Frequently Asked Questions / The Mutual Recognition Agreement
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Email Inquiries: FDA-MRA@fda.hhs.gov

Q1: What is the purpose of a Mutual Recognition Agreement?

A1: Mutual Recognition Agreements are agreements between two or more countries to recognize a specific process or procedure of the other country.

In 1998, the U.S. and the EU signed the Agreement on Mutual Recognition between the European Community and the United States of America (U.S.-EU MRA), which included a Pharmaceutical Annex providing for recognition of each other's GMP inspections. However, this Annex was never fully implemented.

The 2017 amended Sectoral Annex to the 1998 U.S.-EU MRA allows the FDA and the EU inspectorates to use inspection reports and other related information obtained during drug manufacturing facility inspections, whether conducted by an EU inspectorate or by the FDA, to help determine whether a facility is manufacturing high quality drugs. Then, if necessary, the FDA or EU can require further inspections or take other action to protect the public.

Q2: What are the benefits of Mutual Recognition?

A2: Strengthening use of each other's drug inspection expertise and resources will result in greater efficiencies for both regulatory systems and provide a more practical means to oversee the large number of drug manufacturing facilities outside of the U.S. and EU.

Until now, the EU and the FDA sometimes would, in the same year, inspect some of the same facilities even if the facilities had a strong record of compliance. With the 2017 Amended Sectoral Annex, such duplication should be the exception. By utilizing each other's inspection reports and related information, the FDA and EU will be able to reallocate resources towards inspection of drug manufacturing facilities with potentially higher public health risks across the globe. This will benefit patients and reduce adverse public health outcomes.

Q3: What is the scope of the Mutual Recognition Agreement?

A3: The scope of the Amended Sectoral Annex covers a broad range of human drugs and biologics and veterinary drugs with specific exclusions. Veterinary products are not immediately included within the scope of the agreement, but will be considered for inclusion within the product coverage of the agreement by no later than July 15, 2019.

Current good manufacturing practices (CGMPs) inspections of facilities manufacturing vaccines and plasma derived products are not immediately included within the scope of the agreement. The possibility of including vaccines and plasma derived products will be re-evaluated no later than July 15, 2022.

Human blood, human plasma, human tissues and organs, and veterinary immunologicals are not included within the scope of the Amended Sectoral Annex.

Q4: Is the Mutual Recognition Agreement with the entire EU or with 28 individual countries?

A4: The Mutual Recognition Agreement is between the U.S. and the EU. However, the FDA will conduct an assessment of each country's regulatory

authority individually. The capability assessments of all EU countries' inspectorates are scheduled to be completed by 15 July 2019.

Q5: How does the FDA know when another inspectorate is capable of conducting drug manufacturing facility inspections that meet U.S. requirements?

A5: The MRA text defines a capable inspectorate as one that:

- has the legal and regulatory authority to conduct inspections against a standard for GMP;
- manages conflicts of interest in an ethical manner;
- evaluates risks and mitigates them;
- maintains appropriate oversight of manufacturing facilities within its territory;
- receives adequate resources and uses them;
- employs trained and qualified inspectors with the skills and knowledge to identify manufacturing practices that may lead to patient harm; and
- possesses the tools necessary to take action to protect the public from harm due to poor quality drugs or medicinal products.

"Capable" does not require that the inspectorate maintain procedures for conducting inspections and overseeing manufacturing facilities that are identical to the FDA's procedures.

Q6: How does the FDA determine an inspectorate's capability in the EU and what actions have the FDA taken as of March 2, 2017?

A6: The EU is made up of 28 countries each with its own inspectorate(s). Although the overall legal requirements and guidelines for drug inspectorates exist at the EU level, some discretion is necessarily left to the individual countries to

implement the law in the best way for them. Therefore, the FDA believes that it must assess each country's inspectorate(s).

In September 2014, the EU invited the FDA to observe the EU's internal audits of its inspectorates. These audits are meant to ensure consistency across all of the EU inspectorates by assessing each country's inspectorate's processes, workforce skills and compliance with EU laws and, in particular, relevant guidelines. As of March 2, 2017, the FDA has observed the audits of human drug inspectorates in Sweden, Greece, Germany, Croatia, United Kingdom, Czech Republic, Hungary, Italy, Austria, Lithuania, Romania, Malta, Spain and Estonia. The goal is to observe scheduled audits of every EU country before the end of 2017.

The FDA's capability assessment begins with observing the EU's internal audit of an EU country to ensure that the inspectorate is functioning properly and does not deviate in any significant way from EU law and guidance. These audits include observations of drug manufacturing facility inspections conducted by the audited inspectorates and utilize the 78 indicators based on the Pharmaceutical Inspection Co-operation Scheme (PIC/S) compliance assessment program with an EU addendum. PIC/S is an internationally recognized cooperative arrangement between 49 regulatory authorities, including the FDA. The goal of PIC/S is to harmonize inspection procedures worldwide and develop common standards in the field of good manufacturing practices.

After observing an audit of a country's drug inspectorate, the FDA conducts an independent and comprehensive assessment. This assessment includes a review of the country's conflict-of-interest policies, specific legislation related to good manufacturing practices, samples of inspection reports, inspector training records, inventory of drug manufacturing facilities, surveillance program, and numerous standard operating procedures.

Maintenance provisions are also included in the Annex to ensure that each capable country continues to meet FDA requirements.

Q7: Are the credentials for EU pharmaceutical inspectors comparable to FDA investigators?

A7: The FDA evaluates pharmaceutical inspectors' credentials as part of the capability assessment of each EU country. We believe it is important for the authorities to employ trained and qualified inspectors with the skills and knowledge to identify manufacturing practices that may lead to patient harm.

Q8: Has the EU evaluated the FDA?

A8: Yes. In September 2015, EU officials visited three FDA district offices, the White Oak, Maryland, headquarters complex and an FDA laboratory as part of its assessment. The EU team applied the same criteria that it applies within the EU when it audits its own countries. In late 2016, the EU also observed the FDA conducting an inspection as part of its evaluation. The EU assessment of the FDA will formally be concluded by July 2017.

Q9: Does this Mutual Recognition Agreement mean that FDA inspectors will never inspect in the EU?

A9: No. Both the FDA and the EU reserve the right to inspect at any time and in any country. It is however expected to be the exception rather than the rule since, following positive capability assessments, the FDA will recognize the EU inspectorates as capable and thus recognize their drug manufacturing facility inspections.

Q10: If the EU takes an enforcement action against a facility after conducting an inspection, does the FDA have to take the same action, or vice versa?

A10: No. The FDA and EU will individually rely upon the facts obtained from an inspection. Although we expect the impact of different enforcement actions to be similar, the FDA and EU have different legal systems and enforcement tools and can take different enforcement actions.

Q11: What happens now that the 1998 Pharmaceutical Sectoral Annex has been amended?

A11: The EU and the FDA will expand use of the information generated from our respective drug manufacturing facility inspections and expect to be able to decrease the number of inspections each conducts in the other's territory, and reallocate those resources to inspecting facilities in areas of higher risk.

Q12: When does the Mutual Recognition Agreement enter into force?

A12: Many provisions of the agreement have already entered into force. Others will enter into force on November 1, 2017.

Q13: Will FDA begin using a recognized member state's inspection reports from the date of the formal recognition, which is usually the milestone date found in the MRA?

A13: FDA will begin using reports of inspections conducted even earlier than the formal recognition date. For each recognized human drug regulatory authority, FDA will determine an *MRA Reference Date* using the following considerations:

- Completion of a European Union's (EU) Joint Audit Programme audit, with all corrective actions appropriately addressed;
- FDA's review and determination that the EU's conflict of interest provisions provide the same level of impartiality as FDA; and
- Completion of any corrective actions identified by FDA.

This reference date will in fact precede the formal recognition date, which generally coincides with an MRA milestone deadline.

Q14: The MRA defines "post-approval inspections" to mean CGMP surveillance inspections, which are conducted periodically after a product is approved for marketing. How does this differ from FDA's Post-Approval Audit Inspection program?

A14: FDA's Post-Approval Inspection program is an inspection of manufacturing controls associated with specific drug products in recently approved applications (marketing authorizations). The products (and related facilities) inspected are carefully selected by the application assessors and preferentially cover higher risk manufacturing operations, evaluation of changes to manufacturing operations such as the transition from smaller to larger scale operations, and verification that manufacturing processes have been appropriately validated. These inspections are generally timed to occur soon after initial commercial distribution and often before and separate from a general CGMP surveillance inspection.

Q15: The MRA includes pre- and post-approval inspections? Why is FDA focused only on CGMP surveillance inspections?

A15: The MRA facilitates greater information sharing, which helps the FDA and recognized human drug regulatory authorities increase efficiency by reducing duplicate inspections, which then enables inspectional resources to be allocated to other higher risk sites and operations. Reducing duplicate CGMP surveillance inspections will provide the greatest impact on achieving the MRA goals. Therefore, FDA is currently focused on successfully implementing the sections of the MRA that are relevant to CGMP surveillance inspections. Application-specific inspections, such as pre-approval and FDA's post-approval inspections, are within the scope of the MRA; however, because these inspections are based upon the application submitted to a specific human drug regulatory authority, additional coordination and assessments are required.

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