JONES DAY | **Pharmaceutical & Medical Device Regulatory Update**
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Top News

Human Drug Compounding: Trio of Documents Discuss FDA Position on the Prescription Requirement, Hospital Compounding, and Definition of "Facility"
FDA released three new draft guidance documents regarding its implementation of the human drug compounding requirements of Title I of the Drug Quality and Security Act, the "Compounding Quality Act." Fundamentally, the draft guidance documents describe FDA's current thinking on the prescription requirement for human compounded drugs, how it intends to apply the prescription requirement to compounding occurring in a hospital or health system pharmacy, and how the Agency defines "facility."

Section 503A of the Federal Food, Drug, and Cosmetic Act ("FDCA") outlines what conditions must be met for human drugs compounded by a licensed pharmacist in a state-licensed pharmacy or a licensed physician in order to be exempt from the manufacturing, labeling, and new drug application requirements of the FDCA.

Section 503B establishes "outsourcing facilities" and lists the conditions that must be met for human drugs compounded by or under the direct supervision of a licensed pharmacist in such facilities to be exempt from the labeling, new drug approval, and track-and-trace requirements of the FDCA. Products made by an outsourcing facility remain subject to manufacturing requirements.

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RELATED PRACTICES

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FDA Releases Draft Guidance on Data Integrity and Compliance With CGMP
In response to increased current good manufacturing practice ("CGMP") violations involving data integrity, FDA recently released a draft guidance titled "Data Integrity and Compliance With CGMP." Structured in question-and-answer format, the draft guidance addresses specific questions on how data integrity relates to CGMP for drugs and provides guidance on more general data integrity concepts. FDA previously published parts of the draft guidance on its webpage titled "Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance—Records and Reports." Once finalized, the draft guidance will replace the previous online guidance on data integrity in CGMP.

The FDA draft guidance follows on the heels of data integrity guidance published by the UK's Medicines and Healthcare Products Regulatory Agency in March 2015 and draft guidance published by the World Health Organization in September 2015. FDA is requesting comments on the draft guidance by June 14, 2016.

President Obama Signs Two Bipartisan Pharmaceutical Bills into Law
The White House recently announced that President Obama signed into law S. 2512 and S. 483, two pieces of pharmaceutical legislation that received bipartisan support in both the House and the Senate. First, to encourage the development of treatments for the Zika virus, S. 2512 expands the tropical disease product priority review voucher program to include the Zika virus. Specifically, S. 2512 amends Section 524(a)(3) of the FDCA (21 U.S.C. § 360n(a)(3)) to add the Zika virus to the list of tropical diseases included in the voucher program.

Second, S. 483, the Ensuring Patient Access and Effective Drug Enforcement Act of 2016, amends the Controlled Substances Act to define provisions relating to public health considerations and allow registrants and applicants to submit corrective action plans prior to revocation or suspension. The law also directs the Department of Health and Human Services ("HHS") to submit a report that identifies (i) obstacles to legitimate patient access to controlled substances, (ii) issues with diversion of controlled substances, and (iii) how collaboration between state and local enforcement agencies and industry stakeholders can benefit patients and prevent diversion and abuse of controlled substances.

Other News
FDA Announces Creation of Combination Products Policy Council

FDA Office of Generic Drugs Announces Release of First Annual Report

FDA and Foundation for FDA Scheduled to Co-Host May 16, 2016, Public Workshop on Proposed Expanded Access Navigator

House Appropriations Committee, in Report for FDA Appropriations Bill, Directs FDA to Suspend Efforts to Finalize Guidance on Laboratory-Developed Tests ("LDTs") and Work with Congress to Develop "New Pathway for Regulation of LDTs in a Transparent Manner"

Public Citizen Foundation Sues FDA Regarding Information on Advisory Committee Members

EMA's Pharmacovigilance Risk Assessment Committee Adopts Rules of Procedure on Public Hearings on Selected Safety Reviews

Regulatory Updates

FDA Extends Comment Period for Four Draft Guidances Relating to the

Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products
In the April 22, 2016, *Federal Register*, FDA announced extended comment periods for the following draft guidances: (i) *Same Surgical Procedure Exception: Questions and Answers Regarding the Scope of the Exception; Draft Guidance for Industry*; (ii) *Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products; Draft Guidance for Industry and Food and Drug Administration Staff*; (iii) *Human Cells, Tissues, and Cellular and Tissue- Based Products from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry*; and (iv) *Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products; Draft Guidance for Industry and FDA Staff*. ***Comments are due September 27, 2016***.

FDA Reopens Comment Period for Proposed Rule on Fixed-Combination and Co-Packaged Drugs and Combinations of Active Ingredients Under Consideration for Inclusion in an Over-the-Counter Monograph
In the April 18, 2016, *Federal Register*, FDA announced it is reopening the comment period for the proposed rule published in the December 15, 2015, *Federal Register*, revising the regulations on prescription and nonprescription fixed-combination and co-packaged drugs and on combinations of active ingredients under consideration for inclusion in an over-the-counter monograph. After initially providing interested persons until March 22, 2016, to comment, FDA is reopening the comment period based on a March 21, 2016, request for additional time. ***Comments are due May 18, 2016.***

FDA Proposes Rule Banning Electrical Stimulation Devices Used to Treat Self-Injurious or Aggressive Behavior
In the April 25, 2016, *Federal Register*, FDA proposed a ban on electrical stimulation devices used to treat aggressive or self-injurious behavior. This proposal is based on the Agency's determination that these devices present an unreasonable and substantial risk of illness or injury that cannot be corrected or eliminated by labeling. The proposed ban would apply to both new devices and devices already in distribution and use. ***Comments are due May 25, 2016.***

FDA Requests Information for Pharmaceutical Distribution Supply Chain Pilot Projects
In the April 15, 2016, *Federal Register*, FDA announced it is soliciting information regarding issues related to (i) utilizing the product identifier for product tracing, (ii) improving the technical capabilities of the supply chain, and (iii) identifying system attributes necessary to implement Drug Supply Chain Security Act ("DSCSA") requirements. FDA will use the information gathered from public comments in the design and development of pilot project(s) established under the DSCSA. ***Comments are due May 16, 2016.***

FDA Issues Emergency Use Authorization for Device to Detect Zika Virus
In the April 22, 2016, *Federal Register*, FDA announced the issuance of an emergency use authorization ("EUA") for an *in vitro* diagnostic device for detection of the Zika virus. The EUA, requested by the U.S. Centers for Disease Control and Prevention, was issued in response to the Zika virus outbreak in the Americas. On February 26, 2016, HHS determined that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad and that involves the Zika virus. On the basis of such determination, HHS declared that circumstances exist justifying the authorization of emergency use of *in vitro* diagnostic tests for detection of the Zika virus and/or diagnosis of Zika virus infection. ***The authorization was effective March 17, 2016.***

FDA Issues Emergency Use Authorization for Device to Detect Ebola Zaire Virus
In the April 22, 2016, *Federal Register*, FDA announced the issuance of an EUA for an *in vitro* diagnostic device for detection of the Ebola Zaire virus. The EUA, requested by OraSure Technologies, Inc., was issued in response to the Ebola virus outbreak in West Africa. On September 22, 2006, the Department of Homeland Security had determined that the Ebola virus presents a material threat against the U.S. population sufficient to

affect national security. On the basis of such determination, HHS declared that circumstances exist justifying the authorization of emergency use of *in vitro* diagnostic devices for detection of Ebola virus. ***The authorization was effective March 4, 2016.***

FDA Issued the Following Draft and Final Guidance Documents:

Draft Guidance for Industry: Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act, April 18, 2016, *Federal Register*. ***Comments are due July 18, 2016***.

Draft Guidance for Industry: Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act, April 18, 2016, *Federal Register*. ***Comments are due July 18, 2016***.

Draft Guidance for Industry: Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act, April 18, 2016, *Federal Register*. ***Comments are due July 18, 2016***.

Draft Guidance for Industry: Data Integrity and Compliance With CGMP, April 15, 2016, *Federal Register*. ***Comments are due June 14, 2016***.

Guidance for Industry: Radiation Biodosimetry Medical Countermeasure Devices, April 18, 2016, *Federal Register*.

Draft Guidance for Industry: Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information, April 20, 2016, *Federal Register*. ***Comments are due June 20, 2016***.

Guidance for Industry and FDA Staff: Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices, April 20, 2016, *Federal Register*.

Guidance for Industry: Distributor Labeling for New Animal Drugs, April 20, 2016, *Federal Register*.

Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors, April 12, 2016, *Federal Register*.

Draft Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products, April 25, 2016, *Federal Register*. ***Comments are due June 24, 2016***.

Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names, April 2016.

EU Regulatory Notices

French ANSM Announces Consultation on Pharmacovigilance Best Practices
On April 7, 2016, the French National Security Agency for Medicines and Health Products ("ANSM") launched a public consultation on a draft ministerial order setting out pharmacovigilance best practices. Further to the amendment of the French regulations necessary for the implementation of Directive 2012/26/EU of October 25, 2012, amending Directive 2001/83/EC as regards pharmacovigilance and of Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance, the ANSM is now updating the French best pharmacovigilance guidelines, currently based on a 2005 ministerial order, with consideration of the European Medicines Agency ("EMA") good pharmacovigilance practice guidelines ("GVP"). Once adopted, the new French best practices order will apply in addition to EMA's GVP and will detail procedures at the national level. The consultation relates to issues including the role of the ANSM, the role

of health care professionals, patients, Marketing Authorization holders and operators, and the Technical Committee on Pharmacovigilance, as well as the national pharmacovigilance inquiry procedure and the communication good practice on safe drug use. Comments are due June 15, 2016.

EMA's Pharmacovigilance Committee Reviews Diabetes Medicine Canagliflozin
On April 15, 2016, the EMA's Pharmacovigilance Risk Assessment Committee ("PRAC") started a review of the diabetes medicine canagliflozin after an increase in amputations mostly affecting toes was observed in an ongoing clinical trial called CANVAS. Canagliflozin is the active substance in two centrally authorized diabetes medicines, Invokana and Vokanamet. The review of canagliflozin has been initiated at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004. Following PRAC's recommendation, the Committee for Medicinal Products for Human Use will adopt an opinion before the European Commission adopts a legally binding decision applicable in all EU Member States.

EMA Extends the Scope of its Review on Direct-Acting Antivirals for Hepatitis C
On April 15, 2016, PRAC extended the scope of its ongoing safety review of medicines known as direct-acting antivirals (Daklinza, Exviera, Harvoni, Olysio, Sovaldi, and Viekirax) used for treating chronic (long-term) hepatitis C. In March 2016, the Committee had initiated a review following cases of hepatitis B reactivation in patients who have been infected with hepatitis B and C viruses, and who were treated with direct-acting antivirals for hepatitis C. However, in April 2016, data from a study became available regarding the risk of liver cancer (hepatocellular carcinoma) coming back in patients who were treated with these medicines. The study suggested that these patients were at risk of their cancer coming back earlier than in patients with hepatitis C who were not treated with direct-acting antivirals. The scope of the ongoing review has therefore been extended also to assess the risk of liver cancer with these medicines.

EMA Consultations
EMA is consulting on a guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials. The deadline for comments is October 12, 2016. EMA is also consulting on a draft guideline that provides guidance on the documentation expected for sterile products in the quality dossier for a marketing authorization application or a variation application for a medicinal product (called "quality dossier" throughout the guideline), and the selection of appropriate methods of sterilization for sterile products. The consultation is open until October 13, 2016. Finally, on April 20, 2016, EMA opened a public consultation on a draft concept paper on an addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev. 2) to address pediatric-specific clinical data requirements. Comments are due July 31, 2016.

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Prescription Requirement Under Section 503A of the FDCA. A compounded drug product may be exempt under Section 503A only if it is compounded in conjunction with a valid prescription. The guidance discusses compounding that occurs after the receipt of a prescription for an individual identified patient, before the receipt of a prescription for an individual identified patient (referred to as "anticipatory compounding"), and for office use. The guidance describes what constitutes receipt of a valid prescription order or notation approved by the prescriber, when a drug can be compounded, and recordkeeping. FDA states that it does not intend to consider a compounder to have exceeded the limited quantity condition of the FDCA if the compounder holds no more than a 30-day supply of a particular compounded drug product and the amount is based on the number of valid prescriptions for identified individual patients the compounder has received in a 30-day period over the past year. FDA also discusses what is considered a patient-specific prescription in light of some state rules allowing prescriptions to be written without individual patient names.

Hospital and Health System Compounding Under the FDCA. Pharmacies within a hospital or stand-alone pharmacies that are part of a health system provide compounded drugs for administration within the hospital or health system. Because the FDCA does not

distinguish between stand-alone pharmacies and pharmacies in hospitals and health systems, FDA states Section 503A applies to pharmacists, pharmacies, and physicians that compound drugs within a hospital or health system that is not registered as an outsourcing facility. FDA advises that it does not intend to take enforcement action if a hospital pharmacy distributes compounded drug products without first receiving a patient-specific prescription or order, provided that: (i) the drug products are distributed only to health care facilities that are owned and controlled by the same entity that owns and controls the hospital pharmacy and that are located within a one-mile radius of the compounding pharmacy; (ii) the drug products are administered only within the health care facilities to patients within the health care facilities, pursuant to a patient-specific prescription or order; and (iii) the drugs are compounded in accordance with all other provisions of Section 503A and relevant provisions of the FDCA. Note that FDA's allowance does not extend to a drug dispensed to a patient for use outside the hospital.

Facility Definition Under Section 503B of the FDCA. Section 503B defines an "outsourcing facility" as "a facility at one geographic location or address." The draft guidance states that FDA interprets this to mean a business or other entity under one management, direct or indirect, engaged in human compounding at a geographic location or street address. In addition, it considers all activities, equipment, appurtenances, and materials part of such a facility if they are related to human drug compounding under the supervision of the facility's management at the same street address, or in the same building, or in buildings in close proximity to one another. FDA states that the outsourcing requirements of Section 503B cannot be avoided by segregating or subdividing compounding within an outsourcing facility.

Notices of the draft guidance documents were published in the April 18, 2016, *Federal Register*. (See the specific notices for the Prescription Requirement, Hospital/Health System Compounding, and Facility Definition draft guidance documents.) FDA is requesting comments on the draft guidance documents by July 18, 2016.

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