Jones Day | Pharmaceutical & Medical Device Regulatory Update Issue Number 6 | May 2014

Top Stories

FDA's Fifth Draft Guidance on Biosimilars Sheds New Light on Approval Pathway
On May 13, the U.S. Food & Drug Administration ("FDA") issued a draft guidance intended to assist sponsors of biological products with the design and use of clinical pharmacology studies to support a showing that a proposed therapeutic biological product is "biosimilar" to its reference product under the Biologics Price Competition and Innovation Act of 2009 ("BPCI Act"). The guidance specifically relates to therapeutic biologic products for which pharmacokinetic (PK) and pharmacodynamic (PD) data are required as part of a "stepwise" approach to developing the data and information needed to demonstrate biosimilarity. As the most detailed guidance yet on evidence needed to establish biosimilarity, the guidance adds further clarity to the cost of bringing a biosimilar to market. Notably, the guidance introduces the Agency's expectations for bridging data from products marketed outside of the U.S. and lays out key topics about which sponsors should meet with FDA early on in the biosimilar development process. The guidance also introduces four categories of similarity—not similar, similar, highly similar, and highly similar with fingerprint-like similarity—that will affect the extent to which further study is needed to establish requisite biosimilarity for approval.

CDER, CDRH Discuss Efforts to Promote Medical Innovation at House Roundtable
During a May 6 roundtable discussion hosted by the House Energy and Commerce Committee, FDA program directors urged legislators to advance policies that will ease market entry for innovative pharmaceuticals and medical devices. The roundtable was the first of several hearings scheduled for the House Committee's 21st Century Cures Initiative, aimed at promoting an ongoing dialogue among legislators, regulators, researchers, and industry leaders to collaborate in accelerating the pace of medical breakthroughs.
- read more below

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Resources

- *Pharmaceutical & Medical Device Regulatory Update* Issue 6 Printable Version
- Jones Day's Health Care Practice
- Jones Day's Life Sciences Practice

FDA Partners with Foreign Regulators on Global Drug Quality Initiative
Recently, FDA unveiled a new global pharmaceutical quality initiative, strengthening programs with the European Medicines Agency to allow for the inspection of overseas facilities and promote collaborative learning among two agencies' experts. This latest initiative continues FDA's efforts to gain access to inspection information and non-public data of its foreign counterparts. Already, the Agency has

executed 60 information-sharing agreements with regulators around the world, partly enabled by new authority under the Food and Drug Administration Safety and Innovation Act ("FDASIA"). According to FDA, these partnerships are crucial to ensuring the safety of the global drug supply, which accounts for 40 percent of the U.S. market for finished drugs.

ATA Venture Summit Pairs Digital Health Companies with Investor Mentors
Twenty-five emerging digital health companies participated in the second-annual Telemedicine Venture Summit on May 18, where they networked with interested investors and industry consultants and discussed potential strategic partnerships. Cosponsored by the American Telemedicine Association ("ATA") and Jones Day, the event included one-on-one sessions in which investor mentors were able to provide individual feedback on business plans. Participants included medical device manufacturers, technology companies, and health care providers, and for many, this is their first time seeking venture financing. The summit was part of the ATA's three-day annual conference in Baltimore, Maryland, which featured keynote remarks by UnitedHealth Group CEO Stephen Hemsley, educational programs by industry leaders, and exhibits showcasing the latest technologies and business models in digital health.

New 510(k) eSubmissions Pilot Aims to Streamline Process, Ensure Compliance
A new pilot program by CDRH will allow participating medical device sponsors to electronically submit 510(k) notification materials through an electronic portal similar to the approach used for online tax filings. The purpose of the eSubmissions Pilot is to make the 510(k) process more user-friendly and eliminate the need for hard copies, while increasing the level of regulatory compliance. Data will be submitted through a "guided interface" that closely tracks FDA regulations, helping ensure every relevant requirement is met. For now, participation in the CDRH pilot is limited to unbundled, traditional 510(k) submissions for classified devices that will be reviewed by the Cardiac Diagnostic Devices Branch or Peripheral Interventional Devices Branch. FDA has provided a helpful user guide detailing the eight-step eSubmission process. Sponsors interested in participating must submit a letter of interest to CDRH by September 30.

FCC Considering "Reverse Auction" of Spectrum Currently Used for Medical Telemetry
Upcoming actions by the Federal Communications Commission ("FCC") may affect certain wireless medical device operations. FCC plans a "reverse auction" to transfer spectrum from television broadcasters to wireless carriers seeking to improve their wireless data service. For years, wireless medical devices have operated in several spectrum bands, including in the frequency range of broadcast television Channel 37, which is not used by full-power television stations and is largely reserved for wireless medical telemetry service ("WMTS") and other low-power services. The plan to reorganize the use of the broadcaster's spectrum stops short of opening Channel 37 to use by wireless carriers but will make it available for increased use by unlicensed wireless devices such as wi-fi, raising the potential for increased interference with WMTS. An FCC summary of the unreleased rules notes that any expansion of unlicensed operation into Channel 37 will be subject to the development of "appropriate technical parameters" to protect WMTS operations. The exact contours of such protections will not be known until the final rules are released and may still be under development.

FDA Releases Data Trends on Medical Device Submissions and Inspections
FDA recently released several reports assessing trends in the Agency's regulatory programs for medical devices, which indicate a growing focus on postmarket compliance efforts. A series of reports analyzes the findings of quality system regulation ("QSR") inspections over the last three years. In 2012, for example, FDA increased its overall number of routine inspections by 37 percent, with foreign facilities seeing a 93-percent rise in site visits. The most frequent observations from these inspections involved corrective and preventive action procedures, complaint reporting, and internal quality audits. Meanwhile, another report, summarizing the Agency's first quarter meeting on Medical Device User Fee Amendments (MDUFA III), shows that the percentage of 510(k) submissions leading to first additional requests has declined about seven points over the last three years, reversing an almost decade-long rise in the rate. Partly as a result of this trend, CDRH states it is able to review and make decisions on 510(k) submissions in less time than in years past.

NIH Addresses Sex Differences in Preclinical Research
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.
- read more below

Other News
Hospital Association Responds to FDA Draft Guidance on Blood-Glucose Monitors

FDA Proposes Increased Authority to Destroy Small Drug Shipments

CDRH Unveils Online Platform for Submitting UDI Exception Requests

Patient Complaints Spur FDA to Test Side Effects of Blood-Pressure Drugs

Forbes Op-Ed: FDA Draft Guidance Takes the "Social" Out of Social Media

Compounding Pharmacy Cited for 11 Rule Violations

Development of MERS Vaccine Faces High Hurdles in Costs, Regulations

Stanford, UCSF Team Up with FDA on New Center to Develop Innovative Drugs

FDA Commissioner: Drug Approvals by FDA Faster Than European, Japanese Agencies

Most Requests for Compassionate Access to Drugs Get Approved, FDA Says

Colorado Becomes First State to Pass "Right To Try" Law, Allowing Patients to Access Investigational Drugs.

Regulatory Updates

FDA Proposes Rule Regarding the Administrative Destruction of Detained Drug Imports
In the May 6 *Federal Register*, FDA proposed a regulation to implement its authority to destroy a drug valued at $2,500 or less that has been refused admission into the United States, by providing to the owner or consignee notice and an opportunity to appear and introduce testimony to FDA prior to the destruction. The proposed rule is authorized by the FDASIA and represents FDA's latest efforts to help ensure the integrity of the international drug supply. Under the proposal, the $2,500 threshold may be adjusted from time to time to account for inflation, consistent with Department of Treasury regulations. ***Comments are due July 7.***

FDA Down-Classifies Intravascular Automated Air Removal System and Colon Capsule Imaging System as Class II Devices Subject to Special Controls
In the May 16 *Federal Register*, FDA down-classified two devices that were formerly Class III. The intravascular administration set automated air removal systems and colon capsule imaging system, both prescription devices, are now Class II and subject to premarket notification and special controls.

FDA to Release Updated List of Consensus Standards for Medical Devices
In the May 15 *Federal Register*, FDA published modifications to the list of recognized consensus standards the Agency recognizes for use in premarket reviews. FDA periodically revises the list and publishes the modifications to its website. Comments regarding modifications may be submitted at any time.

FDA Issues the Following Guidance Documents:
• *Final Guidance for Industry and FDA Staff on Statistical Evaluation of Stability Data for Veterinary International Cooperation on Harmonisation (VICH GL51)*. May 13 *Federal Register*.
• *Final Guidance for Industry on ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers*. May 15 *Federal Register*.
• *Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment*. May 7 *Federal Register*. ***Comments are due August 5.***
• *Draft Guidance for Industry and FDA Staff on Appropriate Use of Voluntary Consensus Standards in*

Premarket Submissions for Medical Devices. May 13 *Federal Register*. ***Comments are due August 11***.
• *Draft Guidance for Industry on Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*. May 14 *Federal Register*. ***Comments are due August 12***.

FDA Releases Supporting Document for SEND Validation Rules
In the May 20 *Federal Register*, FDA released Validation Rules for Standard for Exchange of Nonclinical Data ("SEND") Formatted Studies document. The document, available on the Center's Study Data Standards Resources webpage, is intended to improve the standardization and quality of nonclinical data that are submitted to CDER as well as to improve the predictability of data quality and usefulness.

CDER Revises Standards for Electronic Common Technical Document
In the May 15 *Federal Register*, FDA announced the revised final versions of four documents that support pharmaceutical manufacturers making regulatory submissions using the electronic Common Technical Document ("eCTD"). The revised documents will be available on FDA's Forms & Submission Requirements webpage for eCTD. FDA estimates it will be able to receive submissions using Module 1 Specifications 2.3 by the fourth quarter of calendar year 2014 and will give 30 days' advance notice to industry.

FDA Announces Opportunity to Comment on the Following Proposed Information Collections:
• Providing Waiver-Related Materials in Accordance With Draft Guidance for Industry on Providing Postmarket Periodic Safety Reports in the International Conference on Harmonisation E2C(R2) Format (***comments due June 9***).
• Custom Device Exemption (***comments due June 9***).
• Animal Drug User Fee Act Waivers and Reductions (***comments due June 16***).
• Food and Drug Administration Safety Communication Readership Survey (***comments due June 16***).
• Comparative Price Information in Direct-to-Consumer and Professional Prescription Drug Advertisements (***comments due July 7***).
• Prescription Drug Labeling Improvement and Enhancement Initiative (***comments due July 7***).

FDA Amends Animal Drug Regulations for Change of Sponsor
In the May 20 *Federal Register*, FDA announced amendments to its animal drug regulations to reflect approval actions of 172 new animal drug applications and 14 abbreviated new animal drug applications to reflect a change of sponsor from Pfizer Inc. to Zoetis Inc.

FDA Determines Regulatory Review Periods for Drug, Biological Patents
In recent issues of the *Federal Register*, FDA published determinations regarding the regulatory review periods for patent extensions of the following drugs: ELELYSO, KYPROLIS, IMPROVEST, INCIVEK, OMONTYS, PALLADIA, PICATO, SURFAXIN, TRADJENTA, and ZIOPTAN. There were also patent review periods announced for biological products: BENLYSTA and PERJETA.

Upcoming Meetings, Workshops, and Conferences

Drugs & Biologics
Public Workshop on Immune Responses to Enzymes Replacement Therapies: Role of Immune Tolerance Induction will be held **June 9** in Silver Spring, MD.

Public Conference on FDA Small Business Regulatory Education for Industry (REdI) will be held **June 16–17** in Burlingame, CA.

Medical Devices
Public Meeting on FzioMed, Inc.'s Petition for Review of FDA's Denial of Premarket Approval of Oxiplex/SP Gel will be held **June 10** in Gaithersburg, MD.

Public Workshop on Center for Devices and Radiological Health Guidance Development and Prioritization, with an opportunity for comment. The meeting will be held June 5 in Silver Spring, MD. ***Comments are due July 7.***

Public Workshop on Proteomics in the Clinic will be held **June 13** in Silver Spring, MD.

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

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

Advisory Committees

• October 16: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting
• June 25: Oncologic Drugs Advisory Committee Meeting
• June 17: Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee Meeting
• June 12: Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting
• June 11–12: Anesthetic and Analgesic Drug Products Advisory Committee Meeting
• June 10: Medical Devices Dispute Resolution Panel of the Medical Devices Advisory Committee Meeting
• June 6: Ophthalmic Devices Panel of the Medical Devices Advisory Committee Meeting
• June 4: FDA Science Board Meeting

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

Enforcement Updates

Product Seizure
On May 16, U.S. Marshalls seized more than $11 million worth of unapproved drugs from a pharmaceutical manufacturer and its distributor. FDA filed a complaint requesting the seizure after a November 2013 inspection revealing that the drugs were marketed without an approved drug application. Product seizures of this magnitude are somewhat rare; FDA has announced just three since the beginning of 2013.

Recent Product Recalls
Since the last Jones Day *Update*, there have been additional recalls of injectable drug products contaminated with glass and metal particulate matter.

FDA also posted three medical device recalls. Two of the devices exhibited mechanical failures. The third device, an anticoagulant monitoring test strip, was voluntarily recalled after nine serious adverse events were reported as being caused by the test strips, producing significantly different results from plasma laboratory tests.

There have been no new biologic recalls since the last Jones Day *Pharmaceutical & Medical Device Regulatory Update*.

Click here for a complete listing of FDA Recalls.

Recent Warning Letters
FDA recently warned three medical device manufacturers for failing to comply with the Quality Systems Regulation, including one facility overseas. The inspections observed inadequacies in the companies' corrective and preventive actions, design and process validations, and device history records. The Agency additionally warned two manufacturers for marketing devices before making premarket submissions.

The maker of a biological drug product was also cited for deviating from current good manufacturing practices. Its violations included not following the manufacturing process described in its biologic license application and failing to perform safety tests to detect toxin contaminants.

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

Based on its review of a promotional brochure, the Office of Prescription Drug Promotion ("OPDP") issued a warning letter to a pharmaceutical manufacturer for making efficacy representations without communicating any risk information and for omitting material facts.

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

Recent Drug and Device Approvals
FDA allows marketing of first prosthetic arm that translates signals from person's muscles to perform complex tasks (May 9).
FDA approves Zontivity to reduce the risk of heart attacks and stroke in high-risk patients (May 8).

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.

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At the hearing, Janet Woodcock, director of FDA's Center for Drug Evaluation and Research ("CDER"), discussed developing clinical trial networks to help coordinate the testing of multiple drugs that target a common health condition. She also encouraged legislators to invest in American drug manufacturing, which would help ensure adequate drug supply in the event of an overseas disruption.

Speaking for the Center for Devices and Radiological Health ("CDRH"), Director Jeffrey Shuren focused on the unique device identifier ("UDI") rule and FDA's desire to integrate data collected from UDIs with electronic health records used by providers. The UDI system gathers information on medical device adverse events, which then can be used to coordinate recalls of similar products and improve patient safety by highlighting known risks. Shuren also discussed the Agency's recent efforts to expedite premarket approval of critical, breakthrough devices—a new program we featured in the last issue of the Jones Day *Pharmaceutical & Medical Device Regulatory Update.*

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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.