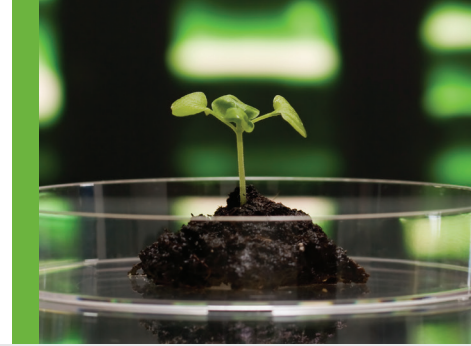




FDA Regulatory and Compliance Monthly Recap



APRIL 2016

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FDA finalizes guidance on drug design in attempt to reduce medication errors

The finalized guidance revises draft guidance published in 2012 to address public comments calling for clarifications and formatting changes, and separates recommendations on labels and labeling for another guidance document. It follows draft guidance on proprietary drug names and will be supplemented by a third guidance document on drug container and carton labeling.

The FDA finalized guidance on product designs to cut the risk of medication errors by enhancing a drug container closure system. The guidance, [Safety Considerations for Product Design to Minimize Medication Errors](#), applies to sponsors of investigational new drugs; applicants for new drug applications, biologics licensing applications or abbreviated new drug applications; and manufacturers of over-the-counter medications. It is the first in a series of three planned guidance documents to reduce or eliminate medication errors at the product design stage. It will be supplemented by guidance on cutting risks associated with the design of drug product container labels and carton labels, and guidance on reducing risks when developing and selecting proprietary names.

The guidance is part of the FDA's goal, under the 2007 reauthorization and expansion of the Prescription Drug User Fee Act (PDUFA IV), to implement measures to lessen medication errors related to similar proprietary names, vague label abbreviations, acronyms, dose designations, and error-prone labeling and packaging designs. It follows recommendations by the Institute of Medicine that the FDA adopt safe labeling practices for regulated products to enhance patient safety, citing statistics suggesting that labeling and packaging issues causes 33 percent of medication errors. The guidance acknowledges that drug product design features may predispose users to medication errors, and may not be overcome by labeling or provider and patient

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education. Therefore, it's best to address these potential issues in the product design.

The guidance outlines questions manufacturers should consider when identifying the end users of their products, as well as the environments they will be used in. It calls on them to consider all aspects of a product's user interface, which includes active ingredients and strength, the product's size, its shape and how it's stored. The FDA notes that user interaction data derived from clinical trials may not be sufficient to determine whether a drug can be used safely and correctly, noting that simulated-use studies with representative users from the intended end user population may be more suitable. These studies involve systematically collecting data from representative end users' realistic use of product designs, including product labels and labeling, derived through direct observations, subjective user feedback, and manual and automated measures of use performance.

Proactive risk assessments reflecting human and environmental factors in drug product use should be undertaken from the earliest stages of product design and before the design is finalized, the guidance states. The agency recommends that a proactive risk assessment begin with an evaluation of why and how problems have occurred with similar products. The guidance discusses examples of known problems and medication errors caused by the design of the drug product and container system and how the lessons learned from these errors can be used to reduce risks going forward.

The guidance recommends failure mode and effects analysis, a systematic assessment of the product within the medication use system, to identify medication error concerns related to product design and container closure. This method is employed by the Center for Drug Evaluation and Research and can provide an understanding of the impact different types of system failures may have on medication errors. It includes:

- An assessment of all the steps involved in user interactions with the products within the environments of use;
- An identification of potential use-related medication errors that could occur at each step of the medication use process;
- An estimate of the probability of these medication errors taking place; and
- An assessment of possible effects and the severity of consequences as a result of those errors.

FDA finalizes guidance on proprietary naming as part of initiative to diminish medication errors

The finalized guidance outlines the content requirements for submissions for proposed proprietary drug names. It describes what information the FDA requires to conduct promotional and safety evaluations of proposed names, and outlines a time frame for submission reviews.

The FDA [finalized guidance](#) outlining the information needed to assess proposed proprietary names for certain drugs under review within the time frames established in Prescription Drug User Fee Act (PDUFA IV) performance goals. The guidance is meant to help drug sponsors submit a complete package of information so the regulatory authority can determine the safety aspects of a proposed proprietary name as well as the promotional implications of that name. It applies for prescription drug products, including those subject to an investigational new drug application (IND), a new drug application (NDA), an abbreviated NDA (ANDA) or a biologics license application (BLA).

The guidance aligns with the FDA's commitment to use user fees to implement measures to address medication errors related to similar proprietary names, unclear label terms and issues with packaging designs. It is based in part on findings from the Institute of Medicine

suggesting that from 44,000 to 98,000 deaths occur yearly due to medical errors and recommendations that product naming be designed for the end user. It's an acknowledgement that product names that look or sound alike can lead to medication errors and potentially harm patients, especially if the wrong name leads to prescribing the wrong product, dispensing the wrong product or dispensing a product inappropriately.

As part of its premarket review of NDA, BLA or ANDA products, the FDA uses the following tools:

- **Safety evaluation:** The agency assesses the potential for confusion throughout the medication user system and to identify potentially problematic proprietary names. This includes examining product characteristics such as the proposed indication, dosage form, route of administration, patient and prescriber population, and product packaging.
- **Promotional evaluation:** The agency will consider whether the name overstates the efficacy, minimizes the risk, broadens the indication or makes unsubstantiated superiority claims about the product. It will also determine whether the proposed name is overly “fanciful” by suggesting unique effectiveness or composition, or is false or misleading in any other way.

The guidance notes that the timeline for a proposed proprietary name won't start if a submission is not complete. Once complete, the PDUFA IV review clock will begin using the date of receipt of the submission. The FDA requires that a complete submission for a proprietary name submitted during the IND phase be reviewed within 180 days of receipt. For those submitted with an NDA or BLA, the agency will review the complete submission within 90 days.

Completed name requests submitted during the IND phase should include a Form 1571, whereas those submitted with an NDA, ANDA or BLA should include a Form 356. They should include a primary and alternate proposed proprietary name, with the intended pronunciation of the name and a derivation of the name,

as well as an explanation of the intended meaning of proprietary name modifiers and the pharmacological or therapeutic category. All submissions should also include information on the likely care environment for dispensing and use, delivery system (e.g., transdermal patch) and measuring device (such as a calibrated dosing cup).

For products with a proposed label and labeling, the submission should include the proposed labeling and proposed container labels and labeling. The FDA requests that this include the size of the actual label, and that sponsors provide the label, labeling and packaging in color and reflect the presentation that will be used in the marketplace. For submissions for a product without proposed labeling, the FDA requests that information on the established name, prescription status, dosage forms, proposed indications for use, routes of administration, and additional dosage and storage information, as well as instructions for use, be provided.

FDA warning letter claims Shionogi copay assistance voucher for Ulesfia is misleading

The FDA sent a warning letter to Shionogi requesting that the company cease misbranding head lice treatment Ulesfia by omitting certain risk information and material facts in its promotional materials, or cease distributing the product altogether.

A [warning letter](#) sent to Shionogi by the FDA's Office of Prescription Drug Promotion (OPDP) said the copay assistance voucher for the company's topical lotion Ulesfia (benzyl alcohol) is false or misleading and misbrands Ulesfia under the meaning of the federal Food, Drug, and Cosmetic Act, making its distribution violative. The FDA said the promotional material omits risk information and certain material facts about the product, such as Ulesfia's approved indication for the topical treatment of head lice infestation in patients 6 months of age and older. These omissions, the letter states, create a misleading view of the product's safety and effectiveness.

While the voucher makes several claims about Ulesfia's efficacy, it fails to communicate any of the risk information contained in the product's approved label — including warnings and precautions regarding neonatal toxicity, eye irritation, contact dermatitis and use in children. These omissions create a misleading impression about the drug's safety, said the FDA, and aren't mitigated by statements directing consumers to the company's website or to a package insert for further prescribing details. In particular, the letter scrutinized the representation of the product as the top prescribed treatment for head lice and as a non-neurotoxic formulation, as well as its failure to properly indicate that the product is approved only for patients 6 months of age and older.

Shionogi was also faulted for failing to submit a copy of the voucher to the OPDP for review under cover of Form FDA-2253 at the time of initial dissemination as required by FDA regulations. As a result of these violations, OPDP requested that Shionogi either cease misbranding Ulesfia or cease distributing it. The department also asked that Shionogi submit a written response to the warning letter detailing its plan to comply with FDA demands, as well as its plan to disseminate corrective messages to audiences having already received the noncompliant promotional materials.

FDA's draft biosimilar labeling guidance relies heavily on reference product labeling

The FDA unveiled its draft guidance on biosimilar labels, basing them largely on reference product labels but outlining clear rules for including data from clinical studies designed to support biosimilarity. The guidance aligns with how the agency labeled Zarxio, the first approved biosimilar in the country.

The FDA's [draft guidance on biosimilar labeling](#) treats biosimilars similarly to generic drugs, calling for a description of data supporting the safety and efficacy of the reference product. It applies only to prescribing information, but also includes recommendations for FDA-approved patient labeling.

The guidance states that the FDA's finding of safety and effectiveness for a reference product, as shown in FDA-approved prescribing information, should be used to ensure health care providers are provided with the information needed to make prescribing decisions for the proposed biosimilar's conditions of use. The agency therefore recommends that biosimilar labeling include all pertinent data and information from reference product labeling, with appropriate product-specific modifications. In instances when labeling is based on the reference product, the FDA expects the text will be similar, though the label doesn't need to be identical to the reference product.

The guidance suggests that information from a study of the biosimilar should be incorporated into labeling only when it's necessary to inform safe and effective use. In all other instances, the FDA says such data should not be included, as a clinical study supporting licensure of the product would generally not be designed to demonstrate the safety and efficacy of the product and the data are unlikely to be relevant to a health care provider's considerations regarding use.

The FDA recommends that a biosimilar product name be used when labeling text is specific to or is referring only to the biosimilar product, whereas the reference product name should be used when data from reference product studies are described. In instances when a biosimilar name is used, the FDA says the proprietary name should be used. Sections where information may be specific to the biosimilar may include indications and usage, dosage and administration, dosage forms and strengths, a description, and storage and handling, as well as boxed warnings, contraindications, warnings and precautions, and drug interactions. The guidance also notes that in labeling sections where risk applies to both the biosimilar product and reference product, the core name of the reference product followed by the word "products" may be used.

The guidance also addresses instances in which a biosimilar product is licensed for fewer conditions of use, indications and dosing regimens than the reference product. It states that while labeling related to conditions for use for the reference product would generally not be included in the biosimilar labeling, as with generic labeling, it may be necessary in some cases to include information relating to an indication not licensed by the biosimilar in order to ensure safe use. In such cases, it's important that the labeling not be written in a manner that implies the biosimilar is approved for that indication or use. In instances when a biosimilar maker is interested in pursuing approval for additional conditions of use following product licensure, new BLAs and supplement submissions for product labeling should include a clean version of reference product labeling, tracked changes of proposed biosimilar product labeling and a clean version of the proposed biosimilar product labeling.

Finally, the guidance notes that biosimilar labeling should include a statement clearly indicating that the product is biosimilar to a reference product, with a footnote defining what a biosimilar is. Using a fictitious product as an example, the agency says the statement should say: "NEXSYMEO (replicamab-cznm) is biosimilar* to JUNEXANT (replicamab-hjxf) for the indications listed." The footnote should say that: "*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product."

For more information on any of these FDA regulatory and compliance updates, please contact [Scott S. Liebman](mailto:sliebman@loeb.com) at sliebman@loeb.com.

Loeb & Loeb LLP's FDA Regulatory and Compliance Practice

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