JONES DAY | **Pharmaceutical & Medical Device Regulatory Update**
Vol. III | Issue 4 | May 2016 JONES DAY

Top News

Group of Republican Senators Push FDA on Draft Guidance Review
Earlier this month, four Republican senators—Lamar Alexander (TN), Richard Burr (NC), Johnny Isakson (GA), and Orrin Hatch (UT)—sent a letter to FDA Commissioner Robert Califf expressing concerns over the amount of time it takes FDA to revise, finalize, or withdraw draft guidance documents. The letter follows FDA's response to a 2014 letter from the same group of senators, which sought clarification regarding FDA's use of draft guidance to make substantive policy changes. Both letters argue that leaving guidance documents in draft form for so long, sometimes for years, makes it difficult to know whether FDA remains committed to the policies outlined in old draft documents.

The 2016 letter acknowledged FDA's previous response and requests that FDA provide updated information on: (i) how long it takes FDA to finalize draft guidance; (ii) which guidance documents are still pending; (iii) the plan for FDA Centers and Offices to systematically review outstanding and future draft guidance documents in a timely manner; (iv) training provided to FDA staff on how to develop and use guidance documents, including information on who conducts these trainings, how frequently they occur, and the content and forum of the trainings; and (v) whether a draft guidance document that has not been finalized should be construed as reflecting the FDA's current thinking.

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FDA Commissioner Califf Highlights Key Concerns for 21st Century Cures Act
FDA Commissioner Robert Califf, during remarks at the Food and Drug Law Institute's annual conference earlier this month, commented on the 21st Century Cures Act passed in the House and related legislation pending in the Senate. Commissioner Califf stressed, "it is vital that the legislation accomplishes the twin goals of promoting innovation and preserving the safety and effectiveness standard" because "[i]nnovative therapies are not helpful to patients if they don't work, or worse, cause harm." He warned that the legislation, "if not carefully crafted, could pose significant risks for FDA and American patients." In addition to citing safety and efficacy concerns, Commissioner Califf noted that "it is equally important that FDA receive adequate resources for any new responsibilities in the legislation."

In January 2016, the Senate Health, Education, Labor and Pensions ("HELP") Committee announced that it would vote on individual biomedical innovation bills in a "step by step" manner. To date, the Senate HELP Committee has passed 19 bills as part of a medical innovation package. Five bills the committee passed last month include a bill to help FDA and the National Institutes of Health ("NIH") recruit top talent (S. 2700), a bill to create a new drug approval pathway for certain antibiotic drugs (S. 185), a bill to encourage the Secretary of Health and Human Services to carry out a precision medicine initiative (S. 2713), a bill to require NIH to develop and facilitate collaboration in research (S. 2745), and a bill to reduce administrative burdens on researchers at NIH (S. 2742). Commissioner Califf's remarks may foreshadow some of the concerns lawmakers will grapple with when the bills go to the Senate floor, which may be as soon as next month if senators can reach an agreement on NIH funding.

New FDA Guidance Targets Electronic Health Records in Clinical Trials
FDA recently published a draft guidance, "Use of Electronic Health Record Data in Clinical Investigation," which is intended to guide sponsors, clinical investigators, contract research organizations, and institutional review boards in the use of electronic health record ("EHR") data as part of investigations of FDA-regulated products. Through its recommendations, FDA hopes to facilitate the use of EHR data in clinical trials and promote interoperability between EHRs and electronic systems supporting clinical investigations. The draft guidance provides FDA's current thinking on the decision to use and how to use EHRs as a source of clinical investigation data, using EHRs that are interoperable with systems that produce electronic records supporting clinical investigations, ensuring the quality and integrity of data collected and used, and ensuring that use of EHR data meets inspection, recordkeeping, and record retention requirements.

The draft guidance is intended to apply to the use of EHR data in prospective clinical trials of medical products (human drugs and biological products, medical devices, and combination products regulated by the Centers for Drug Evaluation and Research, for Biologics Evaluation and Research, and for Devices and Radiological Health), including foreign clinical studies not conducted under an investigational new drug application or investigational device exemption that are submitted to support a marketing application. The draft guidance does not apply to the use of EHR data in postmarketing observational pharmacoepidemiologic studies designed to assess drug exposure risk or test prespecified hypotheses. The draft guidance document includes best practices for the use of EHR data in clinical investigations, stating that sponsors should ensure the EHRs used and the policies and processes for their employment supply electronic source data that is "attributable, legible, contemporaneous, original, and accurate (ALCOA)." It also includes general considerations for the use of EHR in clinical investigations, data modifications, audit trails, informed consent, and the privacy and security of data. FDA is requesting comments on the draft guidance by July 18, 2016.

FDA Issues Newer Version of Medical Foods Frequently Asked Questions Guidance
FDA recently announced the availability of guidance for industry titled, "Frequently Asked Questions About Medical Foods; Second Edition." A medical food is a food formulated to be consumed or administered under the supervision of a physician and that is intended

"for the specific dietary management of a disease or condition" for which distinctive nutritional requirements are established by medical evaluation. FDA published earlier versions of the guidance in May 1997 and May 2007. The second edition of the guidance provides responses to additional questions regarding the definition and labeling of medical foods and updates some prior responses. For instance, FDA clarifies that medical foods that bear a false or misleading claim would be considered misbranded under section 403(a)(1) of the Food, Drug, and Cosmetic Act. In addition, FDA updates its response regarding diabetes, stating that there are no distinctive nutritional requirements associated with the management of diabetes mellitus ("DM") but nutritional recommendations established for persons to manage it. FDA still maintains that DM can be managed by a modification of the diet alone, and hence medical foods cannot be marketed for the treatment of diabetes.

Other News
FDA Website Indicates Final Rule on Generic Drug Labels Delayed Until April 2017

FDA Announces Safety Labeling Changes for Fluoroquinolone Antibiotics

FDA Approves First Buprenorphine Implant for Treatment of Opioid Dependence

FDA Clears Military Traumatic Wound Dressing for Use in the Civilian Population

EMA Reports on the First 10 Years of Its Small and Medium-Sized Enterprises ("SME") Initiative

Regulatory Updates

FDA Announces New Program for Electronically Submitting Vaccine Adverse Events
In the April 29, 2016, *Federal Register*, FDA announced the availability of a Vaccine Adverse Event Reporting System, or VAERS, eSubmitter program for the electronic submission of postmarketing individual case safety reports ("ICSRs") and ICSR attachments of adverse events for human vaccine products. The eSubmitter software is free to download and available for voluntary use by applicants, manufacturers, packagers, distributors, and others subject to mandatory vaccine postmarketing requirements under the final rule, "Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements," which was issued June 10, 2014, and became effective June 10, 2015.

FDA Announces Grant Funds to Support Rare Disease Product Development
In the May 4, 2016, *Federal Register*, FDA announced the availability of grant funds to support the Agency's Office of Orphan Products Development Natural History Grants Program. The program aims to support studies that advance the development of therapies for rare diseases and conditions by: (i) characterizing the natural history of rare diseases and conditions; (ii) identifying genotypic and phenotypic subpopulations; and (iii) developing/validating clinical outcome measures, biomarkers, and/or companion diagnostics. ***Applications are due October 14, 2016, and October 15, 2018***.

FDA Issues Proposed and Direct Final Rule on Standard Preparations, Limits of Potency, and Dating Period Limitations for Biological Products
In the May 4, 2016, *Federal Register*, FDA issued both a proposed and direct final rule amending the general biological products standards relating to dating periods and removing certain standards relating to standard preparations and limits of potency. Issued as part of a retrospective review of the Agency's regulations in response to Executive Order 13563, the amendments are intended to update outdated requirements and accommodate new and evolving technology and testing capabilities, without diminishing public health protections. FDA is issuing the amendments directly as a final rule because the Agency believes they are noncontroversial and FDA anticipates no significant adverse

comments. If no significant adverse comments are received, the rule will be effective September 16, 2016. ***Comments are due July 18, 2016***.

FDA Moves Forward to Study Market Claims in Direct-to-Consumer ("DTC") Prescription Drug Print Ads
In the May 4, 2016, *Federal Register*, FDA announced that it has submitted a proposed collection of information to the Office of Management and Budget. If cleared, the Office of Prescription Drug Promotion plans to investigate the impact of market claims (e.g., #1 Prescribed, New) on individuals' perceptions of prescription drugs in DTC print advertising containing varying levels of quantitative efficacy information. In the submission, FDA addresses comments it received from six organizations and individuals in response to its July 20, 2015, *Federal Register*, notice. ***Comments are due June 3, 2016***.

FDA Announces Public Meeting on Potential User-Fee Program for Over-the-Counter ("OTC") Monograph Drugs
In the May 11, 2016, *Federal Register*, FDA announced a public meeting to gather stakeholder input on the potential development of a user-fee program for nonprescription (i.e., OTC) monograph drugs. If implemented, the program would: (i) provide funding to supplement congressional non-user-fee appropriations and (ii) support timely and efficient FDA review of the efficacy and safety of ingredients included in or proposed for inclusion in a monograph. FDA seeks public comment on the potential user-fee program and suggestions for features to be included in the program. FDA has also published related Frequently Asked Questions on its website. ***The public meeting will be held June 10, 2016***.

FDA Reopens Comment Period for Public Workshop on Liquid Chromatography/ Mass-Spectrometry ("LC/MS")
In the April 29, 2016, *Federal Register*, FDA announced it is reopening the time period for interested persons to submit comments on the public workshop initially announced in the March 9, 2016, *Federal Register*. As it did before, FDA seeks comments on the workshop topics concerning the use of LC/MS-based *in vitro* diagnostic devices in the clinical laboratory. Comments were initially requested by April 20, 2016, and the workshop was initially scheduled to take place May 2, 2016. FDA is reopening the comment period in response to requests for additional time. ***Comments are due June 2, 2016***.

FDA Extends Comment Period for Proposed Ban on Electrical Stimulation Devices Used for Self-Injurious or Aggressive Behavior
In the May 23, 2016, *Federal Register*, FDA announced it is extending the time period for interested persons to submit comments on the proposed ban on electrical stimulation devices used to treat self-injurious or aggressive behavior rule, announced in the April 25, 2016, *Federal Register*. FDA initially set a deadline of May 25, 2016 and is extending the comment period in response to requests for additional time. ***Comments are due July 25, 2016***.

FDA Seeks Comments on Petition to Exempt Method, Metallic Reduction, Glucose (Urinary, Non-Quantitative) Test System from Premarket Notification Requirements
In the May 4, 2016, *Federal Register*, FDA published a notice to obtain comments on a petition it received requesting exemption from the premarket notification requirements for a method, metallic reduction, glucose (urinary, non-quantitative) test system in a reagent tablet format that is intended to measure glucosuria (glucose in urine). Method, metallic reduction, glucose (urinary, non-quantitative) test systems in a reagent tablet format are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, hypoglycemia, and hyperglycemia. ***Comments are due June 3, 2016***.

FDA Issues Final Rule on Antimicrobial Animal Drug Sales and Distribution Reporting
In the May 11, 2016, *Federal Register*, FDA issued a final rule requiring the sponsor of

each approved or conditionally approved new animal drug product containing an antimicrobial active ingredient to submit an annual report on the amount of each such ingredient in drug products sold or distributed for use in food-producing animals, including information on any distributor-labeled product. The final rule codifies the reporting requirements established in section 105 of the Animal Drug User Fee Amendments of 2008 and includes an additional reporting provision intended to enhance FDA's understanding of antimicrobial new animal drug sales intended for use in specific food-producing animal species and the relationship between such sales and antimicrobial resistance. ***The rule is effective July 11, 2016***.

FDA Issued the Following Draft and Final Guidance Documents:

Draft Guidance for Industry, Use of Electronic Health Record Data in Clinical Investigations, May 17, 2016, *Federal Register*. ***Comments are due July 18, 2016***.

Guidance for Industry, Frequently Asked Questions About Medical Foods; Second Edition, May 13, 2016, *Federal Register*.

Draft Guidance for Industry, Special Protocol Assessment, May 4, 2016, *Federal Register*. ***Comments are due July 5, 2016***.

Draft Guidance for Industry, Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment, May 4, 2016, *Federal Register*. ***Comments are due July 5, 2016***.

Draft Guidance for Industry and FDA Staff, Technical Considerations for Additive Manufactured Devices, May 10, 2016, *Federal Register*. ***Comments are due August 8, 2016***.

Draft Guidance for Industry and FDA Staff, Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and Virulence Markers, May 13, 2016, *Federal Register*. ***Comments are due August 11, 2016***.

Guidance for Industry and FDA Staff, Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act, May 16, 2016, *Federal Register*.

Guidance for Industry, Considerations for Use of Histopathology and Its Associated Methodologies to Support Biomarker Qualification, May 16, 2016, *Federal Register*.

Draft Guidance for Industry, Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment, May 20, 2016, *Federal Register*. ***Comments are due July 19, 2016.***

EU Regulatory Notices

European Regulators Consider Ways to Influence Drug Pricing
On May 12, 2016, an article was published in the *New England Journal of Medicine* ("NEJM") in which two representatives of the European Medicines Agency ("EMA") as well as heads of two national agencies discuss potential ways regulators can intervene to influence the pricing of medicinal products. Despite recognizing that "drug regulators aren't supposed to be concerned with pricing," the authors identify five main ways in which European regulators can "contribute to keeping drug spending sustainable":

1. By enabling the rapid approval of generics and biosimilars, as this facilitates competition and drives down prices;
2. By working to ensure that "me-too" products (medicines comparable to already approved options) continue to come on the market at reasonable speed, again to drive down prices through increased competition;

3. By encouraging companies to conduct clinical trials that both satisfy the needs of regulators (i.e., demonstrate quality, safety, and efficacy of the medicine) as well as the health-technology-assessment bodies (i.e., support the demonstration of the value once the medicine is authorized, to guide payers in their reimbursement decisions);
4. By facilitating the collection of other data that are important for payers by taking their needs into account when asking companies to conduct postapproval studies; and
5. By supporting higher efficiency of research and development in the area of medicines. The authors explain that by fostering a better model for the development of medicines, companies would potentially be able to reduce the price of their medicines. The authors suggest that could also mean reflecting on new approaches to medicines' development, such as the adaptive pathways approach that is being explored by EMA.

EMA Seeks to Engage General Practitioners and Family Doctors
On April 19, 2016, EMA held a workshop with representatives of general practitioners and family doctors in order to explore new ways to engage with these providers of primary care in EU Member States and further involve them in EMA activities. EMA's Executive Director Guido Rasi explained that as general practitioners and family physicians play a "key role" in patient care, "their knowledge and experience on how a medicine is used and addresses patient needs in real life can greatly inform [EMA's] decision making." Twenty representatives from three major organizations—the European Forum for Primary Care, the European Union of General Practitioners/Family Physicians, and the World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians Europe—attended the workshop.

The workshop led to the creation of an expert group of general practitioners initially composed of the 20 representatives who attended the meeting. These representatives will be involved in a wide range of EMA activities whenever their specific feedback is needed, including contribution to EMA's scientific advice to medicine developers, input on feasibility and impact on patients of risk minimization measures, and review of product information and dissemination of information to their national networks and patients.

EMA Reviews Inhaled Corticosteroids for Chronic Obstructive Pulmonary Disease ("COPD")
EMA has completed a review of the known risk of pneumonia (lung infection) in patients who take inhaled corticosteroid medicines to treat COPD. The review confirmed the risk of pneumonia with these products, which has been known for many years and is common (can affect between one and 10 COPD patients in 100 using these medicines). The review did not find any conclusive evidence of differences in this risk for different products.

EMA Recommends New Treatment for Rare White Blood Cell Cancer
On April 29, 2016, EMA adopted an opinion recommending extending the authorized indication of Gazyvaro (obinutuzumab) to treat patients with follicular lymphoma. The medicine is to be used in combination with bendamustine in patients who were previously treated with chemotherapy. Gazyvaro was first authorized in the European Union ("EU") in July 2014 for use in combination with chlorambucil in patients with previously untreated chronic lymphocytic leukemia. The opinion adopted by the Committee for Medicinal Products for Human Use ("CHMP") at its April 2016 meeting is an intermediary step on Gazyvaro's path to patient access. The CHMP opinion will now be sent to the European Commission for the adoption of a decision on EU-wide marketing authorizations.

EMA Recommends Five New Medicines Including New Antimicrobial
EMA's CHMP has recommended granting a marketing authorization in the EU for Zavicefta (ceftazidime/avibactam), a new treatment option against multidrug resistant bacteria. The medicine is to be used in adult patients with intra-abdominal infection, urinary tract infection, and pneumonia acquired in a hospital setting. It is also indicated for the treatment of adult patients with infections caused by certain Gram-negative bacteria, for

which there are only limited treatment options.

In addition, the following positive opinions were issued by the CHMP: Ongentys (opicapone) for the treatment of Parkinson's disease and motor fluctuations, Odefsey (emtricitabine/rilpivirine/tenofovir alafenamide) for the treatment of human immunodeficiency virus type 1 ("HIV-1") infection, Enzepi (pancreas powder) for the treatment of exocrine pancreatic insufficiency, and EndolucinBeta (lutetium (177 lu) chloride), a radiopharmaceutical precursor that has to be combined with another medicine, a carrier medicine, in a process called radiolabelling before administration. The carrier medicine then takes EndolucinBeta to the disease site in the body where it gives off beta-radiation, allowing a localized radiation effect.

The positive CHMP opinions described above are an intermediary step on the path to patient access to these medicines. The CHMP opinions will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorization in respect of each medicine.

EMA Recommends Antiseptic Gel for Newborns for Use Outside the EU
EMA has recommended Umbipro (chlorhexidine digluconate), an antiseptic gel to prevent umbilical cord infections (omphalitis) in newborn babies, for use in countries outside the EU. Umbipro was submitted to EMA under a regulatory procedure (Article 58) that allows the Agency to assess the quality, safety, and efficacy of a medicine and give an opinion on its benefit-risk balance when used in low-income countries outside the EU. Article 58 products are assessed by EMA in collaboration with the World Health Organization and are required to meet the same standards as medicines intended for EU citizens. The scientific opinion from EMA's CHMP helps to support regulators in countries where regulatory capacity may be limited, by providing an expert evaluation of the medicine when used in local practice.

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