FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

Draft guidance outlines FDA's take on medical product communications consistent with approved labeling

The draft guidance offers recommendations on how to ensure information presented in communications that are consistent with, but not included in, FDA-required labeling is truthful and non-misleading. It requires that claims be supported by sufficient evidence and that any unfavorable findings in that evidence be disclosed.

The FDA published draft guidance outlining how the agency assesses companies' medical product communications that present information not included in the FDA-required labeling but that may be consistent with such labeling. The guidance states that information that aligns with the FDA-required labeling, which includes labeling approved by the FDA as part of the marketing application review process, is limited to information regarding approved or cleared uses of a product. The guidance does not apply to communication that is inconsistent with FDA-required labeling.

Per the guidance, communication of information not included in, but consistent with, the FDA-required labeling is not alone considered evidence of a new intended use or as failing to comply with the Federal Food, Drug and Cosmetic Act's requirements that labeling bear adequate directions for use.

The guidance outlines three factors the FDA will consider in determining whether representations or suggestions in a communication about a product align with the FDA-required labeling:

1. How the information in the communication compares with information about the indication, patient population, directions for handling/use and dosing or administration in the FDA-required labeling;

2. Whether the representations or suggestions in the communication increase the possibility for harm relative to the information in the FDA-required labeling; and

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3. Whether the directions for use in the FDA-required labeling allow the product to be safely and effectively used under the conditions represented or suggested in the communication.

Since communication of information not included in a label could misbrand a product, it must be conveyed in a truthful and non-misleading manner, which includes revealing facts that are material about the product being promoted, such as risk information. The guidance indicates that to be truthful and non-misleading, communications need to be backed by sufficient evidentiary support and presented with appropriate context. Data used to support the communications must be scientifically apposite and statistically valid and must be accurately characterized in the communication, including limitations of the strength of the evidence and the deductions that can be drawn from it.

The guidance notes that representations in a communication consistent with the labeling will not be considered false or misleading based only on the lack of evidence necessary to satisfy the applicable approval, but the communication could still be false or misleading for other reasons. An analysis of a pivotal trial, for example, may provide information that expands on data reflected in the labeling, but if the trial was insufficiently powered, directly or indirectly suggesting the data supports efficacy conclusions may be false or misleading.

The guidance includes several recommendations for companies to consider to ensure presentation of information that is consistent with the labeling and does not mislead the audience, including:

- Study results and data used as the basis for the communication should be accurately presented and clearly disclosed;
- The communication should correctly characterize and contextualize the pertinent information about the product, including by divulging any unfavorable findings; and
- In instances in which the communication provides information not in the labeling, but where the labeling contains other related data or information, the information from the label should be provided with the appropriate context.

FDA publishes draft guidance on communication of healthcare economic information to payors

The draft guidance offers answers to common questions regarding the communication of healthcare economic information to payors, as well as communication to payors about investigational medical products. It provides recommendations on how the information should be presented and what kind of information may be disseminated.

The FDA issued draft guidance addressing common issues related to the communication of healthcare economic information (HCEI) for prescription drugs to payors as well as communication about investigational drugs and devices prior to approval. The guidance acknowledges that payors often request information on the efficacy, safety and cost-effectiveness of medical products to support drug selection, formulary management and reimbursement decisions. Since such decisions have a marked impact on patients, the agency believes it's critical that the information provided to payors, which can differ from what the FDA reviews during the approval process, be truthful and non-misleading.

The Federal Food, Drug and Cosmetic Act defines HCEI as any analysis that identifies, measures or describes the economic consequences of the clinical outcomes of a drug. Per the guidance, such information can be presented in several ways, including in an evidence dossier, as a reprint of a publication from a peer-reviewed journal or as a budget-impact model. HCEI must relate to an approved indication and should be supported by competent and reliable scientific evidence (CARSE). The FDA states that it will consider the

validity of the data based on the virtues of existing research practices for substantiation established by authoritative bodies such as the Patient-Centered Outcomes Research Institute. The CARSE standard applies to all aspects of HCEI.

HCEI may be provided to entities, such as payors and formulary committees, with the requisite knowledge and expertise in healthcare economic analysis to interpret the data presented to them to inform decision-making. If HCEI is provided to an appropriate audience and meets established criteria, it will not be considered false or misleading. The guidance indicates that the presentation of HCEI should include study design and methodology, generalizability, limitations and other pertinent information. For information that differs from the FDA-approved labeling, a clear statement should be made describing the differences. Companies should also provide the necessary background and contextual information for payors to understand the HCEI, including an accurate overview of the design of the economic analysis. To be considered a balanced and complete presentation, information should also be provided on the FDA-approved labeling, any omitted studies or data, risk information and financial biases.

Payors have indicated that they are interested in receiving information about investigational medical products under FDA review because they may need to plan for and make reimbursement decisions in advance. Per the guidance, the FDA doesn't intend to object to the following information provided to payors about investigational drugs, so long as it is provided in an unbiased, factual, accurate and non-misleading manner:

- Product information such as drug class;
- Information about the indication being pursued;
- Factual presentations of results from clinical or preclinical trials;
- The expected timeline for possible approval;
- Product pricing information;
- Marketing strategies; and
- Product-related programs or services such as patient support programs.

The guidance suggests companies also provide a clear statement regarding the investigational nature of the product and information about the stage of product development.

FDA finalizes nonproprietary naming guidance for biological products

The guidance outlines the agency's plans to implement a naming convention requiring a nonproprietary name comprising a four-letter suffix devoid of meaning attached to a proper name. Sponsors of originator biologicals, related biologics and biosimilars are asked to submit 10 proposed suffixes for consideration.

The FDA finalized guidance describing its naming convention for biological products, requiring a nonproprietary name that includes an FDA-selected suffix. Per the convention, the nonproprietary name for each originator and related biologic and biosimilar product will be a proper name comprising the core name and a meaningless four-letter distinguishing suffix.

The naming convention will be applied to biological or biosimilar products newly or previously licensed under section 351(a) or 351(k) of the Public Health Service Act (PHS Act). It will also apply to biological products approved under the Federal Food, Drug and Cosmetic Act on or before March 23, 2020, if the products are deemed licensed under section 351 of the PHS Act through the Biologics Price Competition and Innovation Act of 2009 on March 23, 2020. Additional guidance will be provided regarding the administrative issues associated with this transition. The FDA also plans to apply a naming convention to interchangeable products featuring a core name and suffix, but has yet to determine the appropriate format.

A proper name reflects scientific aspects of a product, such as chemical structure, and is different from the proprietary name, which is often trademarked and registered for private use. For biologicals licensed under the PHS Act, the FDA designates a proper name in the license for use. However, pharmacovigilance systems may struggle to track a biological product that shares the same proper name with other biological products. At the same time, original biologicals, related biologicals and biosimilar products that share the same proper name may lead to inadvertent substitution and cause confusion among healthcare providers. As such, nonproprietary names that include distinguishing suffixes can help identify specific products in adverse event reporting, aid in accurate product identification and help prevent inadvertent substitution, the guidance states.

The FDA believes a designated suffix will provide a consistent mechanism to identify and record the use of biological products if they are present in the proper name. The four-letter suffixes will be attached with a hyphen to the core name of each originator or related biological or biosimilar product. The use of a shared core name, which will be the adopted name designated by the USAN Council (when available), will signal a relationship among the products. The guidance indicates the FDA may in some cases attach a unique prefix to distinguish products from previously licensed biological products to protect patient safety. For example, a prefix was added to ado-trastuzumab emtansine to distinguish the product from trastuzumab.

The guidance calls on applicants to propose up to 10 suffixes during the investigational new-drug phase or at the time of BLA submissions, in order of preference. A BLA holder may propose a suffix for use in the proper name of a currently licensed product by submitting a prior approval labeling supplement. The FDA recommends proposals include support analyses of the proposed suffixes for consideration. Proposed suffixes should be unique, devoid of meaning, composed of at least three distinct letters, nonproprietary and free of legal barriers that would limit usage. At the same time, they should not be false or misleading, include numerals or other symbols, include abbreviations commonly used in clinical practice, look similar to the name of a currently marketed product, contain a drug substance name or be too like other FDA-designed suffixes.

The FDA will assess the suffixes based on these criteria and any other factors that may impact the utility of the suffix, after which it will notify applicants if a proposed suffix is acceptable. If all proposals are deemed unacceptable, applicants must submit additional proposals for consideration. If none of the suffixes submitted are determined acceptable, the FDA may decide to assign a suffix for inclusion in the proper name designated in the license at time of approval.

Finalized guidance outlines FDA's framework for IDE benefit-risk assessments

The guidance describes the benefit-risk framework the FDA will leverage when making approval or disapproval decisions for IDE applications. The framework takes into account the stage of development of the device, as well as any risk mitigation strategies included in the study.

The FDA finalized guidance, initially published as a draft in 2015, describing the factors the agency takes into account when assessing the benefits and risks of investigational device exemption (IDE) applications for human trials. The benefit-risk framework contained in the guidance is designed to facilitate the incorporation of evidence from different domains, including clinical and nonclinical, to support balanced decision-making, the FDA states. The guidance applies to original IDE applications as well as IDE amendments and supplements for human clinical studies to test the safety and efficacy of certain medical devices.

Per the guidance, the FDA will consider three factors when making an IDE benefit-risk assessment:

1. The stage of development;

2. The maturity of the proposed technology; and

3. The availability of nonclinical testing to supplement or replace the necessity of clinical testing.

The guidance acknowledges that earlier stages of device development and investigational research are associated with a greater degree of uncertainty and outlines how this uncertainty may be quelled by risk mitigation measures to ensure appropriate patient and research participant protections. The approach to benefit-risk assessment should be tailored to the stage of device development. For products at earlier stages of development, the FDA considered whether suitable mitigation measures are in place for expected and unanticipated risks. For later stages of the development, the agency considers whether risk mitigation measures center on the most likely risks. Benefit-risk assessments should factor in whether the degree of uncertainty is appropriate to the stage of development.

Key considerations when assessing the benefits and risks of IDE studies include:

- **Assessment of risks associated with device use:** Sponsors should provide a risk assessment describing and analyzing all increased risks subjects may be exposed to by the trial. Risk assessments should focus on risks supported by objective evidence that are reasonably foreseeable, as well as a description of the relationship between hazard and harm. They should also include an estimate of the probability of risks and the possible duration of risk. A summary should also be provided of any efforts to help mitigate the identified risks, including risk control measures such as device design features and protective measures such as study design.
- **Assessment of other considerations of investigational study:** The FDA review of management measures will consider appropriate measures to control risks related to the interpretation of the study data, such as a false conclusion, as well as risks to others presented by the study. For example, the FDA may consider the risk of radiation exposure.
- **Assessment of direct benefits to study participants:** Sponsors should include an assessment of the anticipated benefits focused on direct benefits supported by valid evidence commensurate with the stage of development. These assessments should explore the types of benefits, the magnitude of benefits and the probability of participants experiencing these benefits, as well as the possible duration of the effect.
- **Assessment of benefits to others:** The FDA may also take into account the possible indirect benefits to others, such as knowledge derived from the study or information that may contribute to developing a treatment.
- **Other factors**: The FDA may take into account the contextual setting in which a study is being proposed, including characterization of the disease being treated and the availability of alternatives and risks associated with them. The agency may also explore subject tolerance for risk, perspective on the benefit and the degree of certainty based on prior investigations.

The FDA recommends sponsors provide a summary of these considerations as part of the IDE application.

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.

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