# FDA Regulatory and Compliance Monthly Recap

## OCTOBER 2015

**KEY FINDINGS**



## FDA releases draft ICH guidance with aim to improve pharmaceutical benefit-risk assessments

*The agency released ICH guidance to regulate how pharmaceutical makers should present benefit-risk information in regulatory submissions. The guidance doesn't call for a particular approach, but specifies what elements should be included in submissions.*

The FDA released draft guidance, "M4E(R2): The CTD—Efficacy," standardizing the presentation of benefit-risk information in pharmaceutical regulatory submissions by offering greater clarification on the format and structure of information included in section 2.5.6 of the submissions.

In recent years, providing improved instructions for benefit-risk assessment has been a priority in drug regulation, as regulators see a high degree of variability in the approaches taken by applicants. The benefit-risk assessment of pharmaceuticals is the fundamental component of regulatory decision-making, since regulatory authorities approve drugs that are demonstrated to be safe and effective, and the divergence in approaches taken by applicants can hamper efficient communication of industry views to regulators.

The draft guidance was prepared under the auspices of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (formerly the International Conference on Harmonisation) and revises the "M4E: The CTD–Efficacy" guidance, first made available by the FDA in August 2001, which focused on preparing the efficacy components of an application file in the common technical document (CTD) format.

The FDA recognizes that there are several reasonable approaches that can be used to conduct a benefit-risk assessment, and given that, the new draft guidance doesn't specify a particular approach

that should be used by the industry. Rather, the draft guidance introduces major elements that should be included in section 2.5.6 of the submissions:

- If multiple indications are proposed for the product, each indication can be supported by a separate section heading where appropriate.
- Certain characteristics, which could be described under benefits or risks, should not be discussed as both; rather, the applicant must decide whether it would like to characterize these as either a benefit or a risk.
- Information available about the patient perspective, including information on patient attitudes or studies intended to elicit the patient perspective, may be considered when completing this section of the submission.
- Tables and figures may now be included to support or clarify key points or conclusions.

Similarly, the revised draft guidance doesn't command a particular approach to be used by a regulator when conducting a benefit-risk assessment. Both applicants and regulators may use a different approach to their submission or approvals so long as it satisfies the requirements of applicable statutes and regulations.

## CDRH looks to keep pace with new technology, bolster patient safety with 2016 regulatory science priorities

*The regulatory science priorities for FY2016 focus on the integration of new technology, including "Big Data," into the regulatory decision-making process, with a particular emphasis on patient safety and experience. The priorities reflect a more patient-centric approach to decision-making, and an attempt to adapt to the changing technological landscape.*

The FDA's Center for Devices and Radiological Health released its Regulatory Science Priorities for FY2016, identifying the top 10 needs after analyzing science needs and gaps. The priorities focus primarily on improving the decision-making process via technology, and include:

1. **Incorporating "Big Data" into regulatory decision-making:** The CDRH concedes that Big Data stockpiles, such as human genome sequences and clinical trial databases, are being underutilized, and recognizes the need for tools to take advantage of such data.
2. **Using evidence from clinical experience across multiple domains in regulatory decision-making:** In recognition that most regulatory decisions are currently based on information provided by manufacturers, CDRH finds that incorporation of reliable clinical evidence is needed to improve regulatory decision-making.
3. **Bolstering the quality and effectiveness of reprocessing reusable medical devices:** Since reuse of devices can increase the risk of infection transmission, the Center finds it's important to develop a comprehensive approach to address the effectiveness of processing.
4. **Creating computational modeling techniques to aid regulatory decision-making:** The integration of computational modeling in regulatory development is lagging, but incorporating such technology could help devices enter the marketplace in a less burdensome manner.
5. **Strengthening digital health and medical device cybersecurity:** Since devices are increasingly being impacted by digital health and cybersecurity, the Center is calling for research to bolster the performance and security of medical devices and of their interoperability.
6. **Designing devices using human factors engineering:** Recent device recalls and adverse event reports have been due to underlying human

factors and engineering issues. Given that, there's a need to create tools and techniques to evaluate device design and usability.

7. **Updating biocompatibility and biological risk evaluation of device materials:** The typical assessment for biocompatibility and biological risk could benefit from alternative approaches to the standard biocompatibility battery of tests.

8. **Moving forward with methods to predict clinical performance of devices and their materials:** Tools to project the clinical impact of new materials and technologies, the CDRH says, could promote the development of alternative materials, while boosting predictability of nonclinical performance and increasing safety in device design.

9. **Continuing to use patients reported outcome measures (PROMs) in decision-making:** Because the quality and validity of PROMs is variable, there is a need for PROM tools that generate high-quality, relevant data on outcomes important to patients, in order to integrate that data into decision-making.

10. **Gathering and leveraging patient experience and preference in decision-making:** In order to move toward more patient-centric data, the Center needs to develop tools to gather high-quality patient experience data and to incorporate such data into decision-making.

## FDA draft guidance outlines appropriate labeling for injectable drug doses

*The FDA released draft guidance on how to label injectable drugs for their appropriate doses, offering a new definition of single- and multiple-dose containers and replacing the term "single-use" with "single-patient-use." Sponsors are being tasked with updating their labels as needed within two years of the guidance finalization.*

The FDA published draft guidance offering recommendations on appropriate package type terms and discard statements for injectable medical products for human use delivered in multiple-dose, single-dose and single-patient-use containers, in an effort to overcome unsafe injection practices. The agency cited the transmission of bacterial infections to patients due to the improper use of single-dose containers, and the outbreak of infections due to a failure to follow standard procedures for multiple-dose containers, including 33 outbreaks of viral hepatitis in the U.S. between 1998 and 2008. The goal of the guidance is to allow for consistent use of correct package type terms and discard statements to promote the proper use of the products, while providing a foundation for educational efforts to minimize the risk of disease transmission.

The guidance revises the definition of both single-dose and multiple-dose containers. Single-dose containers do not need to meet antimicrobial effectiveness testing requirements and are designed for use in a single patient as a single injection or infusion; multiple-dose containers must meet antimicrobial effectiveness testing requirements or be excluded from such testing requirements by FDA regulation, and are intended to contain more than one dose of the drug product.

According to the FDA, the single-dose and multiple-dose terms are properly used, but in some cases a package contains multiple doses of a product that is intended for use in a single patient. Since the drug is designed for multiple doses, the term "single-dose" is not appropriate. Yet the multiple-dose term is inaccurate as well, since the contents may not contain a preservative or be able to pass antimicrobial effectiveness if tested. The agency previously classified products with multiple doses intended for a single patient as single-use, which led to inappropriate use due to the belief the term was interchangeable with single-dose. To address this, the draft guidance introduces the term single-patient-use container — defined as a container of sterile

medication for injection or infusion intended to be used multiple times for a single patient.

The guidance calls on applicants to determine the proper package type term for injectable products and use the correct term throughout labeling, including the container label, the carton and, where applicable, the prescribing information. Applicants are asked to change labeling as needed to adhere to the guidance within two years of the publication of the final version.

## Senate committee passes bill that redefines marketing exclusivity period to allow for DEA scheduling

*The Senate HELP Committee unanimously passed a bill that would push back when the marketing exclusivity period begins for an FDA-approved drug, and proposes measures that require the DEA clearance process to be timelier.*

The Senate Health, Education, Labor and Pensions (HELP) Committee unanimously passed the Improving Regulatory Transparency for New Medical Therapies Act, a bill that would benefit drug manufacturers by providing more certainty on the marketing exclusivity of their approved drugs that require DEA clearance.

After FDA approval, some drugs need to be scheduled by the DEA into a class under the Controlled Substances Act (CSA). Under current law, a drug's marketing exclusivity period begins once it has received FDA approval, but since the DEA classification process can take some time, this effectively cuts short the time that a drug can go to market without generic competition.

The new bill, which passed the House in March, would see the marketing exclusivity clock start after the DEA scheduling rather than after the FDA approval. It would also amend the CSA, requiring that the DEA schedule a drug no later than 90 days after it has received recommendation for controls or after the FDA approves the drug.

Others who will benefit from the bill include clinical researchers, as they will be able to indicate on their DEA application that the controlled substance will be used exclusively for clinical trials of the drug. The DEA would be required to review applications to manufacture a controlled substance (Schedule III, IV or V) for clinical trial use within 180 days of receiving the application, and 90 days for Schedule I or II drugs, not including a notice and comment period and a 90-day application window.

Now that the bill has passed the Senate HELP Committee, it will head to the Senate for a vote.

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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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