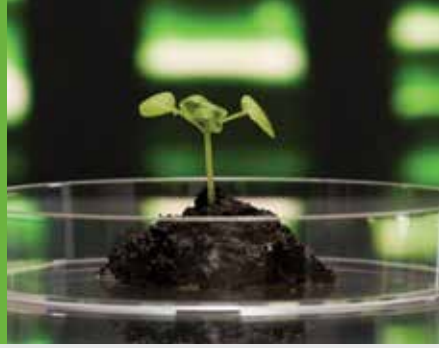
FDA Regulatory and Compliance Monthly Recap



JULY 2016

KEY FINDINGS

FDA publishes draft guidance outlining conflict-of-interest rules for advisory committee members

The draft guidance describes how the agency determines whether members with appearance issues may be allowed to participate in advisory committee meetings.

When determining who can participate in an advisory committee meeting, the FDA screens advisory committee members carefully for two categories of potentially disqualifying interests or relationships:

1. Current financial interests that may create a recusal obligation under federal conflict-of-interest laws; and

2. Other interests and relationships that do not create a recusal obligation under financial conflict-of-interest laws, but may create the appearance that the member lacks impartiality.

In the draft guidance, the FDA addresses the second category of interests – known as appearance issues – and describes its process for determining admissibility to an advisory committee meeting.

Appearance issues are addressed in a government-wide regulation regarding standards of ethical conduct for government employees at 5 CFR 2635.502 (informally known as “Section 502”). To comply with Section 502, the FDA screens its advisory committee members’ financial interests to determine whether they must recuse themselves. Where a recusal obligation is ruled out, the FDA then looks for interests and relationships that may create appearance issues.

In preparation for an advisory committee meeting involving a particular matter, members are required to report any interests related to the subject matter of the meeting via the Confidential Financial Disclosure Report. The form is then reviewed by the FDA to determine whether an appearance issue exists.

Sections IV and V of the guidance explain how the FDA reviews potential appearance issues and grants authorizations for advisory committee members under section 502. The guidance provides several examples of circumstances which may create an appearance issue, including:

- When a member of the household works or is seeking to work for the sponsor with a product before the committee;
- When a member has had past financial interests with the sponsor with a product before the committee; and
- When a member has a current consulting contract with a sponsor, but the contract is not related to the product or issue before the committee.

However, even where appearance issues are identified, it remains at the FDA's discretion whether or not to permit a member to participate in a meeting. It may do so if it determines that the member's participation serves the government's greater interest. In weighing this, the FDA balances the agency's interest in access to quality expert advice with the need to avoid serious questions about the member's impartiality.

While the FDA has previously issued guidance on its process for evaluating advisory committee members for clear conflicts of interest, this is the first time the agency details its approach to determining appearance issues.

The draft guidance is being issued for public comment before final guidance is issued. The agency is specifically requesting comments on whether advisory committee members should be asked to voluntarily and publicly disclose whether or not they've been granted an appearance authorization.

PREA noncompliance letter calls out Mallinckrodt for failing to conduct pediatric study of pain treatment

Mallinckrodt failed to complete a post-marketing pediatric study of its opioid painkiller and failed to respond to the FDA's PREA noncompliance letter. The FDA could deem the product misbranded if Mallinckrodt fails to comply with the law.

The FDA posted a Pediatric Research Equity Act (PREA) noncompliance letter sent to Mallinckrodt for failing to conduct a pediatric post-marketing study of Xartemis XR, an oxycodone hydrochloride and acetaminophen product approved for the management of acute pain in instances when an opioid analgesic is appropriate. The FDA posted the letter as required under section 505B(d)(1) of the Federal Food, Drug and Cosmetic Act for sponsors who fail to submit their pediatric assessments by the final due date or have failed to secure a deferral or deferral extension.

Mallinckrodt's new drug application for the product, which was approved on March 11, 2014, required the drugmaker to conduct a study in pediatric patients between the ages of 12 and 17 years by March 31, 2016. The noncompliance letter states that the pediatric assessment was not submitted and provided the drugmaker with 45 days to respond with the reason for the delayed assessment and a date by which it will be completed. Mallinckrodt failed to respond to the letter, with no response posted as of June 24, 2016.

Only 22 PREA noncompliance letters have been issued to drugmakers since 2013. Failing to respond to such letters is uncommon, and Mallinckrodt's failure drew particular ire as the U.S. grapples with an opioid epidemic. Opioid painkillers such as Xartemis XR have been linked to more than 28,000 deaths in the U.S., with more than 2 million Americans abusing or dependent on the drugs.

Mallinckrodt said it is having active discussions with the FDA regarding the complexities of pediatric research related to opioid pain medications, and is working to engage the agency on the next steps to ensure compliance. Failure to comply could result in the drug being rendered misbranded, which could subsequently lead to an injunction or seizure.

Mallinckrodt is also required to conduct a pharmacokinetics and safety study of an age-appropriate formulation by June 1, 2018, and a pharmacokinetics, safety and efficacy study of an age-appropriate formulation by June 1, 2020.

FDA finalizes guidance on ICH periodic benefit-risk evaluation reports, offers sponsors clarification with Q&A document

The FDA finalized guidance on ICH periodic benefit-risk assessments and published an accompanying Q&A document to help sponsors implement the newly rejigged Periodic Benefit-Risk Evaluation Reports. The finalized guidance brings together two previous ICH guidances on periodic safety updates for marketed drugs, and reflects enhancements to the pharmacokinetic environment.

The FDA published guidances, developed under the umbrella of the International Council for Harmonisation (ICH), on periodic benefit-risk evaluations. The first guidance document, "E2C(R2) Periodic Benefit-Risk Evaluation" [E2C(R2) guidance], outlines the content, format and timing of a Periodic Benefit-Risk Evaluation Report (PBRER) for an approved drug or biologic. It finalizes draft guidance published in April 2011 that updated and combined two ICH guidances on periodic safety reports for marketed drugs.

The E2C(R2) guidance was developed to harmonize the periodic reporting requirements of regulatory authorities and to provide a common format for drug sponsors to report interval safety data at defined post-approval times. When it was initially implemented, the guidance called for a Periodic Safety Update Report (PSUR) to determine whether changes were necessary in the reference safety information for a product. The updated guidance acknowledges that the pharmacovigilance environment has changed and revisions to the PSUR were needed to enhance its usefulness. The name was changed to the PBRER, and it was redesigned to provide more emphasis on the cumulative knowledge of a product while maintaining a focus on new information. The focus of the PBRER shifted from individual case safety reports to aggregate data evaluation. It also incorporated a formal evaluation of benefit, though the guidance recognizes that a concise discussion of benefit is generally sufficient. The goal of a PBRER is to provide a comprehensive, concise and critical analysis of new or emerging risks of a product, as well as its benefit in approved indications.

The updated guidance provides practical options for marketing authorization holders (MAH) to consider in selecting the most appropriate reference product information for the PBRER, as well as advises on managing different frequencies of PBRER submission in different regions. The PBRER relates to any information that may become available following the international birth date, or the date of the first marketing approval, for a product. Sources of available information include data regarding the active substance(s) in the product that the MAH may be reasonably expected to have access to, as well as data relevant to the assessment of the safety or benefit-risk profile of the product. Notably, the guidance has been developed so analogous sections of the PBRER, as well as the development safety update report (DSUR) (ICH E2F guidance), and safety specifications of a risk management plan (ICH E2E guidance) can share content.

The second guidance, "E2C(R2) Periodic Benefit-Risk Evaluation Report – Questions and Answers," provides supplementary information to clarify key issues in the E2C(R2) guidance. It is designed to help sponsors

implement the PBRER, and addresses points to consider when addressing some of the newer aspects of the new safety report. It addresses issues such as managing the submission of PBRERs when regional reporting differs across countries, where in the PBRER information on off-label uses can be provided, and sharing content between PBRER and DSUR.

FDA publishes draft guidance outlining principles for codevelopment of therapeutic products and in vitro companion diagnostics

The draft guidance serves as a guide for sponsors of therapeutic products and their in vitro diagnostic devices to facilitate the simultaneous marketing approval of both products. It outlines critical aspects of the codevelopment process and provides recommendations for codevelopment clinical trials and marketing applications.

The FDA published draft guidance providing recommendations for the codevelopment of in vitro companion diagnostic devices (IVDs) and therapeutic products. The draft guidance is designed to serve as a guide for the codevelopment of companion IVDs and therapeutic products, while providing guidance for FDA staff reviewing such products.

IVD companion diagnostics provide information that is critical for the safe and effective use of the corresponding therapeutic product. Generally, such devices should be approved, granted a de novo request or cleared by the agency simultaneously with the approving of the therapeutic product. The draft guidance details the general principles of codevelopment that support parallel marketing authorization for both products, as well as certain regulatory requirements that sponsors should bear in mind when developing these products. It also outlines considerations for planning and executing clinical trials that include an assessment of an IVD companion diagnostic. Although specific to an IVD companion diagnostic, the FDA states that the principles contained in the guidance may be relevant to the codevelopment of a therapeutic product with IVDs that do not meet the definition of a companion diagnostic but may be relevant to therapeutic product development and decision-making.

The guidance recognizes that therapeutic products and IVDs are generally developed on different schedules and are subject to different regulatory requirements. As such, codevelopment for contemporaneous marketing authorization requires a general understanding of both processes. The guidance states that multiple approaches may be permissible to obtain the data required for concurrent marketing approval for both products, and suggests that sponsors meet with the FDA before launching a trial. The following table outlines the critical points in the codevelopment process.

The guidance recommends that the need for an IVD companion diagnostic be identified early in the course of therapeutic product development, as this allows for an analytically validated test to be incorporated into the design of clinical trials for therapeutic products. In instances in which safety or efficacy issues identified by an IVD do not emerge until late in the course of therapeutic development, approval of the therapeutic product could be delayed until the appropriate IVD companion diagnostic is approved. The FDA notes that while codevelopment does not require parallel development of the IVD and the therapeutic process from start to finish, the availability of an IVD with “market ready” analytical performance characteristics – a test with complete analytical validation – is recommended when starting trials to support approval. These trials can be used to show that the IVD companion diagnostic has sufficient clinical performance characteristics to support its use with the therapeutic product.

The guidance notes that when an IVD is being used to make decisions on how to enroll, assign or manage subjects in a therapeutic product, but it has not been approved for such an intended use, it will be deemed investigational. When investigational IVDs are used in

a trial, the requirements of the Investigational Device Exemption (IDE) regulation at 21 CFR Part 812 will need to be addressed. Since IDE requirements for investigational devices depend on the risk presented, the FDA expects sponsors to assess risks presented to study subjects by use of the investigational IVD in the context of the therapeutic product clinical trial. The guidance indicates that codevelopment clinical trials can include use of an investigational IVD in ways that are categorized by the IDE regulation as either exempt, significant risk or non-significant risk.

When properly designed, clinical trials to support the safety and efficacy of a therapeutic product in a population based on a measurement of detection of a market may be used to establish the clinical validity of the IVD companion diagnostic, the guidance states. The FDA provides an example of two market-based trials that are commonly used, but notes that other designs may be appropriate and should be discussed with review centers.

The guidance also indicates that the FDA plans to coordinate the review process when IVD companion diagnostics are essential to the safe and effective use of a therapeutic product, such that both products can receive marketing authorization at the same time. In order to do so, the FDA recommends sponsors plan ahead to coordinate submissions, with consideration for the review time lines for different products. When contemporaneous marketing authorization is not possible, the FDA will resolve issues on a case-by-case basis, taking into consideration the particular circumstances surrounding the use of the therapeutic product and the characteristics of the IVD companion diagnostic. If approved, the labeling of a therapeutic product/IVD companion diagnostic pair should be consistent, with the IVD labeling specifying the particular analytes that are specific in a therapeutic product labeling.

FDA issues two draft guidance documents with updated approaches to regulating next-generation sequencing

In support of President Barack Obama's Precision Medicine Initiative (PMI), the FDA is focusing on optimizing its regulatory oversight for next-generation sequencing (NGS) in vitro diagnostic (IVD) tests, in view of accelerating safe research and clinical adoption in this field.

The FDA's Division of Antiviral Products (DAVP) anticipates that more companies will make the switch to NGS for future antiviral drug resistance analyses and other additional uses as NGS costs gradually decline. New sequencing technologies can examine millions of DNA variants at an unprecedented rate, requiring flexible and adaptive regulatory oversight to accommodate rapid evolution. In light of these considerations, the FDA issued two draft guidance documents, the first of which provides recommendations for designing, developing and validating NGS-based tests intended to aid in the diagnosis of individuals with suspected rare diseases.

The first draft guidance, titled Use of Standards in the Food and Drug Administration's Regulatory Oversight of Next Generation Sequencing-Based In Vitro Diagnostics Used for Diagnosing Germline Diseases, outlines the agency's proposed approach on the content and possible use of FDA-recognized standards in providing oversight for whole exome human DNA sequencing or targeted human DNA sequencing NGS-based tests. The aim is to demonstrate how well a test can predict the presence or absence of a particular genomic change.

Much of the feedback obtained during two public workshops from genomics experts, industry, health care providers and patients suggested that conformity with standards for analytical validation of NGS-based tests would be a reasonable approach to accommodate the expected rapid evolution of NGS technology. Section VI of the draft guidance describes

the design, development and validation criteria which must be met in order for a standard to be recognized by the FDA. These are a combination of test design activities, performance metrics and thresholds that the FDA believes can help demonstrate a reasonable assurance that an NGS-based test is analytically valid.

The agency states that when defining appropriate test performance, developers should prospectively determine the types of studies that should be conducted and the thresholds that should be met for each in the form of a minimum and target value. After design and development of the test, validation studies will indicate whether the predefined performance is met.

The guidance also outlines considerations for possibly classifying certain NGS-based tests in class II and potentially exempting them from premarket notification requirements. The agency says it will consider, over the longer term, how these recommendations may form the basis for future FDA-recognized standards, or whether it could establish special controls and/or conditions for premarket notification (510(k)) exemption.

The agency adds that while the recommendations in this document are applicable for NGS-based tests for germline diseases – whether results are intended to be provided directly to patients or through health care professionals – additional recommendations and controls would be needed for direct-to-consumer NGS-based tests for germline diseases.

The second draft guidance, titled Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing-Based In Vitro Diagnostics, describes the conditions under which test developers may rely on clinical evidence from FDA-recognized public genome databases to support clinical claims and provide assurance of accurate clinical interpretation of results.

For the purposes of this draft guidance document, the FDA describes "genetic variant database" as "a publicly accessible database of human genetic variants that aggregates and curates reports of human phenotype-genotype relationships to a disease or condition with publicly available documentation of evidence supporting those linkages. Genetic variant databases may also include assertions about specific genotype-phenotype correlations."

The FDA notes that the evidence residing in many genetic variant databases has been collected from multiple sources that can meet the valid scientific evidence definition. For that reason, the agency believes that the aggregation, curation and interpretation of clinical genotype-phenotype associations in genetic variant databases could support the clinical validity of claims made about a variant detected by an NGS-based test and a disease or condition.

In order to determine whether a particular NGS test has a reasonable assurance of safety and effectiveness, the FDA says it must determine that the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results in a significant portion of the target population.

This draft guidance also describes the FDA's considerations in determining whether a genetic variant database is a source of valid scientific evidence that could support the clinical validity of an NGS-based test in a premarket submission. The FDA believes that, generally, the standards for use of evidence set forth by well-recognized professional guidelines appear to parallel the types of evidence appropriate to support an FDA premarket submission.

The agency is looking to further outline the process by which administrators of publicly accessible genetic variant databases could voluntarily apply to the FDA for recognition, and how the FDA would review such applications and periodically re-evaluate recognized databases. The agency will accept comments

during the 90 days following publication of both draft guidance documents.

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.