Jones Day | Pharmaceutical & Medical Device Regulatory Update Issue Number 13 | August 2014

Top Stories

DEA Finalizes Hydrocodone Regulations
Hydrocodone with acetaminophen has been the most widely prescribed drug since 2007, with more than 135 million prescriptions written in 2012. Due to its high potential for abuse, the drug has received much attention in the last several years and has been the subject of federal and state efforts to curb opioid abuse (read Jones Day's previous coverage here). The U.S. Drug Enforcement Agency ("DEA") recently published its final rule moving hydrocodone products from Schedule III to Schedule II, a more restrictive classification reflecting FDA's 2013 recommendation to DEA. Effective October 6, 2014, the rule's intent is to help achieve a better balance between minimizing the recreational use of these drugs and maintaining access for patients with a real need for the drug.

FDA Announces Final Guidance on Evaluation of Sex-Specific Data in Medical Device Clinical Studies
Following significant pressure to promote sex-specific clinical research and product labeling, most recently from Congress and interest groups, FDA recently issued a final guidance on *Evaluation of Sex-Specific Data in Medical Device Clinical Studies* in combination with its FDASIA Section 907 Action Plan. Responding to decades of concern about the disparities in clinical data, the final guidance outlines specific recommendations for considering sex and other variables during the study design stage, to improve consistency of analysis and reporting of information on demographics in labeling and other public documents. The action plan delineates 27 action items across three overarching priorities: data quality, subgroup participation, and data transparency. Certain medical products may elicit different responses in women than men, and these variables may affect the safe and effective use of medical devices. The final guidance outlines specific recommendations for considering sex and other variables during the study design stage, improving consistency of analysis, and reporting information on demographics in labeling and other public documents. According to an announcement made by Commissioner Hamburg on the same day, some action items are likely to be achieved within a year, while others may take as long as three to five years to complete. Critics say FDA's plans for greater inclusion in clinical trials are still

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lacking because they do not include pregnant women and children.

ACA Medical Device Excise Tax is Undercollected
The Treasury Inspector General for Tax Administration said the Internal Revenue Service ("IRS") should improve its compliance rules for the ACA medical device excise tax, identifying several mistakes when it came to collecting money owed to the government. According to the report, the IRS expected to receive between 9,000 and 15,600 forms to pay the tax, raising $1.2 billion in the second and third quarters of 2013. But the previous year's numbers were even lower: 5,100 forms, garnering just $913.4 million. One lawmaker has pointed to the report as more evidence that the tax should be repealed.

Resources

- *Pharmaceutical & Medical Device Regulatory Update* Issue 13 Printable Version
- Jones Day's FDA Regulatory & Compliance Practice
- Jones Day's Health Care Practice
- Jones Day's Life Sciences Practice

FDA Issues Guidance for Unique Device Identification System
In a follow-up to a final rule issued in September 2013, requiring that most medical devices distributed in the United States carry a unique device identifier ("UDI"), FDA has issued a small entity compliance guidance on the Unique Device Identification System. The guidance instructs small businesses on how to label their devices in order to comply with the rule. Under the rule, every UDI must be presented in two forms: plain text and using special data capture technology. Class I devices, according to the guidance, will be permitted to use a universal product code as the UDI on the device label and package. The guidance features key definitions, compliance dates, and formatting requirements related to the UDI system. FDA concurrently issued *Unique Device Identification System: Frequently Asked Questions, Vol. 1 Guidance for Industry and Food and Drug Administration Staff*, which summarizes key aspects of the UDI final rule and addresses UDI basics, UDI placement, the Global Unique Device Identifier Database, and direct marking, as well as exceptions, alternatives, and exemptions.

Other News
FDA Launches, Seeks Participants for Medical Device Development Tools Pilot Program

Doctors Urge FDA to Adopt Distinct Names for Biosimilars

FDA Issues 510(k) Program Guidance for Evaluating Substantial Equivalence

Inks Used in Certain Tattoo Kits Cause Infections

Turkish Man Pleads Guilty to Importing Illegal Cancer Drugs

CDER Official Discusses GDUFA Regulatory Science Program

Whole Foods Hit with Homeopathy Class Action Suit

Court Upholds Ruling that Brand Name Drug Maker Liable for Harm Caused by Generic Rival

India Outlines Plan to Boost Inspections of Drug Facilities

FDA's "TurboTax" Pilot Program for Medical Devices Expanding

Blood Industry Shrinks as Transfusions Decline

Regulatory Updates

FDA Reopens Comment Period for Proprietary Names Draft Guidance
In the August 14, 2014, *Federal Register*, FDA reopened the comment period for the draft guidance *Best Practices in Developing Proprietary Names for Drugs*. The draft guidance was initially published in the May 29, 2014, *Federal Register*. FDA reopened the comment period in response to requests stating

the original 60-day comment period, which closed on July 28, 2014, did not allow sufficient time to develop a meaningful or thoughtful response. ***Comments due September 15, 2014***.

FDA Releases FDASIA Section 907 Action Plan; Reopens Public Docket
In the August 22, 2014, *Federal Register*, FDA announced the availability of the action plan required by Section 907 of the Food and Drug Safety and Innovation Act ("FDASIA") and the reopening of a public docket for comments on the action plan. Section 907 requires FDA to report on and address certain information regarding clinical trial participation by demographic subgroups and subset analysis of the resulting data. The required report was posted on FDA's website in August 2013. Section 907 also requires
FDA to publish an action plan containing recommendations to improve the completeness and quality of analyses of data on demographic subgroups. FDA is reopening the docket for 60 days to provide an opportunity for the public to submit comments on the action plan. ***Comments due October 21, 2014***.

FDA Proposes Removal of Duplicative Biologics Requirements in Regulations
In the August 22, 2014, *Federal Register*, FDA proposed an amendment to the biologics regulations that would remove the general safety test ("GST") requirements for biological products. The proposed changes respond to a January 18, 2011, Executive Order mandating a retrospective review of agency regulations and guidance documents to improve regulation and remove unnecessary obstacles to innovation. According to FDA, existing, codified GST regulations are duplicative of requirements also specified for biologics licenses, or are no longer needed to help ensure the safety, purity, and potency of licensed biologics. Specifically, the proposed change would remove the requirements contained in 21 C.F.R. §§ 610.11, 610.11a, and 680.3(b) from the regulations. ***Comments due November 20, 2014***.

FDA Solicits Nominations for MDDT Pilot Program
In the August 15, 2014, *Federal Register*, FDA requested nominations for interested tool developers to participate in its Medical Device Development Tools ("MDDT") Pilot Program. In November 2013, FDA issued a draft guidance, *Medical Device Development Tools*, outlining the proposed voluntary process for qualification of MDDT for use in device development and evaluation programs. An MDDT is a scientifically validated tool (e.g., clinical outcome assessment, biomarker test, or nonclinical assessment model or method) that aids device development and regulatory approval. The MDDT Pilot Program will allow FDA to work with qualifying tool developers to determine whether such tools may be developed and qualified in order to facilitate more predictable, efficient, and transparent regulatory evaluation when MDDTs are used to generate valid scientific evidence for medical device premarket applications. MDDT qualified by FDA can be relied upon by the medical device industry in support of their device submissions to the Agency, potentially reducing time and other resources needed to develop new products. The Notice provides information on the guiding principles of the MDDT Pilot Program, appropriate candidates, and procedures for assessing candidates. There are no fees associated with submitting a tool for qualification. The MDDT Pilot Program is limited to approximately 15 candidates. FDA intends to accept requests for participation in the MDDT Pilot Program until such time that the MDDT draft guidance is finalized. For information about how to submit an MDDT qualification package, visit the MDDT webpage. ***Nominations accepted starting September 15, 2014.***

FDA Seeks Comments, Will Hold Public Hearing on GDUFA Policy
In the August 19, 2014, *Federal Register*, FDA requested comments and announced a public hearing to solicit public comment on certain topics relating to implementation of the Generic Drug User Fee Amendments of 2012 ("GDUFA") and the GDUFA Commitment Letter that accompanies the legislation. FDA is seeking participation at the public hearing and written comments from all interested parties. The hearing will be held on September 17, 2014, in Hyattsville, MD. ***Comments will be accepted after the hearing until October 13, 2014.***

FDA Amends Medical Device Regulations to Correct Minor Errors
In the August 25, 2014, *Federal Register*, FDA announced the amendment of certain medical device regulations to correct minor errors in the regulations. FDA said the changes were "editorial in nature" and intended to correct outdated website addresses. ***Effective August 25, 2014.***

FDA Announces Availability of Grant Funds for Orphan Drugs Product Development Program
In the August 19, 2014, *Federal Register*, FDA announced the availability of grant funds for supporting FDA's Office of Orphan Drugs Development grant program. The goal of the program is to support the

clinical development of products for use in rare diseases or conditions where no therapy currently exists or where the proposed product will be superior to the existing therapy. FDA provides grants for clinical studies on safety and/or effectiveness that will either result in, or substantially contribute to, market approval of these products. ***Applications due February 4, 2015.***

FDA Requests Nominations to Serve on Public Advisory Committees or Panels
In the August 20, 2014, *Federal Register*, FDA called for consumer organizations interested in participating in the selection of consumer representatives to serve on its advisory committees or panels to notify ***FDA in writing by September 19, 2014***. FDA also called for nominations for consumer representatives to serve on advisory committees or panels that have vacancies. ***Nominations due September 19, 2014***.

FDA Announces Advisory Committee Renewals
In the August 25, 2014, *Federal Register*, FDA announced the renewal of certain FDA advisory committees for an additional two years beyond the charter expiration date, based on the Commissioner's determination that doing so is in the public interest. The affected committees and new charter expiration dates are listed in the notice.

FDA Corrects Errors in Final Rule on Postmarketing Safety Reports for Drugs and Biologics
In the August 14, 2014, *Federal Register*, FDA corrected a final rule entitled "Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements" that appeared in the June 10, 2014, *Federal Register*. The notice corrects two errors: incorrect information regarding the availability of the International Conference on Harmonization's data elements for postmarketing safety reports and an incorrect statement regarding the impact of the final rule on small entities.

FDA Classifies Hemoglobin A1c Test System into Class II
In the August 25, 2014, *Federal Register*, FDA classified the hemoglobin A1c test system into class II (special controls). The device is used to measure the percentage concentration of hemoglobin A1c in blood and aids in the diagnosis and identification of patients at risk for diabetes mellitus. The Agency is classifying the device into class II (special controls) in order to provide a reasonable assurance of safety and effectiveness of the device. Effective September 24, 2014.

FDA Determines Certain Drugs Not Withdrawn for Reasons of Safety or Effectiveness
Since the last Jones Day *Update*, FDA determined several drugs were not withdrawn for reasons of safety or effectiveness:

- DRIXORAL and other drug products. August 14, 2014, *Federal Register*.
- LUPRON DEPOT-PED (leuprolide acetate for depot suspension), Injectable 3.75 milligrams (mg)/vial and 7.5 mg/vial; and LUPRON DEPOT-PED (leuprolide acetate for depot suspension), Injectable 7.5 mg/vial and 7.5 mg/vial. August 20, 2014, *Federal Register*.
- FUSILEV (levoleucovorin calcium), Injection, 175 mg/17.5 milliliters (mL) and 250 mg/25 mL. August 22, 2014, *Federal Register*.
- SULAR (nisoldipine) extended-release tablets, 10 mg, 20 mg, 25.5 mg, 30 mg, and 40 mg. August 25, 2014, *Federal Register*.

FDA Issues the Following Guidance Documents
Guidance for Industry on Evaluation of Sex-Specific Data in Medical Device Clinical Studies. August 22, 2014, *Federal Register*.

Revised Draft Guidance for Industry: Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content, and Format. August 14, 2014, *Federal Register. Comments due October 14, 2014.*

Guidance for Industry on Immunogenicity Assessment for Therapeutic Protein Products. August 14, 2014, *Federal Register*.

Draft Guidance for Industry on De Novo Classification Process (Evaluation of Automatic Class III Designation). August 14, 2014, *Federal Register. Comments due October 14, 2014.*

Guidance for Industry: FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations. August 19, 2014, *Federal Register*.

Guidance for Industry: Unique Device Identification System: Frequently Asked Questions, Vol. 1. Released August 20, 2014.

Information Collection Activities

FDA Announces the Opportunity to Comment on the Following Proposed Information Collections
Temporary Marketing Permit Applications (*comments due September 19, 2014*).

FDA Announces that the Following Collections Have Been Submitted to OMB for Approval
Channels of Trade Policy for Commodities with Residues of Pesticide Chemicals, for Which Tolerances Have Been Revoked, Suspended, or Modified by the Environmental Protection Agency Pursuant to Dietary Risk Considerations (*comments due to OMB by September 22, 2014*).

Upcoming Meetings, Workshops, and Conferences

Drugs and Biologics
Public Meeting on Advancing the Use of Biomarkers and Pharmacogenomics will be held on **September 5, 2014**, in Washington, D.C.

Public Workshop on Clinical Development of Drugs for the Prevention of Serious Infections Caused by *Staphylococcus Aureus* in the Health Care Setting will be held on **September 5, 2014**, in Silver Spring, MD.

Third Annual Patient Network Meeting, Under the Microscope: Pediatric Drug Development, will held **September 10, 2014**, in Washington, D.C.

Public Meeting on Methodological Considerations in Evaluation of Cancer as an Adverse Outcome Associated with Use of Non-Oncological Drugs and Biological Products in the Postapproval Setting will be held **September 10–11, 2014**, in Silver Spring, MD.

Public Workshop on Revamping Microbiological Test Methods for Contact Lenses, Products, and Accessories will be held **September 12, 2014**, in Silver Spring, MD.

FDA/PQRI Conference on Evolving Product Quality will be held **September 16–17, 2014**, in Bethesda, MD.

Public Meeting on GDUFA Policy Development will be held **September 17, 2014**, in Hyattsville, MD.

FDA Small Business and Industry Assistance Regulatory Education for Industry Conference will be held on **September 18–19, 2014**, in Bethesda, MD.

Public Meeting on Patient-Focused Drug Development for Hemophilia A, Hemophilia B, von Willebrand Disease, and other heritable bleeding disorders will be held on **September 22, 2014**, in Silver Spring, MD.

Public Meeting on Patient-Focused Drug Development for idiopathic pulmonary fibrosis will be held on **September 26, 2014**, in Silver Spring, MD.

Public Workshop on Innovations in Breast Cancer Drug Development—Next Generation Oncology Trials, Breast Cancer Workshop will be held on **October 21, 2014**, in Bethesda, MD.

Training Course for Clinical Investigators on Scientific, Ethical, and Regulatory Aspects of Clinical Trials will be held **November 4–6, 2014**, in College Park, MD.

Medical Devices
Public Workshop on Hemostatic Medical Devices for Trauma Use will be held **September 3–4, 2014**, in Silver Spring, MD.

International Medical Device Regulators Forum will be held **September 15–19, 2014**, in Washington, D.C.

Public Workshop on Additive Manufacturing of Medical Devices: An Interactive Discussion on the Technical Considerations of 3D Printing will be held **October 8–9, 2014**, in Silver Spring, MD.

Training Course for Clinical Investigators on Scientific, Ethical, and Regulatory Aspects of Clinical Trials will be held **November 4–6, 2014**, in College Park, MD.

Public Workshop on Brain-Computer Interface Devices for Patients with Paralysis and Amputation will be held **November 21, 2014**, in Silver Spring, MD.

Advisory Committees
September 3, 2014: Nonprescription Drugs Advisory Committee Meeting

September 4–5, 2014: Nonprescription Drugs Advisory Committee Meeting

September 10, 2014: Cardiovascular and Renal Drugs Advisory Committee Meeting

September 11, 2014: Endocrinologic and Metabolic Drugs Advisory Committee Meeting

September 12, 2014: Endocrinologic and Metabolic Drug Products Advisory Committee Meeting

September 17, 2014: Joint Meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

September 18, 2014: Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

September 18, 2014: Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

September 23, 2014: Pediatric Advisory Committee Meeting

October 1, 2014: Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee

October 16, 2014: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting

October 20, 2014: Dermatologic and Ophthalmic Drugs Advisory Committee

November 6, 2014: Cellular, Tissue, and Gene Therapies Advisory Committee

For more comprehensive listings of FDA meetings, please visit these FDA webpages:
Meetings, Conferences, and Workshops (Drugs)

Workshops, Meetings, and Conferences (Biologics)

Workshops and Conferences (Medical Devices)

FDA Advisory Committee Calendar

Enforcement Updates

Recent Product Recalls
Recent recalls included certain lots of two injectible drug products due to the presence of foreign particulate matter. Another drugmaker recalled two lots of a dialysis solution due to the presence of oxidized stainless steel, garment fiber, and PVC particulate matter identified during the manufacturing process.

Additionally, a medical device manufacturer recalled a vascular retrieval snare device due to the potential for the loop of the device to separate from the shaft, resulting in loss of device function and other possible problems.

Click here for a complete listing of FDA Recalls.

Recent Warning Letters
Since the last *Update*, FDA cited two medical device manufacturers for violating Quality System Regulation requirements. The first manufacturer was also warned for violating Medical Device Reporting regulations. The warning letter to the second manufacturer additionally cited failures to carry out appropriate procedures for product corrections and removals (recalls), which require notifying FDA of such actions.

FDA warned a pharmaceutical manufacturer in India for violations of the current good manufacturing practice regulations for finished pharmaceuticals, including numerous recordkeeping violations and a failure to ensure that staff had the necessary education, training, and experience.

FDA also warned a mammography facility of several violations of the Mammography Quality Standards Act and a clinical investigator for several violations related to the conduct of a clinical investigation.

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") did not issue any warning letters since the last *Update*.

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

Recent Drug and Device Approvals
FDA approves new drug to treat a form of Gaucher disease (August 19, 2014)

FDA approves Avastin to treat patients with aggressive and late-stage cervical cancer (August 14, 2014)

FDA approves new type of sleep drug, Belsomra (August 13, 2014)

FDA approves donor lung preservation device that may result in more lung transplants (August 12, 2014)

FDA approves first noninvasive DNA screening test for colorectal cancer (August 11, 2014)

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

Jones Day | Pharmaceutical & Medical Device Regulatory Update Issue Number 13 | August 2014

Top Stories

FDA Publicly Responds to Opioid Drug Controversy (*May 2014*)
Federal policymakers appear to be responding to growing national concerns about opioid abuse and increased state efforts to block or limit the use of FDA-approved opioids. In a recent blog post, FDA Commissioner Margaret Hamburg commended the widespread focus by state officials to address the public health issue, while cautioning that policies on opioid use should be science-based and comprehensive. She noted that regulators should not focus on one particular drug, such as Zohydro, but instead should pursue policies targeting abuse triggers in general while respecting proven pain management therapies. Dr. Hamburg's public overture comes on the heels of FDA approving labeling changes requiring opioid drugs to be labeled for severe pain only.

States Continue Protest Zohydro Approval; Massachusetts Bans Sales (*April 2014*)
Several states have protested FDA's approval of hydrocodone drug Zohydro ER based on concerns that a lack of abuse-deterrent features creates a higher-than-acceptable risk of abuse. In March, attorneys general from six states sent a letter to Health and Human Services Secretary Kathleen Sebelius asking her to overturn FDA's approval of Zohydro ER. Last week, Massachusetts Gov. Deval Patrick announced that Zohydro ER may not be sold in the state because its current form does not guard against potential conversion to rapid release. According to Reuters, the manufacturer of Zohydro called the state's ban misguided and noted that other painkillers without abuse-resistant technologies are already on the market. This letter follows similar requests by other state attorneys general and proposals by federal legislators to reverse the drug's regulatory approval.

DEA Acts on FDA Proposed Rescheduling of Hydrocodone Combination Products (*April 2014*)
In late February, the U.S. Drug Enforcement Agency issued a notice of proposed rulemaking to reschedule hydrocodone combination products from schedule III to schedule II of the Controlled Substances Act ("CSA"). The proposed rule was in response to a recommendation issued by FDA last year around the same time that the agency approved Zohydro (see story above), a single-entity hydrocodone product.

Single-entity products are already listed in schedule II of the CSA; however, Zohydro is the first single-entity hydrocodone product to enter the marketplace. Comments ***on the proposed rule are due April 28***.

Senator Proposes Bill to Reverse Approval of Hydrocodone Drug (*March 2014*)
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.

Jones Day | Pharmaceutical & Medical Device Regulatory Update Issue Number 13 | August 2014

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Legislators and Groups Urge FDA to Require Sex-Specific Data, Labeling in New Action Plan (*July 2014*)
Members of Congress and interest groups are pressuring FDA to promote sex-specific clinical research and product labeling, as the Agency develops an action plan to address deficiencies in the way industry collects, analyzes, and communicates demographic data.

Fulfilling a requirement of the Food and Drug Administration Safety and Innovation Act of 2012 ("FDASIA"), FDA studied the extent to which demographic subgroups (sex, race, and ethnicity) participate in clinical trials and how this information is used and disclosed. The Agency delivered a summary report to Congress in August 2013. Testifying before the House Energy and Commerce Committee earlier this month, Center for Drug Evaluation and Research ("CDER") Director Janet Woodcock said FDA will soon issue an action plan based on those findings. In response to questions about the "sex gap" in drug and device research, Woodcock indicated the Agency is making efforts to ensure females are equally represented in clinical trials. Interest groups, such as the National Women's Health Network, have been pressuring the Agency to set standards to ensure adequate clinical participation so that safety and effectiveness data can be analyzed based on sex, race, and ethnicity. The American Medical Association also has encouraged sex-specific disclosures (such as modified dosage recommendations) in product advertisements to physicians.

Meanwhile, the National Institutes of Health is developing its own rules for preclinical research grant proposals, which would mandate the inclusion of both male and female animals or tissues.

NIH Addresses Sex Differences in Preclinical Research (*May 2014*)
Earlier this month, the National Institutes of Health ("NIH") unveiled a plan to begin requiring preclinical research proposals to include both male and female animals or tissues in their studies. Announcing the plan in a Nature magazine column, NIH Director Francis Collins and Janine Clayton, associate director of Research on Women's Health, said sex differences should be taken into account because

they affect various health conditions, including multiple sclerosis and substance abuse.

The proposal comes in response to public pressure by organizations and members of Congress to eliminate gender bias in research. As reported in *The New York Times*, a heavy focus on one gender can conceal certain side effects of new treatments such as sleeping medication, which is metabolized more slowly in women. Today, more than half of NIH clinical-study participants are women, and the new requirement aims for similar gender parity at the preclinical stage. Researchers sometimes rely on male mice in their studies due to concerns about the compounding effects of female hormonal cycles, but Collins and Clayton said analyses confirmed that female mice display no more variability than males. NIH is expected to release formal changes to its preclinical research programs in October, including policies to encourage medical journals to disclose data about the sex of lab animals.

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