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Guidance for European MA Holders to Prepare for Brexit

The EMA has published a Q&A guidance for marketing authorization holders of centrally authorized medicinal products to prepare for the United Kingdom's withdrawal from the European Union. This follows an earlier notice issued by the EMA and the European Commission calling for marketing authorization holders to prepare in advance and proactively screen authorizations they hold and to apply to make any necessary changes in good time.
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EMA Calls for Public Consultation on Clinical Trial Protocol

The EMA has opened for public consultation a draft guideline for the notification of serious breaches of the Clinical Trial Protocol (Regulation (EU) No 536/2014). The guideline is intended to provide advice on what is to be classified as a serious breach and sets out the types of incidents that should be reported. The consultation is open until August 22, 2017.

New French Decree Clarifies the Scope of Biomedical Research

French Decree n° 2017-884 of May 9, 2017, was adopted to implement certain provisions of the Legal Ordinance of June 16, 2016, with respect to biomedical research. Such research should now be referred to as "research involving human subjects." The new decree defines the scope of RIPH as investigations organized and carried out on willing participants, in the context of developing biological or medical knowledge.
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Publications of Interest

Supreme Court Opines in *Sandoz Inc. v. Amgen Inc.*: Biosimilar Applicants May Provide Commercial Marketing Notice Before FDA Approval

By Gasper J. LaRosa, Jennifer J. Chheda, Matthew J. Hertko, Timothy J. Heverin

On June 12, 2017, the United States Supreme Court issued an opinion in *Sandoz Inc. v. Amgen Inc.* The Court decided two important questions under the Biologics Price Competition and Innovation Act ("BPCIA"), which provides an abbreviated pathway for the approval of generic biologics: (i) the BPCIA's requirement that an applicant provide its abbreviated biologics license application and manufacturing information to the sponsor of the referenced product is not enforceable through an injunction under federal law (although it may be under state law); and (ii) an applicant's required 180-day "notice of commercial marketing" is effective even if given before the FDA has approved the application.

A Jones Day *Commentary* provides a detailed overview of the opinion and its implications.

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The Agency is reorganizing the ORA staff in order to help the FDA implement the Food Safety Modernization Act signed by President Barack Obama in 2011. The ORA will more closely mirror the Agency's organizational model and enhance the effectiveness of its communications and processes to keep pace with scientific innovation and protect public health, according to the website.

Prior to the reorganization, the 20 ORA district offices reported to five regional heads. After implementing the ORA's new program-based management model, there are seven key programs for operations:

- Pharmaceutical quality
- Medical devices
- Tobacco
- Animal and human food
- Biologic drugs, which are made from living organisms and include vaccines
- Research, including protecting research subjects and ensuring data quality
- Enforcement and import operations.

Except for the tobacco product office, each product-specific office is, in turn, organized in two or more regional divisions, which will be served by the agency's 20 existing districts and 13 field laboratories. According to the FDA, the field laboratories also will be aligned by product area, focusing on food, medical products and tobacco, or both.

In departing from the ORA's historic geography-based model, the ORA staff will now specialize in the specific substantive areas and will no longer do work in more than one program area. The FDA envisions that these changes will result in a high level of technical expertise and more uniform application of the ORA's policies and processes.

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On May 15, 2017, Senators Charles Grassley (R-IA), John McCain (R-AZ), and Amy Klobuchar (D-MN) sent a letter to the Office of Management and Budget ("OMB") Director Mick Mulvaney prompting him to work with the Department of Health and Human Services' Secretary, Tom Price, to lower prescription drug costs and to certify the importation of prescription drugs from Canada, where drug prices, in many instances, are half the cost. This letter follows a previous request from February 14, 2017, that the same senators made to Secretary Price.

The May letter follows on their previous request, which urged the Secretary to exercise authority granted under the Medicare Prescription Drug Improvement and Modernization Act of 2003 ("Act"). The Act provides FDA with the authority to permit pharmacists and wholesale retailers to import prescription drugs from Canada, as well as to issue waivers to individuals to import prescription drugs for personal use. As the letter states, FDA's authority over importation of prescription drugs cannot be exercised unless the Secretary first certifies importation would pose no additional risk to the public's health and safety and would result in a significant reduction in the cost of covered products to the American consumer. It is in this context that the senators requested the Secretary to use existing statutory authority to fast-track the approval of less expensive prescription drugs from Canada and thus restore competition to the market.

Acknowledging the difficulty of meeting the standard, the senators proposed that the Secretary limit certification of importation to the following cases: (i) the drug is off patent or no longer marketed in the United States by the innovator company that initially developed the drug; (ii) in cases where there are significant and unexplained increases in price; (iii) no direct competitor drug is currently in the market, and introduction of a competitor drug will benefit the prices paid by taxpayers and consumers; or (iv) the drug is produced in another country by the same brand manufacturer that initially developed the drug or by a well-known generic manufacturer that commonly sells pharmaceutical products in the United States.

In addition, senators welcome his support to bring down the costs of prescription drugs through the personal importation program set forth in the Safe and Affordable Drugs from Canada Act, which was reintroduced on January 9, 2017, by Senators McCain and Klobuchar. If the program becomes law, it would allow individuals to import prescription drugs from an approved Canadian Pharmacy if: (i) dispensed by a pharmacist licensed in Canada; (ii) purchased for personal use in quantities not greater than a 90-day supply; (iii) filled using a valid prescription issued by a physician licensed to practice in the United States; and (iv) the imported drug has the same active ingredients, route of administration, dosage form, and strength as a prescription drug approved under the Federal Food, Drug and Cosmetic Act.

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EMA Green Lights New EudraVigilance System for Adverse Reactions

On May 22, 2017, the European Medicines Agency ("EMA") announced the full functionality of the new EudraVigilance system for the collection and monitoring of suspected adverse reactions with medicinal products that are authorized or being studied in clinical trials in the European Economic Area ("EEA"). In accordance with Article 24(2), third subparagraph of Regulation (EC) No 726/2004 of the European Parliament, and of the Council of March 31, 2004, the EMA confirmed the EudraVigilance database is fully functional and meets necessary functional specifications after the consideration of an independent audit and subsequent favorable recommendation by the Pharmacovigilance Risk Assessment Committee.

The new and improved version of the EudraVigilance database will be launched on November 22, 2017. The system's enhanced functionalities for reporting and analyzing suspected adverse reactions aim to better support the safety monitoring of medicinal products and intend to allow a more efficient reporting process for stakeholders. More specifically, the EMA expects the new EudraVigilance database to bring the following benefits:

- Marketing authorization holders will no longer be required to submit individual case safety reports ("ICSRs") to individual national competent authorities. They will submit such reports directly to EudraVigilance, resulting in a simplified reporting of ICSRs;

- The centralized nature of the EudraVigilance database will enable better detection of new or changing safety issues, allowing rapid action to protect public health;

- The broad access to reports of suspected adverse reactions by health care professionals and the general public via a public interface will increase transparency concerning suspected adverse reactions in the EEA;

- The enhanced database will result in increased system capacity and performance to support the large volumes of users and reports; and

- Since the EMA will make the reports of individual cases of suspected adverse reactions within the EEA available to the World Health Organization ("WHO") Uppsala Monitoring Centre directly from EudraVigilance, there will be more efficient collaboration with the WHO.

To prepare for the system's official launch, users—including national authorities, marketing authorization holders, and clinical trial sponsors—must adapt their processes and local IT infrastructures to ensure they are compatible with the new system. Marketing authorization holders must be ready to start submitting all suspected adverse reactions into the new EudraVigilance system six months after its launch (i.e., around May 2018).

The EMA announced it intends to support national authorities, marketing authorization holders, and clinical trial sponsors in the EEA through targeted e-learning and face-to-face training, webinars, and information days. In addition, users will be able to test the new functions of the EudraVigilance system and the internationally agreed format for ICSRs in a test environment available on June 26, 2017.

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EU Medical Device Regulation 2017/745 and In Vitro Diagnostic Regulation 2017/746

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These Regulations will replace the current Medical Devices Directive (93/42/EC on medical devices), the Active Implantable Medical Devices Directive (90/385/EC on active implantable medical devices), and the In Vitro Diagnostics Directive (98/79/EC on in vitro diagnostic ("IVD") medical devices). The new Regulations are designed to improve the quality, safety, and reliability of medical devices and in vitro diagnostics; to strengthen transparency of consumer information; and to enhance vigilance and market surveillance while supporting innovation.

Summary of the Key Changes

Below is a high-level summary of some of the key changes brought by the MDR and IVDR to the regulatory framework applicable to medical devices.

Inclusion of Products Without Medical Purpose and New Classification Rules. Certain groups of products that do not have an intended medical purpose but that present a risk profile similar to medical devices have been included in the scope of the new MDR. Examples include contact lenses; facial, dermal, or mucous membrane filling substances or articles; and liposuction equipment and laser equipment for skin treatment. For IVDs, entirely new risk-based classification rules have been introduced by the IVDR. Beginning May 26, 2022, IVD medical devices will have to be categorized in classes A to D.

New Post-Market Clinical Requirements. As of the date of application of the new Regulations, medical device manufacturers will be required to include a post-market clinical follow-up or post-market performance follow-up (for IVDs) in their post-market surveillance system in order to continuously update the clinical evaluation of the device. For implantable and class III devices, a summary of safety and clinical performance must be drawn up by manufacturers and validated by notified bodies before being made publicly available.

Stricter Rules for Notified Bodies. All notified bodies will have to be redesignated under the MDR/IVDR and comply with all requirements laid down in the respective Annex VII of the new Regulations. Notified bodies must employ medically trained staff and, among other things, must have documented procedures regarding unannounced on-site audits of manufacturers and, where applicable, of subcontractors and suppliers. The MDR and IVDR also introduce a mechanism for scrutiny of certain high-risk medical devices. Under this procedure, a manufacturer's notified body will be required to notify the competent authorities of certificates it has granted for such high-risk devices. The competent authorities and, where applicable, the European Commission may request scientific advice from expert panels in relation to the safety and performance of any device, based on its reasonable concerns.

Introduction of the Unique Device Identification ("UDI") System. The new Regulations enhance traceability requirements of medical devices throughout the supply chain by requiring that a UDI be affixed to a medical device or to its packaging. Each component that is considered a device and is commercially available on its own will be assigned a separate UDI.

Joint Responsibility of Authorized Representatives. Non-EU manufacturers of medical devices and IVDs must appoint a European Authorized Representative in the European Union. Under the new Regulations, the European Authorized Representative will be responsible for verifying that the EU Declaration of Conformity and technical documentation have been drawn up by the manufacturer and, where applicable, that an appropriate conformity assessment procedure has been conducted. Most importantly, the European Authorized Representative would be legally liable, jointly and severally, with the manufacturer, for defective devices placed on the EU market if the medical devices are not compliant with the Regulations' requirements.

Increased Transparency. The UDI, along with post-market vigilance data and ongoing clinical investigations, must be entered into the European Databank on Medical Devices ("EUDAMED"), which will become accessible to the public. The EUDAMED database is expected to be put into place by 2020.

Transitional Provisions

The two Regulations include transitional provisions permitting CE Certificates of Conformity issued by notified bodies in accordance with the current Directives and prior to May 25, 2017, to remain valid until the end of the period indicated on the Certificates. Notified bodies will also be allowed to issue CE Certificates of Conformity in accordance with the current Directives after May 25, 2017. These Certificates will be issued for a period of validity not exceeding five years and will become void at the latest on May 27, 2024.

It should be noted that medical devices to which these Certificates relate may be placed on the EU market or put into service in the European Union only if, from May 26, 2020, or May 26, 2022, as the case may be, they remain in compliance with the relevant current Directives, and provided there are no significant changes in the design and intended purpose of the medical devices. Moreover, there will be related changes in some obligations related to the devices. The requirements of the MDR and IVDR relating to post-market surveillance, market surveillance, vigilance, and registration of economic operators and of devices will apply in place of the corresponding requirements in the Medical Device and In Vitro Diagnostic Directives.

Conclusion

Medical devices that comply with the MDR may be placed on the EU market before the MDR date of application (anticipated in May 2020) if they have been audited by a notified body designated under the MDR. Notified bodies can apply for redesignation from six months after the regulations take effect. They can test for compliance with the MDR requirements only once they have been redesignated. It has been reported that this process could take up to 18 months from the date of application for redesignation.

Therefore, in addition to monitoring the validity of their Certificates of Conformity, medical device manufacturers should ensure as soon as possible that their notified bodies will be redesignated or otherwise, initiate the process of contracting with a notified body that meets the new requirements of the new Regulations and will therefore be redesignated quickly.

In addition, the European Commission is set to adopt approximately 80 delegated and implementing acts to further specify applicable requirements and obligations under the new Regulations. Manufacturers of medical devices and in vitro diagnostics should monitor closely relevant developments.

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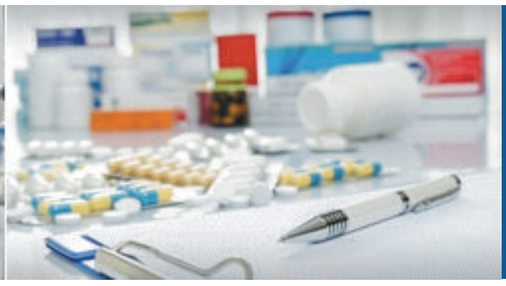

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Guidance for European MA Holders to Prepare for Brexit

The EMA has published a Q&A guidance for marketing authorization ("MA") holders of centrally authorized medicinal products to prepare for the United Kingdom's withdrawal from the European Union. This follows an earlier notice issued by the EMA and the European Commission ("EC") calling for marketing authorization holders to prepare in advance and proactively screen authorizations they hold and to apply to make any necessary changes in good time.

The guidance confirms that UK-based pharmaceutical companies will be required to transfer their marketing authorizations and orphan designations for their medicines to entities established in the EEA when Brexit takes effect. They also must ensure that the qualified person for pharmacovigilance activities as well as the pharmacovigilance system master file are located within the EEA. In addition, there is guidance regarding relocation of manufacturing sites, batch control, and batch release sites. A similar set of guidance has been issued by the Co-ordination Group for Mutual Recognition and Decentralised Procedures, which is responsible for coordinating nationally authorized medicines between two or more EU Member States.

Marketing authorization holders should carefully review the guidance and consider how this affects their product portfolio. The administrative processes involved may require significant resources and are likely to be time-consuming, so it is recommended that companies start the planning process immediately. The EMA has set up a dedicated website with additional guidance for companies, which will be updated as further information becomes available.

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More specifically, RIPH may include investigations regarding: (i) functioning mechanisms of a human organism (whether normal or pathological); or (ii) the efficiency and safety of actions undertaken, or the use of products for the purposes of diagnostic, treatment, or prevention of a pathological state. Investigations regarding cosmetic products, even if carried out on normal or pathological human subjects, do not qualify as RIPH as long as the purpose of such research is to test the product's capability to clean, perfume, change the appearance of human bodies, correct body odors, and/or protect human bodies.

Additionally, research that includes only a satisfaction survey regarding cosmetic or food products, any other type of satisfaction survey among patients, or experimentations in human or social science in the health field should not be considered RIPH. It should be noted that such definition seems to contradict the terms of a ministerial order dated May 3, 2017. The Order states that noninterventional RIPH on cosmetic or food products does not require the opinion of an ethics committee, nor does it require registration if such investigation includes only interviews or surveys regarding the subject's feelings about the efficiency or tolerance of the product.

The Decree of May 9, 2017, also creates a reduced application file for any noninterventional research that includes only interviews or surveys (on other products than cosmetics or food, as mentioned above). Such provision is mainly designed to facilitate thesis or research memos by health professional students, but it may also benefit the industry.

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