Top Stories

FDA Accepts First Application for Biosimilar Product
In a significant step for generic biologic products, FDA accepted for review the first application for a biosimilar product. If approved, it could be the first biosimilar product to enter the U.S. market under the nearly five-year-old Biologics Price Competition and Innovation Act ("BPCIA"). Last week, Sandoz, a division of Novartis AG, announced that it had submitted, and FDA had accepted for review, an application for approval of a biosimilar version of Neupogen, a filgrastim product made by Amgen Inc. to reduce the risk of infection in cancer patients who experience a drop in infection-fighting white blood cells when undergoing certain treatments.

Before making a decision on the Sandoz application, FDA will likely establish a naming policy for biosimilar products and determine, specifically, whether a biosimilar must use the same International Nonproprietary Name ("INN") as its reference biological product. Sandoz's product is marketed in other countries and already has its own INN, but the naming debate has been ongoing for some time. The World Health Organization recently considered promoting the use of biological qualifiers for INNs, and earlier this month, a group of pharmacies, health insurers, and pension plans urged FDA not to give unique names to biosimilars, arguing that such a policy would undermine the potential cost savings generated by these generic products.

Enacted as part of the Affordable Care Act in 2010, the BPCIA created an abbreviated regulatory pathway for biosimilars consisting of a standard, 10-month review process. FDA officials expect to receive several more biosimilar applications this year, and the Agency has been preparing for a ramp-up in reviews. In May 2014, FDA issued its fifth draft guidance on biosimilars, which aims to assist product sponsors with the design and use of clinical pharmacology studies to support a showing of "biosimilarity," or that a proposed therapeutic biological product is similar to its reference product. The guidance is discussed in further detail in a *Jones Day Commentary*.

FDA Using Big Data Methods to Discover Drug Risks, Provide Access to Recall Information

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Resources

- *Pharmaceutical & Medical Device Regulatory Update* Issue 11 Printable Version

Through recently deployed initiatives, FDA is taking advantage of new data systems to gather and assess drug risk data and promote easier public access to adverse event and recall information. The two projects, Mini-Sentinel and openFDA, offer greater efficiencies than existing methods, such as the voluntary reporting process and Freedom of Information Act requests.

- Jones Day's FDA Regulatory & Compliance Practice
- Jones Day's Health Care Practice
- Jones Day's Life Sciences Practice

The openFDA initiative focuses on enhancing the Agency's public disclosure of information on adverse events, medication errors, and product recalls. In a recent blog post, FDA Chief Health Informatics Officer Taha Kass-Hout discusses the rollout of an application programming interface that provides software developers and researchers access to millions of drug and device recall reports. Several companies are already integrating this data into their products and services, and at least one new website allows users to query adverse event information. The *San Francisco Gate* outlines other potential benefits of the interface for startup companies, such as using its information to improve existing technologies and learning to avoid mistakes others have encountered during the FDA review process.

Mini-Sentinel, a $116 million pilot program partnering FDA with private companies, actively pursues adverse event data by mining medical record databases for signs that drugs may be linked to problems. Before this initiative, FDA had to rely on voluntary reports from manufacturers, health care providers, patients, and caregivers—a method that yields copious amounts of information but has limited value because of its random reporting. Mini-Sentinel's standardized approach for gathering data directly from the 18 health plans and insurance companies participating in the program enables FDA scientists to hone in on the root causes of an adverse symptom, and the Agency has already required new warning labels as a result of these analyses. Although the pilot contract ends in September 2014, FDA officials and many industry leaders would like to see some form of Mini-Sentinel adopted as a permanent program.

Legislators and Groups Urge FDA to Require Sex-Specific Data, Labeling in New Action Plan
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. For more information about that proposal, see our story in a prior issue of the Jones Day's *Pharmaceutical & Medical Device Regulatory Update*.

Generics Association Raises Concerns About Misuse of REMS Program
The Generic Pharmaceutical Association ("GPA") recently released a study indicating that U.S. annual spending on pharmaceuticals in the United States could be cut by $5.4 billion if generic versions of 40 drugs were available to consumers. According to the report, 40 generic products have been delayed by misuse of Risk Evaluation and Mitigation Strategies ("REMS") plans. FDA often requires manufacturers of approved drug products to implement REMS plans for purposes of monitoring distribution and educating physicians on safety issues. The study examines GPA members' claims that brand-name manufacturers have improperly relied on REMS plans as a basis to deny product samples to generic

companies, which are needed for product testing. In the past, the Federal Trade Commission has expressed similar concerns about the potentially anticompetitive misuse of REMS plans.

Other News
FDA Approves New Abuse-Deterrent Opioid Product

HHS Issues Interpretive Rule on 340B Policy for Orphan-Drug Discounts

Expansion of FDA's India Office Delayed by Staffing Issues

FDA Finalizes Guidance on Evaluating Substantial Equivalence in 510(k) Submissions

ONC Director Defends Health IT Safety Center, Says It Won't Be a Regulatory Body

FDA's Informed Consent Guidance Requires Disclosure of Clinical Trial Outcomes

Shipping Company Charged with Assisting Illegal Pharmacies

Group of Senators Urge OMB to Release FDA Guidance on Laboratory-Developed Tests

House Committee Advances Bipartisan Bill to Expedite FDA Review of Sunscreen Ingredients

Regulatory Updates

FDA Updates Guidance Documents for Product-Specific Bioequivalence Recommendations
In the July 23, 2014, *Federal Register*, FDA announced draft product-specific bioequivalence ("BE") recommendations, either new or revised, for about three dozen active ingredients. The recommendations for each product, developed using the process described in the 2010 Guidance for Industry: Bioequivalence Recommendations for Specific Products, provide guidance on BE study design to support ANDAs for the relevant active ingredient. A complete list of active ingredients and links to the recommendations for each can be found on FDA's website. ***Comments are due September 22, 2014***.

FDA Establishes Public Docket to Explore Possibility of Reserving Proprietary Names for Drugs
In the July 28, 2014, *Federal Register*, FDA announced the creation of a public docket to discuss issues related to reserving proprietary names for drug products. FDA agreed to several performance goals related to the review of proprietary names for drugs and biologics during the negotiations for the 2007 reauthorization of the Prescription Drug User Fee Amendments Act, or PDUFA IV. Among other goals, FDA and industry discussed the possibility of "reserving" proprietary names for drugs once the Agency tentatively accepts the names, with the goal of reducing medication error. This notice initiates a public process to discuss issues around reserving proprietary names. ***Comments are due October 27, 2014***.

FDA Announces Public Hearing on Confidentiality of Interim Results in Cardiovascular Outcome Safety Trials
In the July 15, 2014, *Federal Register*, FDA requested comments and announced a public hearing on the confidentiality of interim results for certain cardiovascular outcomes trials ("CVOTs") submitted to the Agency while the trials are still ongoing. The hearing is meant to initiate constructive discussion among regulators, researchers, health care providers, representatives from the pharmaceutical industry and health care organizations, and the general public, about appropriate handling of the results of these CVOTs. FDA is also opening a public docket to receive comments on the topic. ***Comments were due on July 28, 2014; the hearing will be held August 11, 2014***.

FDA Withdraws Approval of ANDAs for Certain Pain Medications Containing Acetaminophen
In the July 17, 2014, *Federal Register*, FDA withdrew approval of seven abbreviated new drug applications ("ANDAs") for prescription drug products containing more than 325 mg of acetaminophen. The withdrawal is consistent with FDA's 2011 announcement that it planned to reduce the maximum dosage unit strength of acetaminophen in drugs. FDA's decision is based on its reevaluation of the risks and benefits of prescription acetaminophen products and subsequent determination that fixed-combination prescription drugs containing more than 325 mg of acetaminophen per dosage unit do not

provide a sufficient margin of safety to protect the public against the serious risk acetaminophen-induced liver injury. Although FDA offered affected ANDA holders the opportunity for a hearing to demonstrate why approval of their ANDAs should not be withdrawn, none of the ANDA holders requested such a hearing.

FDA Issues Final Orders Classifying and Reclassifying Gastroenterology–Urology Devices Into Class II
In the July 25, 2014, *Federal Register*, FDA reclassified implanted blood access gastroenterology–urology devices from Class III into Class II (special controls). The decision is based on FDA's belief that the proposed special controls provide a reasonable assurance of safety and effectiveness. In the same *Federal Register*, FDA classified the implantable transprostatic tissue retractor system into class II (special controls). ***Effective July 25, 2014, and August 25, 2014, respectively***.

CDER and Duke University to Cosponsor Three-Day Training Course for Clinical Investigators
In the July 25, 2014, *Federal Register*, FDA's CDER announced it will cosponsor a three-day training course on scientific, ethical, and regulatory aspects of clinical trials with the Duke University Office of Continuing Medical Education on November 4-6, 2014. The course is intended to provide investigators with expertise in the design, conduct, and analysis of clinical trials, to improve the quality of clinical trials, and to enhance the safety of trial participants. ***Registration is due October 17, 2014***.

FDA Issues the Following Guidance Documents
Draft Guidance for Industry on Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics. July 15, 2014, *Federal Register*. ***Comments due November 18, 2014***.

Final Guidance for Industry: The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]. July 28, 2014, *Federal Register*.

Draft Informed Consent Information Sheet: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors. July 15, 2014, Federal Register. ***Comments due September 15, 2014***.

Draft Guidance for Industry: Providing Submissions in Electronic Format—Postmarketing Safety Reports for Vaccines. July 18, 2014, *Federal Register*. ***Comments due September 16, 2014***.

Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the Electronic Common Technical Document Specifications. July 25, 2014, *Federal Register*. ***Comments due September 23, 2014***.

INFORMATION COLLECTION ACTIVITIES

FDA Announces the Opportunity to Comment on the Following Proposed Information Collections
Regulations for *In Vivo* Radiopharmaceuticals Used for Diagnosis and Monitoring (***comments due September 19, 2014***)

513(g) Request for Information (***comments due September 22, 2014***)

FDA Announces that the Following Collections Have Been Submitted to OMB
Exception from General Requirements for Informed Consent (***comments due to OMB August 15, 2014***)

User Fee Waivers, Reductions, and Refunds for Drug and Biological Products (***comments due to OMB by August 15, 2014***)

Exception from General Requirements for Informed Consent (***comments due to OMB by August 15, 2014***)

Exceptions or Alternatives to Labeling Requirements for Products Held by the Strategic National Stockpile (***comments due to OMB by August 15, 2014***)

Experimental Study of Direct-to-Consumer Promotion Directed at Adolescents (***comments to OMB due August 20, 2014***)

Customer/Partner Service Surveys (***comments due to OMB by August 25, 2014***)

FDA Announces that the Following Collections Have Been Approved by OMB
Generic Food and Drug Administration Rapid Response Surveys

Annual Reporting for Custom Device Exemption

Guidance for Industry—Pharmacogenomic Data Submissions

Medical Devices; Reports of Corrections and Removals

Animal Generic Drug User Fee Cover Sheet

Upcoming Meetings, Workshops, and Conferences

Drugs and Biologics
Public Workshop on the Development of New Antibacterial Products: Charting a Course for the Future will be held **July 30, 2014**, in Bethesda, MD.

A Question and Answer Session on the Regulation of Nonprescription Drug Products will be held **August 4–5, 2014**, via Adobe Connect.

Public Hearing Before the Commissioner on Confidentiality of Interim Results in Cardiovascular Outcomes Safety Trials; Part 15 will be held **August 11, 2014**, in Silver Spring, MD.

Public Meeting on 2014 Scientific Meeting of the National Antimicrobial Resistance Monitoring System will be held **August 12–13, 2014**, in Silver Spring, MD.

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

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

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

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 (IMDRF) 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.

Advisory Committees
July 31, 2014: Blood Products Advisory Committee Meeting

August 1, 2014: General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting

August 14, 2014: Pulmonary-Allergy Drugs Advisory Committee Meeting

September 10, 2014: Cardiovascular and Renal 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 23, 2014: Pediatric Advisory Committee Meeting

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

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

Workshops, Meetings, and Conferences (Biologics)

Workshops & Conferences (Medical Devices)

FDA Advisory Committee Calendar

Enforcement Updates

Recent Product Recalls

FDA announced two voluntary, company-initiated recalls. The first recall was from a compounding pharmacy recalling all nonexpired sterile drug preparations due to FDA's concerns about the lack of sterility associated with the company's compounding processes. The second recall, initiated by a medical packaging company, involved a recall of certain hospital dose units of ibuprofen tablets due to the mislabeling of some blistered doses.

Click here for a complete listing of FDA Recalls.

Recent Warning Letters

Since the last *Update*, FDA cited only one medical device manufacturer for violating Quality System Regulation requirements. The infractions in the warning letter included other violations, such as failure to establish procedures for corrective and preventative action and medical device reporting requirements. The firm was also cited for not obtaining premarket approval, 510(k) clearance, or an investigational device exemption for its device prior to marketing.

FDA continues to aggressively cite compounding pharmacies. FDA warned four compounding pharmacies for multiple violations and noted that the pharmacies were each deficient in their practices

for producing sterile drug products. Three of the four compounding pharmacies were also cited for failing to obtain valid prescriptions for their compounding products.

FDA has seen an increase in Warning Letters to foreign drug manufacturers on data integrity issues, according to a CDER director in a July 14, 2014, presentation. In fiscal year 2013, CDER issued eight such letters due to data integrity. As of July 14, 2014, CDER has seen a 50 percent increase to 12 letters. In contrast, international Warning Letters on chain supply issues have dropped significantly from 2013. Issues of Agency concern include not recording activities contemporaneously, backdating, fabricating data, copying existing data as new data, re-running samples, and discarding data.

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 one letter to a company after reviewing the company's professional telephone script for a prescription drug. OPDP determined the script was false and misleading because it omitted important risk information associated with the use of the drug and omitted material facts, rendering the drug misbranded within the meaning of the FDCA.

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

Recent Drug and Device Approvals

FDA expands approved use of Imbruvica for chronic lymphocytic leukemia (July 28, 2014)

FDA approves new extended-release oxycodone with abuse-deterrent properties (July 23, 2014)

FDA approves Zydelig for three types of blood cancers (July 23, 2014)

FDA approves Ruconest to treat rare genetic disease hereditary angiodema (July 17, 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.