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

FDA Proposes Regulatory Framework for Next Generation Sequencing-Based Tests
FDA recently released, as a part of President Obama's Precision Medicine Initiative, two draft guidance documents proposing what the Agency is calling a "flexible and streamlined approach" for regulating next generation sequencing ("NGS")-based tests. The first guidance document, "Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases," proposes, in part, that certain NGS-based tests (those for germline, e.g., hereditary, diseases) may be suitable for *de novo* classification and, if FDA makes a class II determination, potentially appropriate for exemption from premarket notification requirements.

In evaluating whether a 510(k) is needed to provide reasonable assurance of the safety and effectiveness of an NGS-based test for germline diseases, FDA will consider, among other things, assurances of analytical and clinical validity. These assurances are consistent with the parameters that are assessed as part of most IVD premarket reviews—analytical performance and clinical performance. (For more on IVD premarket reviews, see the Overview of IVD Regulation page on FDA's website.)

To provide assurance of analytical validity for an NGS-based test for germline diseases, FDA proposes that NGS-based test developers can follow the recommendations outlined in Section VI of the guidance document referenced above. (The section

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provides "Recommendations for Design, Development and Validation of NGS-based Tests for Germline Diseases," which "FDA believes can help demonstrate a reasonable assurance that an NGS-based test for germline diseases is analytically valid.")

In the future, FDA suggests it may recognize standards consistent with those recommendations, and conformance with those standards could support or provide reasonable assurance of a test's analytical validity. FDA also suggests that its analytical validity-related recommendations could also form the basis for special controls or conditions for 510(k) exemption in the future.

To provide assurance of clinical validity for any NGS-based test (i.e., not limited to those for germline diseases), FDA proposes that NGS-based test developers may utilize assertions of genotype-phenotype correlations and underlying data from FDA-recognized public genetic variant databases, as outlined in and consistent with FDA's second guidance document, "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics." In some instances, FDA suggests that NGS-based test developers may not need to submit additional clinical data beyond what is provided from the recognized genetic variant database. Comments on both draft guidances are due October 6, 2016.

FDA Continues to Refine Regulatory Approach for Compounding Pharmacies: "Essentially a Copy" Provisions and Inspection Protocol for Non-Outsourcing Facilities

On July 7, 2016, FDA released two draft guidance documents setting forth the Agency's policies for applying the "essentially a copy" provisions of Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act ("FDCA"). Under Section 503A, a drug product may be exempt from the FDCA's manufacturing, labeling, and new drug application requirements if, among other things, the pharmacist or physician "does not compound regularly or in inordinate amounts … any drug products that are essentially copies of a commercially available drug product." 21 U.S.C. § 353a(b)(1)(D). The 503A guidance outlines FDA's proposed approach to applying this provision, including the Agency's interpretation of the terms *commercially available*, *essentially a copy of a commercially available product*, and *regularly or in inordinate amounts*. Under Section 503B, a drug compounded by a registered outsourcing facility may be exempt from the FDCA's labeling, new drug application, and distribution requirements if, among other things, the drug "is not essentially a copy of one or more approved drugs." 21 U.S.C. § 353b(a)(5). The 503B guidance explains how FDA plans to apply the statutory definition of the term *essentially a copy of an approved drug*, *id.* § 353a(d)(2), when comparing a compounded drug to an approved drug or, alternatively, a covered over-the-counter ("OTC") drug. We previously discussed other guidance documents related to Sections 503A and 503B here.

In addition, in response to feedback from stakeholders, FDA is changing its inspection procedure for drug compounders that are not registered as outsourcing facilities under Section 503B of the FDCA. Before closing the inspection, FDA investigators will now make a preliminary assessment of whether the entities are compounding in accordance with certain conditions of Section 503A. An inspector will include observations representing deviations arising solely from current good manufacturing practice ("CGMP") requirements—which do not apply to a drug if the conditions of Section 503A are satisfied—only if the inspector's preliminary assessment reveals that the firm compounds drugs that do not qualify for exemption under Section 503A.

CMS Issues Guidance on Value-Based Purchase Agreements and Best Price

CMS recently issued Medicaid Drug Rebate Program Release No. 176 regarding value-based purchasing ("VBP") arrangements. Among other things, the notice responds to manufacturers' questions regarding how VBP arrangements, which often include price reductions and the provision of services to payers, affect a drug's best price for Medicaid reporting and rebate purposes. Generally speaking, "best price" is the lowest price

available from a manufacturer, including applicable discounts, rebates, and other arrangements (e.g., services) that lower the effective price paid for a drug. When applicable, a manufacturer must report a drug's best price on a quarterly basis and use the value in calculating any rebates that are due under the Medicaid Drug Rebate Program.

In the notice, CMS stated that a VBP arrangement's impact on a drug's best price will vary based on the structure of the VBP arrangement. CMS also provided an email address manufacturers can use to contact its CMCS Division of Pharmacy with questions regarding specific VBP arrangements. CMS plans to publish subsequent guidance with answers and lessons learned from common questions and arrangements.

Post-Brexit: EMA and MHRA Issue Statements on the Outcome of the UK Referendum
Following the United Kingdom ("UK") referendum on whether to remain or leave the European Union ("EU"), in which the UK voted 52 percent to 48 percent in favor of leaving the EU, the European Medicines Agency ("EMA") as well as the UK's competent authority for medicines, the Medicines and Healthcare products Regulatory Agency ("MHRA"), have both issued statements. EMA's statement addresses the possibility that the EMA will have to relocate out of London upon the UK's withdrawal from the EU, stating that "the implications for the seat and operations of EMA depend on the future relationship between the UK and the EU." The MHRA, in its statement, reminds that the MHRA "contribute[s] significantly in both the centralised and decentralised regulatory procedures, including new rapporteur and RMS appointments." According to the statement, the MHRA will maintain the program for implementing the clinical trial regulation. Of course, both the MHRA's role in European regulatory procedures and the fate of clinical trial regulation post-Brexit will depend on the outcome of the exit negotiations between the EU and the UK, which are yet to begin, and the nature of the UK's relationship with the EU once the UK withdraws from the EU. For more discussion on Brexit generally, see our previous Jones Day *Alert*.

Other News
FDA Commissioner Calls for National Evaluation System for Medical Devices

FDA Extends Goal for Orphan Drug Review Time Given Continued Increase in Designations

President Signs Opioid Addiction Bill, the Comprehensive Addiction and Recovery Act of 2016

Senate Expected to Finish Work on Companion to 21st Century Cures in September

FDA Discusses Steps the Agency is Taking in Response to Zika Virus

Regulatory Updates

FDA Proposes Rule Regarding OTC Antiseptic Drug Products
In the June 30, 2016, *Federal Register*, FDA proposed an amendment to its 1994 tentative final monograph for OTC antiseptic drug products (originally published in the June 17, 1994, *Federal Register*). The proposed rule applies to active ingredients used in consumer antiseptic rub products, also known as rubs, leave-on products, or hand sanitizers, as well as to consumer antiseptic wipes. In light of recent scientific developments and changes in product use patterns, FDA proposes that additional safety and effectiveness data are necessary to support a generally recognized as safe and generally recognized as effective ("GRAS"/"GRAE") determination for OTC antiseptic rub active ingredients intended for use by consumers. FDA also proposes that all consumer antiseptic rub active ingredients have *in vitro* data characterizing the ingredient's antimicrobial properties and *in vivo* clinical simulation studies showing that use of the ingredient achieves specified log reductions in the amount of certain bacteria. ***Comments***

are due December 27, 2016.

FDA Announces Public Workshop on ICH Guideline Q3D Regarding Elemental Impurities
In the July 8, 2016, *Federal Register*, FDA announced a public workshop titled "Regional Public Workshop on ICH Q3D Implementation of Guideline for Elemental Impurities." The purpose of the public workshop is to elaborate on key aspects of the International Conference on Harmonisation ("ICH") Guideline Q3D: Guideline on Elemental Impurities in order facilitate a harmonized interpretation and implementation by industry and regulators. The public workshop is not intended to provide additional guidance beyond the scope of Q3D. Participants will be able join in person or via the internet. ***The public workshop will be held August 22 and 23, 2016***.

FDA Announces Public Workshop on Medical Device Refurbishing, Reconditioning, Rebuilding, Remarketing, Remanufacturing, and Servicing
In the July 18, 2016, *Federal Register*, FDA announced a public workshop titled "Refurbishing, Reconditioning, Rebuilding, Remarketing, Remanufacturing, and Servicing of Medical Devices Performed by Third-Party Entities and Original Equipment Manufacturers." The workshop will address topics including the current regulatory environment for these activities, various definitions FDA proposed in is prior *Federal Register* notice and request for comments on the subject, and whether these activities should appropriately be regulated by FDA or a nongovernmental organization. ***The public workshop will be held October 27 and 28, 2016***.

FDA Issues Technical Specifications Document for Quality Metric Data
In the June 27, 2016, *Federal Register*, FDA announced the availability of a technical specifications document titled "Quality Metrics Technical Conformance Guide, Version 1.0." The document provides technical recommendations for submitting quality metric data. It also supplements and serves as the technical reference for implementing the FDA's draft guidance for industry titled ''Request for Quality Metrics'' (published July 28, 2015). ***Comments are due September 26, 2016***.

FDA Issued the Following Draft and Final Guidance Documents:
Draft Guidance for Stakeholders and FDA Staff: Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases, July 8, 2016, *Federal Register*. ***Comments are due October 6, 2016***.

Draft Guidance for Stakeholders and FDA Staff: Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics, July 8, 2016, *Federal Register*. ***Comments are due October 6, 2016***.

Draft Guidance for Industry: Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act, July 11, 2016, *Federal Register*. ***Comments are due October 11, 2016***.

Draft Guidance for Industry: Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act, July 11, 2016, *Federal Register*. ***Comments are due October 11, 2016***.

Draft Guidance for Industry: Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn, July 11, 2016, *Federal Register*. ***Comments are due September 9, 2016***.

Draft Guidance for Industry and FDA Staff: Principles for Codevelopment of an In Vitro Companion Diagnostic Device With a Therapeutic Product, July 15, 2016, *Federal Register*. ***Comments are due October 13, 2016***.

Guidance for Industry and FDA Staff: Information to Support a Claim of Electromagnetic

Compatibility (EMC) of Electrically-Powered Medical Devices, July 11, 2016, *Federal Register*.

Draft Guidance for the Public and FDA Staff: Gifts to FDA: Evaluation and Acceptance, June 29, 2016, *Federal Register*. ***Comments are due September 12, 2016***.

Draft Guidance for Industry: Elemental Impurities in Drug Products, July 1, 2016, *Federal Register*. ***Comments are due August 30, 2016***.

Guidance for Industry: Early Clinical Trials With Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information, July 1, 2016, *Federal Register*.

Guidance for Industry: E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER), July 18, 2016, *Federal Register*.

Guidance for Industry: E2C(R2) Periodic Benefit-Risk Evaluation Report, Questions and Answers, July 18, 2016, *Federal Register*.

Draft Guidance for Industry: Bioequivalence Recommendations for Paliperidone Palmitate, July 1, 2016, *Federal Register*. ***Comments are due September 6, 2016***.

Draft Guidance for Industry: Vulvovaginal Candidiasis: Developing Drugs for Treatment, July 1, 2016, *Federal Register*. ***Comments are due September 29, 2016***.

Draft Guidance for Industry: Recurrent Herpes Labialis: Developing Drugs for Treatment and Prevention, July 1, 2016, *Federal Register*. ***Comments are due September 29, 2016***.

Draft Guidance for Industry: Bacterial Vaginosis: Developing Drugs for Treatment, July 14, 2016, *Federal Register*. ***Comments are due October 12, 2016***.

EU Regulatory Notices

The EU–U.S. Privacy Shield Approved
Designed to replace the Safe Harbor Program with a more robust and comprehensive trans-Atlantic data-transfer scheme, the much-anticipated EU–U.S. Privacy Shield has finally received approval from the European Commission. Every potentially interested company will need to evaluate the Privacy Shield and determine whether compliance with the new framework is the most effective option for accessing EU personal data in the U.S. For more information, see our Jones Day *Alert*.

EU Commission Consults on App Safety
The European Commission has launched a consultation on the safety of apps and other non-embedded software (i.e., software and apps that are neither embedded nor contained in a tangible medium at the time of their placement in the market, their supply to consumers, or when they are otherwise made available to consumers). Health and wellbeing apps that can be used on a mobile device are examples of such software. The purpose of the consultation is to gather input from various stakeholder groups, in particular consumers, businesses, and authorities, on their experience related to the safety of apps and other non-embedded software. The questions aim at obtaining a better understanding of the possible risks and problems that non-embedded software may pose and how these problems could be addressed. The views gathered during the consultation will help to define potential next steps and future policies at the EU level, including, if appropriate, possible revisions of existing horizontal and/or sector-specific EU legislation. The consultation is open for comments until September 15, 2016.

Infringement Procedure Against Roche—EMA Update
The EMA has concluded its second inquiry within the framework of its infringement

procedure against Roche. The infringement procedure was started by EMA on October 23, 2012, at the request of the European Commission in the framework of Commission Regulation (EC) No 658/2007, the so-called Penalties Regulation. The aim of the inquiry was to investigate allegations that Roche failed to comply with its pharmacovigilance obligations in relation to 19 of its centrally authorized products, following a pharmacovigilance inspection carried out in 2012 by the MHRA, which identified serious shortcomings of the pharmacovigilance processes of the marketing authorization holder.

The Agency's review has not identified any important new safety concerns and has not led to any changes in the terms of the marketing authorizations of these medicines. EMA's report has been sent to the European Commission and will form the basis for the European Commission's decision on whether or not the matter should be pursued and financial penalties should be imposed.

MHRA Publishes New Guidance on Remanufacturing of Single-Use Devices
On July 5, 2016, the MHRA published new guidance on the remanufacturing of single-use devices ("SUDs") and expectations for their use. This follows a three-year review by the MHRA of remanufacturers in which the MHRA assessed the technical, regulatory, and clinical processes of such remanufacturers. The key points of the guidance are:

- SUDs may be remanufactured for use in the UK. However, the remanufacturer, prior to placing a device in the UK market or to putting it into service, should meet all relevant criteria under the appropriate medical devices directive and place a CE mark on the product to declare conformity with that directive.
- The remanufacturer accepts all liabilities and obligations for the remanufacturing of the SUD. The intended use of the remanufactured device should not differ from the intended use of the original product.
- The supply of a particular remanufactured SUD should be through a closed-loop contract between the remanufacturer and the health care institution (e.g., hospital, clinic). At no time should a remanufacturer or health care institution sell or provide a remanufactured SUD to any other third party.
- A remanufactured SUD should be used only on an individual patient during a single procedure; after that use, the SUD should be returned to the contracted remanufacturer.
- The packaging or device must have a specific symbol indicating "Do not reuse/Use only once/Single-use only."

This document is aimed at all companies that remanufacture medical devices that were originally "single use"; notified bodies; UK trade associations; all providers of medical devices, e.g., NHS Supply Chain, remanufacturers; chief executives and managers of institutions where medical devices are used; and health care institutions and professionals who use medical devices.

EU Publishes Guide on Zika and Substances of Human Origin
On July 15, 2016, the European Centre for Disease Prevention and Control published a guide for the preparation and implementation of a national preparedness plan for the safety of substances of human origin ("SoHO"), such as blood, tissue, and cells, in the event of a Zika virus outbreak in Europe. Zika virus is mainly transmitted to humans through mosquitoes but can potentially also be transmitted through SoHO. The activities set out in this guide aim to assist the Member States in decision-making on how to assess and manage the risks posed by Zika to the safety of SoHO. The guide identifies concrete activities to be considered at the local, national, and EU levels.

EMA Completes Zydelig Review
EMA's Pharmacovigilance Risk Assessment Committee ("PRAC") has completed its review of Zydelig (idelalisib), confirming that the medicine's benefits outweigh its risks in the treatment of two types of blood cancers, chronic lymphocytic leukemia ("CLL") and follicular lymphoma. The PRAC, however, confirmed that there is a risk of serious infections with Zydelig, including Pneumocystis jirovecii pneumonia, and has updated

recommendations to manage this risk issued at the beginning of the review. The review started after a higher rate of serious adverse events related to infections, such as pneumonia, was seen in three clinical trials among patients who received either Zydelig or placebo in addition to other cancer medicines (see previous Jones Day *Update*). The PRAC's recommendations will now be passed to EMA's Committee for Medicinal Products for Human Use, or CHMP, for adoption of the Agency's final position.

French Publish Study on Safety of Medical Devices Software
On July 13, 2016, the French national Agency for Medicines and Health Products Safety published a study on the safety of medical devices software. The study's objectives are to assess the European normative framework for software development and safety and produce recommendations for manufacturers.

In order to correctly implement the current standards, the study recommends that manufacturers focus on data related to principles (e.g., sustainability and confidentiality) identified in the software database, specification and design verification, impact analysis of software changes, and a thorough risk analysis. The study also proposes to clarify or create new requirements to existing NF EN 62304, EN 62366, and ISO 14971 standards and provides various recommendations intended to cover most of the software types to fill gaps identified in applicable norms regarding process, development techniques, and safety and security categories. The proposed reform aims to address new risks in a context of health care technological revolution and to ensure the safety of medical devices software.

MHRA Publishes Statistics on Early Access to Medicines Scheme
The MHRA has published official statistics on its Early Access to Medicines Scheme ("EAMS"). The published tables show that 27 applications were made to EAMS for the promising innovative medicine designation and the scientific opinion. The tables also show the number of applications that have been granted (17) and refused (four), as well as the number of pending (five) applications. The scheme, which was launched in 2014, aims to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorization when there is a clear unmet medical need. The first drug to be approved through EAMS was pembrolizumab for the treatment of advanced melanoma in March 2015 (see previous Jones Day *Update*).

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