Issue Number 2 | March 2014

Jones Day to Host FDLI Drug Law and Regulation Conference

We are pleased to announce that **Christopher M. Mikson, M.D.,** Of Counsel at Jones Day, is a key presenter at the Food and Drug Law Institute's industry standard two-day "Introduction to Drug Law and Regulation: The Legal Framework for Drug Regulation." Chris will present an overview of the law surrounding biologics and biosimilars, including relevant statutes and current developments. The course will be held at Jones Day's Washington Office on April 2–3. Don't miss your opportunity to attend this important program that, for more than 20 years, has taught thousands to think like a seasoned drug professional. Register today through FDLI.

Top Stories

Draft Guidance Promises Major Changes in New Chemical Entity Exclusivity Provisions
In recognition of the increasingly important role fixed-combination products play in treating cancer, cardiovascular, and infectious diseases, FDA issued draft guidance in February that significantly departs from its historical interpretation of the five-year New Chemical Entity ("NCE") exclusivity provision. Historically, FDA has interpreted these provisions such that a fixed-combination was ineligible for five-year NCE exclusivity if it contained a previously approved active moiety, even if the product also contained a new active moiety (i.e., an active moiety that the Agency had not previously approved). The new draft guidance focuses on FDA's evolving interpretation of the term "drug" in the eligibility clause of the five-year NCE exclusivity statutory provisions to improve incentives for producing new drugs in fixed-combinations, a practice that is often safer and more effective. For more on this topic, read the Jones Day *Alert* and Law 360 article.

President Proposes 8 Percent Increase for FDA's Budget
Earlier this month, President Obama released his proposed budget for fiscal year 2015. The President's budget requests $4.7 billion in resources for FDA, an 8.1 percent increase over the agency's 2014 budget. Specifically, the budget includes a $61 million increase for medical product safety programs, including premarket reviews. The budget allots $25 million for strengthening oversight of the pharmacy compounding industry and includes another $25 million for promoting products to prevent or protect against bioterrorism, the same as in fiscal year 2014.

Senator Proposes Bill to Reverse Approval of Hydrocodone Drug
On March 13, Sen. Joe Manchin (D-WV) introduced a bill to overturn FDA's marketing approval of Zohydro ER, an opioid drug made from pure hydrocodone. According to *The Wall Street Journal*, the drug has been criticized by more than 24 state attorneys general and several federal legislators concerned about abuse and potential overdose deaths. A similar bill was introduced in the House of Representatives by Rep. Stephen Lynch (D-MA), Rep. Hal Rogers (R-KY), and 11 other cosponsors. FDA approved the drug last year over the objections of a medical advisory panel. FDA Commissioner Margaret Hamburg continues to defend the drug's approval for select pain treatments.

Group of Generic Drug Manufacturers Opposes Labeling Proposal
Late last year, FDA announced a proposed rule to revise and clarify procedures for application holders of an

approved drug or biologic to update the product labeling with newly acquired information in advance of FDA's review of the change, commonly referred to as the Changes Being Effected procedure. The proposed rule would require ANDA holders to revise their labeling under the same procedure as brand-name pharmaceutical manufacturers. Generic manufacturers also would have to inform the brand-name manufacturers about any safety-labeling changes.

In a public comment filed this month, a group of small generic drug companies argue that FDA lacks authority under the Food, Drug, and Cosmetic Act to enact the rule because it would establish an exception to the "sameness" requirement, which requires that generic drug labeling match the labeling of the reference listed drug ("RLD"). The comment contends that the only legitimate exceptions to this rule are expressly provided for in statute and that FDA's proposed rule purports to create an exception by allowing generic drug labeling to differ from RLD labeling "on a temporary basis." Additionally, generic manufacturers argue this exception threatens patient safety and would force generic drug manufacturers to engage in costly, duplicative safety reviews that FDA already performs.
The comment period for the proposed rule closed on March 13.
For further details and background, view our *Jones Day Commentary*.

New "openFDA" Project Revamps Public Data on Drug Side Effects
A recently announced FDA project known as openFDA aims to make public information on adverse events, product recalls, and product labeling more accessible and useful through new database applications and structured file downloads. Every day, FDA receives thousands of reports from practitioners and patients about drug side effects. FDA publishes this data in quarterly bulk files, but as *Businessweek* reports, the sheer volume of submissions, duplicate records, and frequently misspelled drug names makes these files difficult to use. While some private companies already organize this information into handy reports, openFDA would streamline the initial data release for practical use by researchers, providers, and the general public.

FDA and European Medicines Agency Strengthen Collaboration in Medicine Safety
In late February, FDA announced a new "cluster" program with the European Medicines Agency ("EMA") focusing on pharmacovigilance, or medicine safety. The monthly teleconferences will promote a more coordinated exchange of information on the safety of medicines. FDA already clusters with EMA on other topics, including biosimilars, cancer-treating medicines, orphan medicines, and blood-based products, and it maintains similar partnerships with regulators in countries such as Canada and Japan. These clusters recognize that any action taken in one country has global repercussions on public health.

Other News

FDA Commissioner Hamburg testifies at Senate hearing about mechanisms to streamline CDRH review of medical device applications.

FDA announces April 1 public hearing on action plan for gathering and analyzing demographic subgroup data for approval of medical products.

FDA initiates the Secure Supply Chain Pilot Program to enhance security of imported drugs.

FDA considers fertility method involving mitochondrial combination.

Federal advisory committee recommends DNA test replace traditional pap smear as primary screening tool for cervical cancer.

Regulatory Updates

FDA Issued Rules or Guidance on the Following Topics:
Administrative Procedures for CLIA Categorization—On March 12, FDA issued guidance on "Administrative Procedures for CLIA Categorization." The guidance describes the administrative procedures related to Clinical Laboratory Improvement Amendments of 1988 requirements for each category of medical device regulatory review, including premarket review by the Center for Devices and Radiological Health, premarket review by other FDA centers, exempt from premarket notification, and waiver.

Placental/Umbilical Biologics—In the March 5 *Federal Register*, FDA issued "Guidance for Industry: Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients With Disorders Affecting the Hematopoietic System," dated March 2014. This finalizes the draft guidance dated June 2013.

Annual Reporting of CMC Changes—In the March 3 *Federal Register*, FDA issued guidance for industry entitled "CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports." This guidance provides recommendations to holders of new drug applications ("NDAs") and ANDAs regarding chemistry, manufacturing, and controls changes to be documented in annual reports.

Regulations for New Animal Drugs and ANADAs—In the February 27 *Federal Register*, FDA amended animal drug regulations to reflect: approval actions for new animal drug applications ("NADAs") and abbreviated new animal drug applications ("ANADAs") during December 2013; withdrawal of approval of 69 NADAs and 22 ANADAs for use of arsanilic acid, carbarsone, or roxarsone Type A medicated articles to manufacture combination drug Type B and Type C medicated feeds; and a change of sponsor for 54 NADAs and 1 ANADA for topical, intramammary, and certain other dosage form new animal drug products.

Electronic Transmission of ICSR Data—In the February 21 *Federal Register*, FDA issued guidance entitled "E2B(R3) Electronic Transmission of Individual Case Safety Reports (ICSRs): Implementation Guide—Data Elements and Message Specification." This guidance revises standards for the submission of ICSRs in human drugs and improve the inherent quality of data.

Feedback on Medical Device Submissions—In the February 18 *Federal Register*, FDA issued guidance entitled "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff." This guidance provides an overview of the ways to obtain FDA feedback regarding potential or planned medical device submissions reviewed in the CDRH and the Center for Biologics Evaluation and Research, including the Pre-Submission program (formerly the pre-Investigational Device Exemption program).

FDA Issued Proposed Orders or Draft Guidance on the Following Topics:

Enforcement Policy for Fecal Microbiota Uses—In the February 26 *Federal Register*, FDA issued draft guidance entitled "Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies," dated March 2014. When finalized, this guidance will supersede the July 2013 guidance document on this subject. Comments due March 28.

Regulations for New Chemical Exclusivity Determinations—In the February 24 *Federal Register*, FDA issued draft guidance entitled "New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products." If the guidance is finalized, a drug product will be eligible for five-year NCE exclusivity if it contains a drug substance that meets the definition of "new chemical entity," regardless of whether that drug substance is approved alone or in certain fixed-combinations. *Comments due April 25.*

Antiviral Product Development—In the February 28 *Federal Register*, FDA issued draft guidance entitled "Attachment to Guidance on Antiviral Product Development—Conducting and Submitting Virology Studies to the Agency: Guidance for Submitting HIV-1 Resistance Data." The draft aims to assist sponsors in submitting HIV clinical virology data to support clinical trials of treatment products. *Comments due April 29.*

Publications About "Unapproved New Uses"—In the March 3 *Federal Register*, FDA issued draft guidance entitled "Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices." The draft guidance provides FDA's recommended practices for drug and medical device manufacturers to follow when distributing scientific or medical articles or clinical guidelines that discuss unapproved new uses for approved drugs or devices marketed in the United States. *Comments due May 2.*

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis—In the March 11 *Federal Register*, FDA issued draft guidance entitled "Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: Developing Drug Products for Treatment." The purpose of this draft guidance is to assist sponsors in the development of drug products for the treatment of chronic fatigue syndrome/myalgic encephalomyelitis. *Comments due May 12.*

Methods Validation for Drugs and Biologics—In the February 19 *Federal Register*, FDA announced revisions to its draft guidance on "Analytical Procedures and Methods Validation for Drugs and Biologics." These revisions supersede the 2000 draft guidance and the 1987 guidance for industry on "Submitting Samples and Analytical Data for Methods Validation." *Comments due May 20.*

Reclassification of Shortwave Diathermy ("SWD") Device—In the February 21 *Federal Register*, FDA issued a proposed order to reclassify the SWD for all other uses, a preamendments class III device, into class II (special controls), and to rename the device "nonthermal shortwave therapy (SWT)." FDA withdrew a prior proposal that would have required the filing of a premarket approval application or a notice of completion of a product development protocol for the device. *Comments due May 21.*

Injectable Drug and Biological Products—In the March 14 *Federal Register*, FDA issued draft guidance entitled "Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products." This guidance clarifies FDA requirements and regulations pertaining to allowable excess volume in injectable vials and reinforces the importance of appropriate packaging sizes for injectable drug and biological products. *Comments due June 12.*

FDA published the following *Federal Register* Notices Regarding Agency Information Collection Activities:

Approval for collection of information on Over-the-Counter Human Drugs; Labeling Requirements.

Approval for collection of information on Medical Devices; Third Party Review Under the Food and Drug Administration Modernization Act (FDAMA).

Approval for collection of information on Human Tissue Intended for Transplantation.

Opportunity for comment on proposed collection of information on paperwork burden of recordkeeping by institutional review boards reviewing clinical research studies *(comments due April 3).*

Opportunity for comment on proposed collection of information on paperwork burden of donor screening recommendations for serological test systems for the detection of antibodies to Trypanosoma cruzi *(comments due April 4).*

Opportunity for comment on proposed collection of information on guidance regarding citizen petitions and petitions for stay of agency action *(comments due April 10).*

Opportunity for comment on proposed collection of information on paperwork burden of importer's entry notices for FDA-regulated products *(comments due April 14).*

Opportunity for comment on proposed collection of information on required disclosures for direct-to-consumer prescription drug TV advertisements *(comments due April 21).*

Opportunity for comment on proposed collection of information on paperwork burden of animal drug sponsors filling out the Animal Generic Drug User Fee Act (AGDUFA) cover sheet *(comments due April 21).*

Opportunity for comment on proposed collection of information on reporting requirements for prescription drug advertisements *(comments due April 28).*

Opportunity for comment on proposed collection of information on User Fee Waivers, Reductions, and Refunds for Drug and Biological Products *(comments due May 5).*

Upcoming Meetings, Workshops, and Conferences

Medical Devices

Training program on Regulatory Science and Sustainable Implementation of National and International Medical Device Registries in collaboration with the Medical Device Epidemiology Network, March 24 in San Francisco, CA.

Regulatory capacity-building training program on Medical Devices Regulatory Capacity Building Training Program for AHWP, ASEAN, Latin American and Other Medical Devices Regulators in collaboration with the World Health Organization, March 27–28 in San Francisco, CA.

Public FDA/AAO Workshop on Developing Novel Endpoints for Premium Intraocular Lenses, March 28 in Silver Spring, MD.

Public Workshop on Advancing Regulatory Science for High Throughput Sequencing Devices for Microbial Identification and Detection of Antimicrobial Resistance Markers, April 1 in Silver Spring, MD.

Public Workshop on Methods for Thrombogenicity Testing, April 14 in Silver Spring, MD.

Drugs & Biologics

Conference on Predicting Serious Drug-Induced Liver Injury (DILI) in Patients: Who Gets It? Who Doesn't? Why?, March 19–20 in Hyattsville, MD. Additional information and registration available here.

Conference on Leadership in a Global Supply Chain in collaboration with PharmaLink and Xavier University, March 19–20 in Cincinnati, OH.

Public Hearing on Over-the-Counter Drug Monograph System, March 25–26 in Silver Spring, MD.

Rescheduled Public Meeting on Fibromyalgia Patient-Focused Drug Development, March 26 in Silver Spring, MD.

Conference on Generic Drug User Fee Amendment (GDUFA) and You, March 27–28 in Lake Buena Vista, FL.

Public Workshop on Synergizing Efforts in Standards Development for Cellular Therapies and Regenerative Medicine Products, March 31 in Silver Spring, MD.

Public Hearing on Action Plan for the Collection, Analysis, and Availability of Demographic Subgroup Data in Applications for Approval of Food and Drug Administration-Regulated Medical Products, April 1 in Silver Spring, MD. *Comments are due May 16.*

Comments are due April 10 regarding the recent Public Workshop on Application of Physiologically Based Pharmacokinetic Modeling To Support Dose Selection.

Public Meeting on Pulmonary Arterial Hypertension Patient-Focused Drug Development, May 13 in Silver Spring, MD.

Public Meeting on Patient-Focused Drug Development for pulmonary arterial hypertension (part of PDUFA V's performance commitments), along with an opportunity for public comment. The meeting will be held May 13 in Silver Spring, MD. *Comments are due July 14.*

Public Meeting on Study Approaches and Methods To Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting, along with an opportunity for public comment. The meeting will be held May 28–29 in Silver Spring, MD. *Comments are due June 30.*

Advisory Committee Meetings

March 20: Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee Meeting Announcement

March 20: Vaccines and Related Biological Products Advisory Committee Announcement

March 26–27: Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee Meeting Announcement

March 31: Anti-Infective Drugs Advisory Committee Announcement

April 1: Endocrinologic and Metabolic Drugs Advisory Committee Meeting Announcement

May 5: Risk Communication Advisory Committee Meeting Announcement

May 6: Risk Communication Advisory Committee Meeting Announcement

Note for Advisory Committees: FDA Launches Membership Nomination Portal
Earlier this year, FDA launched an online, interactive system that allows interested individuals to submit nominations for membership to any of the agency's 33 advisory committees. The portal will also enable nominees to submit their application from FDA's website.

For more comprehensive listings of FDA meetings, please visit these FDA web pages:
Workshops & Conferences (Medical Devices)
Meetings, Conferences, & Workshops (Drugs)
Workshops, Meetings & Conferences (Biologics)
FDA Advisory Committee Calendar

Enforcement Updates

Recent Product Recalls

Recent drug recalls have included an antidepressant drug due to one bottle containing a foreign tablet, several injection and enzyme replacement therapy products due to particulate matter or potential for other contamination, and an eye drop product manufactured in Vietnam due to sterility issues at the production facility.

Recent medical device recalls have been for reasons of operational difficulties of device controls, incorrect statements in the instructions for use, and a physical defect leading the product not to function properly. No biologic products have been posted to FDA's website in the last 60 days.

Click here for a complete listing of FDA Recalls.

Recent Warning Letters

FDA has recently issued warning letters to pharmaceutical manufacturers for Current Good Manufacturing Practices violations. At least one letter was issued to a drug manufacturer in India and accompanied by an import ban on the company's drugs. FDA additionally issued warning letters to two compounding pharmacies for producing unapproved drugs, as well as significant violations related to the sterile manufacture of the drugs. FDA also cited the lack of valid individual prescriptions for each of the drugs produced, which is typical when FDA suspects that a compounding pharmacy is actually acting as a drug manufacturer and should therefore be subject to regulation as such. Lastly, we continue to see warning letters to medical device manufacturers for marketing a device without marketing clearance or approval.

Click here for FDA's Warning Letters Home page (scroll down for listing of recently posted Warning Letters).

The Office of Prescription Drug Promotion ("OPDP") issued a warning letter to a drug manufacturer, alleging that the company's Facebook page contained false and misleading representations about a drug's efficacy and for failing to communicate risk information.

Click here for a complete listing of 2014 OPDP Warning Letters.

Recent Drug and Device Approvals
FDA allows marketing of first medical device to prevent migraine headaches (March 11).
FDA approves Myalept to treat rare metabolic disease (February 25).
FDA approves Northera to treat neurogenic orthostatic hypotension (February 18).

For additional information on drug and device approvals and clearances, please visit FDA's web pages on Drug Approvals and Databases (includes biologics) and Device Approvals, Denials, and Clearances.

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