JONES DAY | **Pharmaceutical & Medical Device Regulatory Update**
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Events

Please join Jones Day for a CLE program on "Compliance in the Precision Medical Era: Legal Considerations for the Contemporary Life Sciences Industry" from 11:00 a.m.–2:00 p.m. on May 4, 2016, in Washington, D.C. *Register here*.

Top News

FDA Releases Draft Guidance on Biosimilar Labeling
Earlier this week, FDA announced the availability of its long-awaited draft guidance on biosimilar labeling, titled "Labeling for Biosimilar Products." In the draft guidance, FDA advised that "biosimilar product labeling [should] incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications." Notably, however, FDA believes that data designed to demonstrate biosimilarity should not be included because of their potential to cause confusion. The draft guidance goes on to provide specific recommendations and examples related to product identification (e.g., when to use the biosimilar name, reference product name, core name, or a combination), content presentation (i.e., specific to the biosimilar product's conditions of use), and specific labeling sections. The draft guidance concludes with information on drafting patient labeling, updating safety information, seeking additional conditions of use, and submitting initial and revised labeling. Interestingly, the draft guidance leaves open the possibility of future direction for labeling interchangeable biological

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UPCOMING EVENTS

"Compliance in the Precision Medical Era: Legal Considerations for the Contemporary Life Sciences Industry" from 11:00 a.m.–2:00 p.m. on May 4, 2016, in Washington, D.C. *Register here*.

RELATED PRACTICES

FDA Regulatory & Compliance Counseling

products should they be established. The draft guidance is the first biosimilar-specific guidance published by FDA this year (Jones Day published *Commentaries* on previous biosimilars guidance documents here, here, and here).

Health Care

Life Sciences

The draft guidance comes weeks after FDA's "Deemed to be a License" guidance, which we discussed in our last Jones Day *Update*, and one day before FDA announced approval of a second biosimilar product. Given the biosimilar market's infancy, FDA recently stated that the "labeling guidance has been issued in draft to provide an opportunity for public comment." FDA compared the format to that used for the recent draft guidance on nonproprietary naming, for which FDA is currently reviewing comments. FDA affirmed its commitment to finalizing both draft guidance documents but offered no deadline for comments.

FDA Announces Black Box Warning for Immediate-Release Opioid Paid Medications

As part of FDA's previously announced action plan to reassess the Agency's approach to opioid medications, FDA announced on March 22, 2016, that it will require safety labeling changes for immediate release ("IR") opioid pain medications. The changes include a new boxed warning about the serious risks of misuse, abuse, addiction, overdose, and death. This change and others are similar to the changes the Agency started requiring for extended-release/long-acting ("ER/LA") opioid products in 2013. In addition, labeling for IR and ER/LA opioid products will now include safety information regarding drug interactions that can cause serotonin syndrome and opioid effects on the endocrine system, both of which can occur regardless of whether opioid medication is being taken to treat pain or as part of medication-assisted treatment. Finally, FDA is reviewing available scientific information regarding potentially serious outcomes that can result from interactions between benzodiazepines and opioids.

FDA Modifies Lesser Administrative Actions Imposed on IRBs

On April 4, 2016, FDA announced a direct final rule amending and a proposed rule to amend the regulation describing lesser administrative actions that may be imposed on an Institutional Review Board ("IRB") that fails to comply with IRB regulations. The two notices clarify that FDA may require the IRB to withhold approval of new FDA-regulated studies, stop the enrollment of new subjects in ongoing studies, and terminate ongoing studies, or any combination of these actions until the noncompliance with the IRB regulations is corrected. Specifically, FDA is amending 21 CFR § 56.120(b) by clarifying that FDA has authority to require the IRB to withhold approval of new FDA-regulated studies conducted at the institution or reviewed by the IRB, direct that no new subjects be added to ongoing studies, and terminate ongoing studies provided that doing so would not endanger study subjects. FDA published the direct final rule with the intention of clarifying an existing regulation and does not anticipate any significant adverse comment regarding the amendment. The proposed rule is a companion to the direct final rule and codifies FDA's interpretation of the regulation, that FDA may impose restrictions on a noncompliant IRB until the IRB takes appropriate corrective action. The rule is effective August 17, 2016. Interested parties can submit comments on this direct final rule or its companion proposed rule by June 20, 2016.

FDA Proposes Amendment to OTC Drug Regulations

On April 4, 2016, FDA proposed amending regulations guiding nonprescription or "over-the-counter" ("OTC") drug products by augmenting the time and extent application ("TEA") process for OTC drugs. The proposed rules would establish timelines and performance metrics for FDA's review of non-sunscreen TEAs, as required by the Sunscreen Innovation Act ("SIA"). The SIA added section 586F to the Food, Drug, and Cosmetic Act ("FDCA") and directs FDA to issue regulations establishing timelines and related performance metrics for the review of certain submissions under FDA's regulation governing TEAs. The TEA regulation establishes the criteria and procedures by which OTC

drugs initially marketed in the United States after the OTC Drug Review began in 1972, as well as those without any U.S. marketing experience, can be considered in the OTC drug monograph system. FDA is also proposing to amend the TEA regulation to make the TEA process more efficient and predictable for both product sponsors and FDA by adding filing determination requirements and criteria and by addressing the withdrawal of consideration of TEA and safety and effectiveness data submissions. In addition, FDA is proposing to add a provision under which the Agency would perform an initial assessment as to whether a TEA contains sufficient information for FDA to undertake a substantive scientific review. FDA is accepting comments on the proposed rule through June 3, 2016.

Other News
Senate Panel Approves Five Medical Innovation Bills

FDA Revises Policy to Allow Prioritization of Submissions for "Sole-Source" Generics

Device Manufacturer Agrees to Pay $34.8 Million to Settle Kickback Allegations Despite Continuing "Good Faith Belief" that Services Provided as "Permissible Bundled Discount"

FTC Files Novel Case Challenging Agreement Not to Market Authorized Generic (a "no-AG commitment")

SEC Settles With Biotech Company Accused of Misleading Investors By Omitting FDA Recommendation for Second Clinical Trial

FDA Approves Updated Label for Mifeprex, Expanding Access in Some States

Regulatory Updates

FDA Issues Proposed Rule to Amend OTC Drug Regulations
In the April 4, 2016, *Federal Register*, FDA issued a proposed rule to amend its nonprescription OTC drug regulations. The proposed rule, if finalized, would supplement the TEA process for OTC drugs by establishing timelines and performance metrics for FDA's review of non-sunscreen TEAs, as required by the Sunscreen Innovation Act. FDA is also proposing other changes to streamline the TEA process. ***Comments are due June 3, 2016***.

FDA Amends Regulation Describing Lesser Administrative Actions that May Be Imposed on Failing IRBs
In the April 4, 2016, *Federal Register*, here and here, FDA issued a proposal to amend the regulation, and, in a direct final rule issued the same day, amended the regulation describing lesser administrative actions that may be imposed on an IRB that has failed to comply with FDA's IRB regulations. FDA clarified that it may require the IRB to withhold approval of new FDA-regulated studies, stop the enrollment of new subjects in ongoing studies, and terminate ongoing studies, or any combination of these actions, until the noncompliance with FDA's IRB regulations is corrected. FDA is taking the action to ensure clarity and improve the accuracy of the regulations. ***Comments are due June 20, 2016; the rule is effective August 17, 2016***.

FDA Announces Issuance of EUA for Device to Diagnose Zika Virus
In the March 26, 2016, *Federal Register*, FDA announced the issuance of an Emergency Use Authorization ("EUA") (the "Authorization") for an *in vitro* diagnostic device for diagnosis of Zika virus infection in response to the Zika virus outbreak in the Americas. FDA issued the Authorization under the FDCA in response to a request by the U.S. Centers for Disease Control and Prevention. Among other things, the Authorization contains conditions on the emergency use of the authorized device. On February 26, 2016, the Department of Health and Human Services ("HHS") determined there is a significant potential for a public health emergency with significant potential to affect national security or the health and security of U.S. citizens living abroad involving Zika virus. On the basis

of such determination, HHS declared that circumstances exist justifying the authorization of emergency use of the in vitro diagnostic tests. ***The Authorization was effective February 26, 2016***.

FDA Issues Final Rule Adding Patient Engagement Advisory Committee
In the March 21, 2016, *Federal Register*, FDA issued a final rule amending the standing advisory committees' regulations to add the Patient Engagement Advisory Committee (the "Committee"). The Committee was established on October 6, 2015, and will provide advice to the FDA Commissioner on complex issues relating to medical devices, regulation of devices, and device use by patients. Topics the Committee will consider include Agency guidance and policies, clinical trial or registry design, patient preference study design, benefit–risk determinations, device labeling, unmet clinical needs, available alternatives, patient-reported outcomes, and device-related quality of life or health status issues. ***The rule was effective March 21, 2016***.

FDA Announces Proposal to Ban Powdered Surgeon's Gloves Devices
In the March 22, 2016, *Federal Register*, FDA announced its determination that Powdered Surgeon's Gloves, Powdered Patient Examination Gloves, and Absorbable Powder for Lubricating a Surgeon's Glove present an unreasonable and substantial risk of illness or injury and that the risk cannot be corrected or eliminated by labeling or a change in labeling. Consequently, FDA is proposing these devices be banned. Nonpowdered gloves are not included in this ban. ***Comments are due June 20, 2016***.

FDA Announces Modifications to FDA Recognized Consensus Standards for Premarket Reviews of Medical Devices
In the April 4, 2016, *Federal Register*, FDA announced a publication containing modifications the Agency is making to the list of standards it recognizes for use in premarket reviews ("FDA Recognized Consensus Standards"). This publication, titled "Modifications to the List of Recognized Standards, Recognition List Number: 041," will assist manufacturers who elect to declare conformity with consensus standards to meet certain requirements for medical devices. ***The modifications were effective April 4, 2016***.

FDA Announces Filing of Color Additive Petition for Intraocular Lenses
In the March 22, 2016, *Federal Register*, FDA announced the filing of a petition, submitted by Milton W. Chu, M.D., proposing that the color additive regulations be amended to provide for the safe use of titanium dioxide and [phthalocyaninato (2-)] copper as orientation marks for intraocular lenses. ***The petition was filed February 19, 2016***.

FDA Announces Submission to OMB of Information Collection on Quantitative Information in Direct-to-Consumer Television Advertisements
In the March 18, 2016, *Federal Register*, FDA announced that a proposed collection of information was submitted to the OMB, titled "Quantitative Information in Direct-to-Consumer Television Advertisements." ***Comments are due April 18, 2016***.

FDA Issued the Following Draft and Final Guidance Documents:

Draft Guidance for Industry: Labeling for Biosimilar Products, April 4, 2016, *Federal Register*. ***Comments are due June 3, 2016***.

Draft Guidance for Industry: Emergency Use Authorization of Medical Products and Related Authorities, April 4, 2016, *Federal Register*. ***Comments are due June 3, 2016***.

Final Guidance for Industry: Comparability Protocols—Chemistry, Manufacturing, and Controls Information for New Animal Drugs, April 4, 2016, *Federal Register*.

Draft Guidance for Industry: General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products, March 25, 2016, *Federal Register*. ***Comments are due May 24, 2016***.

Guidance for Industry: Assessment of Radiofrequency-Induced Heating in the Magnetic Resonance (MR) Environment for Multi-Configuration Passive Medical Devices, March 22, 2016, *Federal Register*.

Draft Guidance for Industry: Question-Based Review for the Chemistry, Manufacturing, and Controls Technical Section of Animal Drug Applications, March 18, 2016, *Federal Register*. ***Comments are due May 17, 2016***.

EU Regulatory Notices

EMA Recommends New Safety Measures for Zydelig
The European Medicines Agency ("EMA") has published new recommended safety measures for the use of Zydelig (idelalisib). The new measures were triggered by an increased rate of serious adverse events, including deaths due mostly to infections (see the previous Jones Day *Update*). EMA's Pharmacovigilance Risk Assessment Committee ("PRAC") is issuing provisional advice for doctors and patients using the cancer medicine Zydelig to ensure that it continues to be used as safely as possible. Along with other recommendations, PRAC recommends that all patients treated with Zydelig receive antibiotics to prevent a particular type of lung infection (*Pneumocystisjirovecii* pneumonia).

EMA Recommends Approval of New Gene Therapy for Ultra-Rare Immune Disorder
The EMA has recommended granting a marketing authorization ("MA") in the EU for orphan-designated Strimvelis, a new gene therapy, for the treatment of patients with adenosine-deaminase-deficient severe combined immunodeficiency ("ADA-SCID") who have no matching donor for a stem cell transplant. ADA-SCID is an ultra-rare immune disorder caused by a faulty gene inherited from both parents that stops the production of adenosine deaminase. Strimvelis is manufactured from a patient's own immature bone marrow cells into which a normal adenosine deaminase enzyme gene has been inserted. Following an assessment by an EMA specialized scientific committee, the Committee for Medicinal Products for Human Use ("CHMP") adopted the opinion at its March 2016 meeting. Adopting the opinion is an intermediary step on Strimvelis's path to patient access. The CHMP opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide MA**.**

CMDh Endorses Revocation of Authorizations for Fusafungine Sprays
The Coordination Group for Mutual Recognition and Decentralised Procedures—Human ("CMDh"), the medicines regulatory body representing the EU Member States, has endorsed by consensus the revocation of marketing authorizations for fusafungine sprays in the EU. This follows a review by EMA's PRAC, which concluded that the benefits of fusafungine do not outweigh its risks, particularly the risk of serious allergic reactions. Fusafungine is an antibiotic and anti-inflammatory nose and mouth spray used to treat upper airway infections such as rhinopharyngitis (common cold). Serious allergic reactions have occurred soon after the use of these sprays and involved bronchospasm (excessive and prolonged contractions of the airway muscles leading to difficulty breathing). Although the review found that serious allergic reactions are rare, they can be life-threatening, and no measures have been identified to sufficiently reduce or manage this risk. Following the CMDh consensus position, EU Member States will begin revoking the marketing authorizations of these medicines in their territories according to an agreed timetable.

EMA Recommends New Medicines for Approval in the EU
The EMA's CHMP has recommended several new medicines for approval at its March 2016 meeting. The CHMP recommended granting a conditional MA for Darzalex (daratumumab) for the treatment of relapsed and refractory multiple myeloma. Darzalex has an orphan designation and was reviewed under EMA's accelerated assessment scheme. The CHMP

also recommended granting an MA for orphan-designated Galafold (migalastat) for the treatment of Fabry disease, a rare genetic disorder. Pandemic influenza vaccine H5N1 MedImmune also received a positive opinion from the CHMP, together with a biosimilar monoclonal antibody, Flixabi (infliximab), for the treatment of rheumatoid arthritis, adult and pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis; Neparvis (sacubitril/valsartan) for the treatment of chronic heart failure with reduced ejection fraction; and Palonosetron Accord (palonosetron) for the prevention of nausea and vomiting associated with chemotherapy.

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