nonclinical testing protocols or the design of clinical trials. Although the program is voluntary, the guidance encourages early interactions with the agency as a means of improving the quality of the submission, shortening review times and facilitating the development process. The guidance indicates that feedback may be most effective when requested before a submitter executes planned testing. Although raising issues in a Pre-Sub doesn't require that submitters address or resolve the concerns in a subsequent submission, the guidance notes that any future submission related to the topic should address why a different approach was taken or why the issue was left unsettled.

Apart from a Pre-Sub, submitters may also submit a Submission Issue Request (SIR) seeking feedback on a proposed approach to address issues with hold letters related to marketing submissions, Clinical Laboratory Improvement Amendments (CLIA) Waiver by Applications (CW), Investigational Device Exemption (IDE) or Investigational New Drug (IND) applications. These may include requests for additional information for marketing submissions, letters citing major deficiencies, complete response letters for BLAs, and non-approval or approval with conditions letters. A SIR is meant to facilitate interaction with the agency to resolve or clarify issues identified in such letters to move development forward. Submitters may also request a Study Risk Determination, requesting feedback on whether a planned clinical study is significant risk, non-significant risk or exempt from IDE regulations. Informational meetings may also be requested to share information with the FDA without the expectation of feedback.

The guidance notes that while there are important opportunities for industry to share information with the FDA and that the interactions tracked in the Q-Sub program may be used throughout the product life cycle for a device, the program isn't meant to be an iterative process, and the number of Q-Subs should be judiciously considered. For those intending to submit more than one request on additional topics for the same device, the initial Q-Sub should include an overview of anticipated submissions, including general time frames. Per the guidance, Q-Subs

should include an indication of what type is being sought, the purpose of the submission, an overview of the device function and general scientific concepts behind the device, proposed indications for use or intended use, and a list of pertinent previous communications with the FDA about the device. Upon submission, a unique identification number is assigned to all Q-Subs.

The guidance outlines the review process for each type of Q-Sub, along with a time line and recommended content. Pre-Subs, for instance, should include information on any planned future submissions, background information and supporting documents to allow the FDA to provide feedback on the questions being asked, and a list of clear questions about review issues to a planned application, which the agency recommends be limited to no more than three to four substantial questions. Per the guidance, the FDA will conduct an acceptance review, using an acceptance checklist, within 15 days of receiving a Pre-Sub, and written feedback will be provided within 70 days. If a meeting is requested, written feedback will be provided at least five days before the scheduled meeting. For SIRs, the FDA similarly recommends that submissions include a list of clear questions about review issues pertinent to the planned response to the pending submission hold letter, as well as specification of the preferred mechanism for securing feedback. There is no acceptance review for a SIR, and the FDA will prioritize those submitted within 30 days of the marketing submission hold, IND clinical hold or IDE letter.

FDA kicks off patient-focused drug development efforts with draft guidance on sampling methods, research considerations

The guidance is the first in a series of four that the agency plans to publish as part of its efforts to make drug development and review more patient-centered. The guidance outlines sampling methods for collecting meaningful and representative patient and caregiver data for drug development, and provides a general overview of the relationship between research questions and methods when ascertaining from whom to get input.

As part of its Patient Focused Drug Development (PFDD) efforts, the FDA published the first draft guidance in a series of four being developed to address how stakeholders can collect and submit patient experience data, and other information from patients and caregivers, in support of medical product development and regulatory decision-making. Informed by a series of PFDD meetings conducted under PDUFA V, the guidance documents will provide input on methods that may be used to solicit patient perspectives.

The first guidance document addresses sampling methods that may be used to collect information on patient experience that is representative of the intended population, as well as methods to operationalize and standardize the collection, analysis and dissemination of such data. The guidance provides a glossary of terms the agency will use throughout the remaining guidance documents. For instance, it defines patient experience data as data about patients' experiences with a disease or condition, related treatment, or clinical investigation, as well as patient preferences for treatment. Per the guidance, a patient perspective may be informed by input from patient partners, defined as an individual patient, caregiver or patient advocacy group, and from clinicians. The guidance notes that patient experience data may be collected throughout product development, from early development to the precompetitive setting, and recommends that patients be engaged throughout the process.

Different methodological approaches, including qualitative, quantitative or mixed methods, may be appropriate for collecting robust and meaningful patient experience data. Since the level of rigor needed may vary across studies, the guidance recommends that stakeholders engage early with the FDA to ascertain

which approach should be used. The guidance also notes that, depending on the type of patient experience data, different content and formats may be needed to submit data. The agency is planning to publish guidance on how to submit data, and notes that, at a minimum, sponsors should provide a study report and protocol when submitting patient experience data, along with information about the primary data capture. Patient experience data may be leveraged to inform trial design, endpoint selection and regulatory review, and the FDA encourages stakeholders to engage the agency during the design phase of trials.

The upcoming guidance documents in the series will address:

- methods for garnering information from patients about their symptoms, impacts of their disease and other issues important to them, including best practices for qualitative research such as interviews and surveys;
- what should be measured in medical product development programs to demonstrate clinical benefit, and how to identify and develop fit-for-purpose clinical outcome assessments (COAs) to investigate outcomes important to patients; and
- the development and interpretation of COA-related endpoints.