JONES DAY | **Pharmaceutical & Medical Device Regulatory Update**
Vol. III | Issue 5 | July 2016 JONES DAY

Top News

FDA Takes Steps to Streamline Individual Patient Expanded Access
On June 2, 2016, FDA announced the availability of three final guidance documents aimed at simplifying and clarifying expanded access for investigational drugs and assisting health care professionals, patients, and industry in navigating the expanded access process.

In the FDA blog, *FDA Voice*, Dr. Richard A. Moscicki, Deputy Center Director for Science Operations, Center for Drug Evaluation and Research, heralded the documents, writing that "FDA has recently made significant changes to streamline and simplify the process for single patient expanded access requests." The term "expanded access" refers to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition (as compared to investigational purposes).

Under current regulations, there are three categories of expanded access—for individual patients, including for emergency use; for intermediate-size patient populations; and for widespread treatment use through an investigational new drug or treatment protocol.

The three final guidance documents address:

- "Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers" (FDA-2013-D-0446). The guidance provides industry, researchers, physicians, institutional review boards, and patients with information about the

CONTACTS

Edgar Asebey
Miami

Maureen Bennett
Boston / San Francisco

Cristiana Spontoni
Brussels

Colleen M. Heisey
Washington

Christian B. Fulda
Munich

Chiang Ling Li
China

Katherine M. Llewellyn
Brussels

Katherine S. Makielski
Chicago

Laura E. Koman
Washington

Armelle Sandrin-Deforge of the Paris Office assisted in the preparation of this Update.

Detailed Contact Information

RELATED PRACTICES

FDA Regulatory & Compliance Counseling

Health Care

Life Sciences

implementation of FDA's regulations on expanded access to investigational drugs for treatment use under an investigational new drug application ("IND"). The document is in question-and-answer format and explains what expanded access is, when and how to request expanded access, and the type of information that should be included in requests, among other frequently asked questions. The guidance finalizes a May 2013 draft.

- "Charging for Investigational Drugs Under an IND—Questions and Answers" (FDA-2013-D-0447). The guidance informs the same audiences about FDA's implementation of the rules regarding charging for investigational drugs under an IND for the purpose of either clinical trials or expanded access for treatment use. The document is in question-and-answer format and addresses FAQs, including general questions and questions about charging in clinical trials, charging for expanded use, and cost recovery calculations. The guidance finalizes a May 2013 draft.
- "Individual Patient Expanded Access Applications: Form FDA 3926" (FDA-2015-D-0258). The guidance describes the availability of Form FDA 3926, which may be used by licensed physicians to request expanded access for individual patients. Individual patient expanded access allows for the use of an investigational new drug outside of a clinical investigation, or the use of an approved drug where availability is limited by a risk evaluation and mitigation strategy, for an individual patient who has a serious or immediately life-threatening disease or condition when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition. The form may be used in lieu of an IND for individual patient expanded access, including for emergency use. The guidance finalizes a February 2015 draft.

The finalization of these documents is only part of recent FDA efforts on expanded access. In May 2016, FDA held a public workshop with the Reagan-Udall Foundation where interested stakeholders explored viable options to help patients and their physicians understand the request process for access to unapproved drugs. FDA held an educational webinar on the documents on July 12, 2016, which was open to the public but directed toward physicians seeking more information about expanded access to an investigational drug.

FDA Issues Draft Revised Guidance on Categorizing IDE Devices

FDA categorizes Investigational Device Exemption ("IDE") devices as either Category A (Experimental) or Category B (Nonexperimental/investigational) to assist CMS in making Medicare coverage decisions for devices provided in FDA-approved IDE studies. Medicare may pay for a Category B device if the study meets certain criteria, but Medicare will not pay for a Category A device. The framework for FDA's categorization was originally created in 1995 through an Interagency Agreement ("IA") with CMS (then HCFA) and IDE Guidance Memorandum #95-2 (which includes the IA as Attachment A).

Following CMS IDE regulatory updates in 2013 (C.F.R. § 405 Subpart B) and a 2015 Memorandum of Understanding between FDA and CMS (effective June 2, 2016, and replacing the 1995 IA), FDA recently announced the availability of a draft guidance document titled "FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) with Coverage Decisions; Draft Guidance for Sponsors, Clinical Investigators, Industry, Institutional Review Boards, and Food and Drug Administration Staff." The draft guidance modifies the criteria FDA will use when initially categorizing a device to be studied and then deciding whether to change a device's categorization, for example, based on new data. Once finalized, the guidance will supersede the Agency's 1995 guidance memorandum #95-2. FDA has requested comments on the draft guidance by August 1, 2016.

FDA Issues Draft Guidance on Appearance Issues for FDA Advisory Committee Members

On June 29, 2016, FDA announced the availability of a draft guidance document titled "Procedures for Evaluating Appearance Issues and Granting Authorizations for

Participation in FDA Advisory Committees; Guidance for the Public, FDA Advisory Committee Members, and FDA Staff." FDA advisory committees provide independent, expert advice to FDA on a range of issues affecting public health. To protect the credibility and integrity of such advice, FDA screens members for potentially disqualifying interests or relationships, including financial interests that may create a recusal obligation under federal conflict of interest law, and other interests and relationships that may create the appearance of impartiality, also referred to as "appearance issues."

The guidance document addresses FDA's process for evaluating the second category—that is, whether an advisory committee member has an appearance issue—and describes FDA's process for determining whether to authorize a member with an appearance issue to nonetheless participate in an advisory committee meeting. Because the Agency is not permitted to disclose confidential information provided by advisory committee members, FDA is also requesting comments by September 27, 2016, on whether FDA should ask individuals with appearance issues who are authorized to participate in advisory committee meetings to voluntarily disclose those appearance issues to the public.

Other News
FDA Launches Campaign to Encourage Diverse Clinical Trial Participants

FDA Announces New Oncology Center of Excellence to Support National Cancer Moonshot Initiative

FDA Requests Additional Data Supporting Efficacy and Safety of Topical Consumer Antiseptic Rubs (Including Hand Sanitizers)

Open Payments (Sunshine Act) Data for 2015 Now Available on CMS Website

EMA Introduces New Operating Model for Procedure Management to Improve Support for Evaluation Procedures

Regulatory Updates

FDA Announces Public Workshop on Sequencing Quality Control 2
In the May 31, 2016, *Federal Register*, FDA announced an upcoming public workshop called "Sequencing Quality Control II." The public workshop is part of a new MicroArray Quality Control project called Sequencing Quality Control 2 ("SEQC2"). SEQC2 is the FDA-led communitywide consortium efforts to develop best practices with recommended standard analysis protocols and quality control metrics for whole genome sequencing and target gene sequencing technologies that will support regulatory science research and precision medicine. Sessions for the public workshop include (i) germline mutation; (ii) somatic mutation; (iii) bioinformatics challenges; and (iv) clinical application. ***The public workshop will be held September 13 and 14, 2016***.

FDA Announces Public Workshop on Antibacterial Drug Development
In the May 31, 2016, *Federal Register*, FDA announced an upcoming public workshop regarding antibacterial drug development for patients with unmet need and developing antibacterial drugs that target a single species. Discussions will focus on potential development pathways; aspects of clinical trials, including patient population; trial designs and endpoints; and the role of clinical trial networks in antibacterial drug development. FDA will post a draft agenda before the meeting and invites individuals, industry, health care professionals, researchers, public health organizations, and other interested persons to attend. Input from this public workshop will also help in developing topics for future discussion. ***The public workshop will be held July 18 and 19, 2016***.

FDA Holds Public Workshop on OpenFDA System
In the June 1, 2016, *Federal Register*, FDA announced it would hold a public workshop as a forum for the openFDA system user community to: (i) engage in a robust interactive

discussion and provide feedback regarding openFDA's platform, application programming interfaces, downloadable harmonized datasets, and possible enhancements to the openFDA platform; and (ii) view demonstrations of various applications specifically developed to utilize openFDA data. ***The public workshop was held on June 20, 2016***.

FDA Extends Comment Period for Biosimilar Labeling Guidance
In the June 6, 2016, *Federal Register*, FDA announced it is extending the comment period for the draft guidance for industry titled "Labeling for Biosimilar Products" (published in the April 4, 2016, *Federal Register*, with a 60-day comment period). FDA believes an additional 60 days will allow adequate time for interested persons to submit comments without compromising timely publication of the final guidance. ***Comments are due August 2, 2016***.

FDA Issues Final Rule on Symbols in Labeling
In the June 15, 2016, *Federal Register*, FDA issued a final rule revising the Agency's medical device and certain biological product labeling regulations. The final rule allows labeling to use stand-alone symbols (i.e., graphical representations of information, or symbols, without adjacent explanatory text) if certain requirements are met. In addition, the final rule revises FDA's prescription device labeling regulations to allow the use of the symbol statement "Rx only" in the labeling for prescription devices. ***The rule is effective September 13, 2016***.

FDA Modifies List of Recognized Consensus Standards
In the June 15, 2016, *Federal Register*, and June 27, 2016, *Federal Register*, FDA published modifications to the list of standards FDA recognizes for use in premarket reviews. The publications, titled "Modifications to the List of Recognized Standards, Recognition List Number: 042," and "Modifications to the List of Recognized Standards, Recognition List Number: 043," respectively, will assist manufacturers that elect to declare conformity with consensus standards to meet certain requirements for medical devices. FDA will incorporate these modifications in the list of FDA Recognized Consensus Standards in the Agency's searchable database. ***Modifications were effective June 15 and 27, 2016, respectively***.

FDA Announces New and Revised Product-Specific Bioequivalence Recommendations
In the June 17, 2016, *Federal Register*, FDA announced the availability of 19 new and 19 revised draft product-specific bioequivalence recommendations. The draft recommendations provide product-specific guidance on the design of bioequivalence studies to support abbreviated new drug applications. These 38 draft recommendations and FDA's other product-specific bioequivalence recommendations (1,454 total) are available on FDA's website. ***Comments are due August 16, 2016***.

FDA Issues Final Rule Amending Regulations Relating to Embryos Donated for Reproductive Use
In the June 22, 2016, *Federal Register*, FDA issued a final rule amending certain donor eligibility regulations to increase access to embryos donated for reproductive use. The rule expands the exceptions under 21 C.F.R. § 1271.90 and allows the use of embryos originally formed for reproductive use for a specific individual or couple and now intended for directed or anonymous donation for reproductive use, provided that specific criteria (e.g., labeling requirements) are met. The final rule is substantially similar to the proposed rule FDA issued in the December 31, 2014, *Federal Register*. ***The rule is effective August 22, 2016***.

FDA Issues Technical Specifications Document for Adverse Event Reporting System
In the June 23, 2016, *Federal Register*, FDA announced the availability of a technical specifications document titled "FDA Regional Implementation Specifications for ICH E2B(R3): Postmarket Submission of Individual Case Safety Reports for Drugs and Biologics, Excluding Vaccines." The document supplements the final guidance for industry

titled "E2B(R3) Electronic Transmission of Individual Case Safety Reports (ICSRs) Implementation Guide—Data Elements and Message Specification" and describes FDA's technical approach for receiving individual case safety reports, incorporating regionally controlled terminology, and adding region-specific data elements when reporting to the FDA Adverse Event Reporting System.

FDA Issued the Following Draft and Final Guidance Documents:
Guidance for Industry: Individual Patient Expanded Access Applications: Form FDA 3926, June 3, 2016, *Federal Register*.

Guidance for Industry: Charging for Investigational Drugs Under an IND—Questions and Answers, June 3, 2016, *Federal Register*.

Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers, June 3, 2016, *Federal Register*.

Draft Guidance for Sponsors, Clinical Investigators, Industry, Institutional Review Boards and FDA Staff: FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) with Coverage Decisions, June 1, 2016, *Federal Register*. ***Comments are due August 1, 2016***.

Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Procedures for Evaluating Appearance Issues and Granting Authorizations for Participation in FDA Advisory Committees, June 29, 2016, *Federal Register*. ***Comments are due September 27, 2016***.

Draft Guidance for Industry: Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs, June 1, 2016, *Federal Register*. ***Comments are due August 1, 2016***.

Guidance for Industry: Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act, June 10, 2016, *Federal Register*.

Guidance for Industry: Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act, June 10, 2016, *Federal Register*.

Draft Guidance for Industry: Dissemination of Patient-Specific Information from Devices by Device Manufacturers, June 10, 2016, *Federal Register*. ***Comments are due August 9, 2016***.

Draft Guidance for Industry: Osteoporosis: Nonclinical Evaluation of Drugs Intended for Treatment, June 14, 2016, *Federal Register*. ***Comments are due August 15, 2016***.

Guidance for Industry and FDA Staff: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process," June 16, 2016, *Federal Register*.

Draft Guidance for Industry and FDA Staff: Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions, June 16, 2016, *Federal Register*. ***Comments are due September 14, 2016***.

Draft Guidance for Industry: Quality Attribute Considerations for Chewable Tablets, June 17, 2016, *Federal Register*. ***Comments are due August 16, 2016***.

Draft Guidance for Industry and FDA Staff: Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies, June 20, 2016, *Federal Register*. ***Comments are due September 19, 2016***.

Guidance for Industry and FDA Staff: Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices, June 21, 2016, *Federal Register*.

Draft Guidance for Industry: Oncology Drugs for Companion Animals, June 10, 2016, *Federal Register*. ***Comments are due August 9, 2016***.

Guidance for Industry: Modified Release Veterinary Parenteral Dosage Forms: Development, Evaluation, and Establishment of Specifications, June 17, 2016, *Federal Register*.

EU Regulatory Notices

New EU Rules on Medical Devices
On May 25, 2016, the EU agreed on new rules on medical devices and in vitro diagnostic medical devices—almost four years since the European Commission first published its proposal. The European Parliament finally, on June 14, 2016, published the agreed texts of the two regulations set to replace the existing three directives that currently regulate medical devices in Europe. The new rules seek to reform the regulation of medical devices in the EU and ensure the safety of medical devices by two means: strengthening the rules on placing devices on the market and tightening surveillance once they are available.

The new rules introduce a number of key changes. First, the scope of the rules is expanded to include devices with purposes related to prediction and prognosis of diseases and groups of products without an intended medical purpose, such as contact lenses for cosmetic purposes, fillers, equipment for liposuction, and products used for tattooing. Notified Bodies (the independent bodies that are responsible for assessing medical devices before they can be placed on the market) will face stricter rules and will have the right and duty to carry out unannounced factory inspections. Certain high-risk devices, such as implants, may undergo additional checks by experts before they are placed on the market. There is also a focus on traceability, and manufacturers will be required to place a unique device identification on their medical devices.

Sign-off by Parliament and Council is expected by autumn, with the texts being adopted by the end of autumn and official publication at the beginning 2017. The new rules will apply three years after official publication with regard to medical devices and five years after official publication with regard to in vitro diagnostic medical devices.

EMA Reflects on First-in-Human Clinical Trials Following Fatal Rennes Trial
On May 27, 2016, the European Medicines Agency ("EMA") announced that it has started a review of the guidelines that describe first-in-human clinical trials and the data needed to enable their appropriate design and allow initiation. The review will identify which areas may need to be revised in the light of the tragic incident which took place during a Phase I first-in-human clinical trial in Rennes, France, in January 2016. The trial led to the death of one participant and hospitalization of five others. EMA's review will take into account the findings from two in-depth investigations into what went wrong during this trial, one carried out by the Temporary Specialist Scientific Committee set up by the French medicines agency ANSM and the other by the *Inspection générale des affaires sociales*, the inspectorate for social affairs in France. Both reports include a series of recommendations regarding the requirements for authorization and conduct of first-in-human clinical trials for further examination by the international regulatory and public health community. The aim of EMA's work is to agree on a concept paper by July 2016 identifying areas for change and proposals to further minimize the risk of similar accidents. Meanwhile, French prosecutors have announced they have started an involuntary manslaughter investigation in connection with the incident.

TTIP Update—Annex on Medicinal Products
On May 24, 2016, The European Commission published a proposal for an annex to the

Transatlantic Trade and Investment Partnership ("TTIP") on medicinal products together with a Report of the 13th Round of Negotiations for the TTIP. The proposal describes the conditions under which each competent authority makes decisions on marketing authorizations, promotes international harmonization, and establishes frameworks for the mutual recognition of Good Manufacturing Practice ("GMP") inspections, for the exchange of confidential information
including trade secrets and for bilateral regulatory cooperation. Discussions on the proposal will continue at the next round of negotiations.

European Commission Publishes Draft Code of Conduct on Privacy for mHealth Apps
On June 7, 2016, the European Commission published its final draft Code of Conduct on privacy for mobile health apps ("Code"). The Code aims to raise awareness of the data protection rules in relation to mHealth apps, facilitating and increasing compliance at the EU level for app developers. The issues covered by the Code are: user's consent, purpose limitation and data minimization, privacy by design and by default, data subjects' rights and information requirements, data retention, security measures, principles on advertising in mHealth apps, use of personal data for secondary purposes, disclosing data to third parties for processing operations, data transfers, personal data breach, and data gathered from children. The Code has been formally submitted for comments to the Article 29 Data Protection Working Party. Once approved by this independent EU advisory group, the Code will be applied in practice. App developers will be able to voluntarily commit to follow its rules, which are based on EU data protection legislation.

First Medicines Approved under EU's Priority Medicines Scheme
On June 1, 2016, EMA announced the outcome of the assessment of the first batch of applications received from medicine developers for its PRIME (PRIority MEdicines) scheme, a new initiative that aims to foster research on and development of medicines that have the potential to address an unmet medical need. Eighteen applications for PRIME were received as of April 6, 2016, and subsequently assessed by EMA's Scientific Advice Working Party, Committee for Advanced Therapies, and Committee for Medicinal Products for Human Use. Four medicines have been accepted for PRIME.

Single, Central Platform Now Mandatory for All Periodic Safety Update Reports
As of June 13, 2016, all periodic safety update reports ("PSURs") for human medicines authorized in the EU must be submitted to the PSUR repository, which has been developed by EMA in close collaboration with EU Member States and the industry. The PSUR repository is a single, central platform for PSURs and related documents to be used by all regulatory authorities and pharmaceutical companies in the EU. It was introduced by the EU pharmacovigilance legislation to facilitate the exchange of information on the safety of authorized medicines between regulators and pharmaceutical companies. Marketing authorization holders must now use the repository as a single point for all submissions and should no longer submit their PSURs to national competent authorities. The eSubmission Gateway is available on the eSubmission website.

EU Launches Four Clinical Trial Public Consultations
On June 1, 2016, the European Commission launched four public consultations in the field of clinical trials. The consultations cover the following topics: "Risk Proportionate Approaches in Clinical Trials"; "Summary of Clinical Trial Results for Laypersons"; "Definition of Investigational Medicinal Products and use of Auxiliary Medicinal Products" (previously called "Guidance on Investigational Medicinal Products and Non-Investigational Medicinal Products); and "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors." All the consultations are open for comments from stakeholders until August 31, 2016.

UK Regulator Recalls Progesterone Produced by India-Based Akums Drugs and Pharmaceuticals
The UK's Medicines and Healthcare Products Agency has ordered India's Akums Drugs and Pharmaceuticals to recall four batches of progesterone produced at its Hardiwar facility

due to critical deficiencies uncovered during an April 2016 inspection. The Statement of Non-Compliance with GMP published on the EudraGMP website noted that one critical and three major deficiencies were uncovered during the inspection. The critical deficiency was for lack of sterility assurance, and the major deficiencies were for inadequate control and validation of sterilization, deficiencies across all aspects of the quality management system, and lack of a robust environmental monitoring program. Thirteen other deficiencies covering all aspects of GMP were recorded but not formally reported so as not to distract from the critical and major deficiencies.

EMA Publishes Report on Regulation of Advanced Therapy Medicines
On June 3, 2016, EMA published its report from a multi-stakeholder meeting held to explore possible ways to foster the development of Advanced Therapy Medicinal Products ("ATMPs") in Europe and expand patients' access to these new treatments. ATMPs comprise gene therapies, tissue engineered products, and somatic cell therapies. According to EMA, such medicines have the potential to reshape the treatment of a wide range of conditions, particularly in disease areas where conventional approaches are inadequate. However, eight years since EU legislation on ATMPs entered into force in 2008, only five ATMPs are currently authorized. The report details concrete proposals to encourage development and authorization of ATMPs in the EU.

First Financial Penalty Decision by the French ANSM
On May 19, 2016, the French National Drug and Health Product Authority ("ANSM") posted on its website its first two financial penalty decisions, adopted on May 12, 2016. The May 2016 decisions were taken against two medical device manufacturers that had advertised their products (through an ad in professional publications or direct mail) without a prior authorization by the ANSM. These decisions remained available on the ANSM website for one month. While the ANSM has been empowered by an Act dated December 29, 2011, to impose financial penalties on health care companies ("HCCs"), the French authorities had not taken such opportunity until May 2016. The industry was expecting the ANSM to start using financial penalties, considering the ANSM's increasingly stringent policy.

Financial penalties may become another powerful tool against HCC, as they are based on the annual turnover of an HCC for all or part of the products sold in France (not including exports or taxes), although the financial penalties cannot reach more than €1 million. The penalties imposed in May 2016 were respectively €28,756 and €315. It seems, based on the explanations given by the ANSM for the most lenient decision, that the decision to impose a small penalty was based on the diligence shown by the HCC to take corrective measures regarding the noncompliance.

Noncompliance that may result in financial penalties by the ASNM include in particular violation of pharmacovigilance obligations, noncompliance with GMP, and failure to make mandatory notifications to the ANSM regarding the level of sale or stock of some products, and also violation of advertisement regulations, regarding pharmaceutical specialties as well as medical devices.

Jones Day FDA Regulatory & Compliance Counseling Contacts

Edgar Asebey
Miami
+1.305.714.9707
easebey@jonesday.com

Maureen Bennett
Boston/San Francisco
+1.617.449.6884/
+1.415.875.5772
mbennett@jonesday.com

Cristiana Spontoni
Brussels
+32.2.645.14.48
cspontoni@jonesday.com

Colleen M. Heisey
Washington
+1.202.879.3449
cmheisey@jonesday.com

Christian B. Fulda
Munich

Chiang Ling Li
China

Katherine M. Llewellyn
Brussels
+32.2.645.14.47

Katherine S. Makielski
Chicago

+49.89.20.60.42.200
cfulda@jonesday.com

+852.3189.7338
chianglingli@jonesday.com

kllewellyn@jonesday.com

+1.312.269.4269
kmakielski@jonesday.com

Laura E. Koman
Washington
+1.202.879.3601
lkoman@jonesday.com

Follow us on:

Jones Day is a legal institution with 2,400 lawyers on five continents. We are One Firm Worldwide[SM].