U.S.-EU Mutual Recognition Agreement / Frequently Asked Questions and Answers July 2023

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

The following is a link to the 1998 U.S.-EU MRA:
Agreement on Mutual Recognition Between the European Community and the United States of America

The 2017 amended Sectoral Annex to the 1998 U.S.-EU MRA allows the FDA and the EU regulatory authorities to use inspection reports and other related information obtained during current Good Manufacturing Practice (GMP) surveillance inspections, whether conducted by an EU authority 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 products are covered under the U.S.-EU MRA?
A2: Products covered under the U.S.-EU MRA are listed in Appendix 3. Specifically for animal drugs, the MRA covers veterinary pharmaceuticals, including prescription and non- prescription drugs, with the exclusion of veterinary immunologicals; pre-mixes for the preparation of veterinary medicated feeds (EU); and Type A medicated articles for the preparation of veterinary medicated feeds (U.S.).

Q3: What are the benefits of Mutual Recognition?
A3: 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 United States and EU.
Prior to implementing the MRA, 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 has been the exception. By utilizing each other's inspection reports and related information, the FDA and EU have been 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.

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

A4: The Mutual Recognition Agreement is between the U.S. and the EU. However, the FDA assesses each country's regulatory authority individually. Although the overall legal requirements and guidelines for drug inspectorates were regulated at the EU level, some discretion is necessarily left to the individual countries to implement the laws in their country. For this reason, the FDA determined that an assessment of each country's regulatory authority was necessary. The capability assessments of all EU countries' human drug regulatory authorities were completed by 11 July 2019. On 30 May 2023, the FDA completed capability assessments for 16 EU regulatory authorities of veterinary drugs.

Q5: What does the FDA mean by the term "capable"?

AS: The MRA text defines a capable regulatory authority 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 regulatory authority maintain procedures for conducting inspections and overseeing manufacturing facilities that are identical to the FDA's procedures.

Q6: How has the FDA determined a regulatory authority's capability in the EU?

A6: The European Union is made up of 27 countries each with its own regulatory authority(s). Although the overall legal requirements and guidelines for regulatory authorities 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 undertook to assess each country's regulatory authority(s).

In September 2014, the EU invited the FDA to observe the EU's internal audits of its regulatory authorities. EU' s internal audits are meant to ensure consistency across all the EU countries by assessing each regulatory authority's processes, workforce skills and compliance with EU laws and, in particular, relevant guidelines.

The FDA's capability assessment process begins with observing the EU's internal audit of an EU country to ensure that the authority 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 authorities 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 over 50 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 authority, 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 each capable country continues to meet FDA requirements.

Q7: What is the MRA Reference date:
A7: To obtain the most benefit from a capability determination, FDA calculates a specific date that precedes the formal recognition date, known as the *MRA Reference date*. FDA considers the latest PIC/S reassessment, the MRA partner's conflict of interest provisions, completion of corrective and preventive actions to determine the *MRA Reference date*. FDA will use reports of inspections from MRA partners that are completed on or after the *MRA Reference date*.

Q8: Has the European Union evaluated the FDA?
A8: Yes. The EU assessment of the FDA for human drugs was formally concluded in July 2017. The EU assessment of FDA for animal drugs was formally concluded July 27, 2022.

Q9: Do countries in the European Union share GMP surveillance inspection reports with the FDA and vice versa?
A9: Yes. The foundation of this agreement is the ability to share information, particularly GMP surveillance inspection reports. With the passage of the Food and Drug Administration Safety and Innovation Act in 2012, Congress gave the FDA the authority to share certain types of trade secret information relating to drug facility inspections and investigations without first obtaining written sponsor consent with foreign governments provided that certain requirements are met. The FDA must first certify that the government has the "authority and demonstrated ability" to protect trade secret information from disclosure. Once certified, the FDA needs to obtain a written agreement that includes a commitment from the foreign government to protect the information exchanged from disclosure.

The FDA has certified that the national governments of all EU countries have the authority and demonstrated ability to protect trade secret information from disclosure and has obtained written agreements from all EU human drug regulatory authorities. Therefore, FDA is able to share GMP surveillance inspection reports containing trade secret information with EU country authorities

Q10: Does this Mutual Recognition Agreement mean that FDA inspectors will never inspect in the European Union?
A10: No. Both the FDA and the EU reserve the right to inspect at any time and in any country. However, surveillance inspections are expected to be the exception rather than the rule. Following positive capability assessments, the FDA will recognize the EU authorities as capable and thus recognize their drug manufacturing facility inspections.

Q11: What percentage of drug manufacturing facility inspections is relied upon under this Mutual Recognition Agreement?
A11: We have not set any target percentage. Our intent is that we will routinely rely on information obtained from surveillance inspections conducted by capable EU authorities.

Q12: If the European Union takes an enforcement action against a facility after conducting an inspection, does the FDA have to take the same action, or vice versa?
A12: No. The FDA and European Union will individually rely upon the facts obtained from an inspection. Although the impact of different enforcement actions is similar, the FDA and EU have different legal systems and enforcement tools and can take different enforcement actions.

Q13: How does the FDA use resources saved from EU drug manufacturing facility surveillance inspections?
A13: The FDA has a robust risk-based model for surveillance that determines which drug facilities should be inspected each year. With the amended Pharmaceutical Sectoral Annex to the U.S.-EU Mutual Recognition Agreement in place, the FDA is able to shift resources on drug manufacturing facility inspections in the EU to other areas of higher risk.

Q14: What is the FDA's interpretation of the MRA as it relates to the inclusion of application-based inspections?
Q14: FDA conducts several types of inspections to ensure protection of consumers and patients from unsafe products. Among the types of inspections, there are good manufacturing practice (GMP) surveillance inspections to routinely monitor whether a manufacturer is complying with GMP requirements. In addition, FDA conducts application-based inspections (i.e. pre-approval and post-approval inspections). FDA's pre-approval inspections are part of the marketing application review process to determine whether the product is manufactured in compliance with FDA regulations, to verify authenticity of the data submitted in the application, and to ensure the facility is capable of manufacturing the product consistently and in conformance with application. Pre-approval inspections must be tailored to the underlying application and FDA uses information from the inspection in conjunction with other information to determine whether to approve a drug application within a specific and mandatory timeline.

Post-approval inspections are similar to pre-approval inspections in that they are also application-based, but unlike pre-approval inspections, they are conducted after applications have been approved. This type of inspection ensures commercial-scale processes for an approved drug product conform to application commitments and GMP requirements. Findings from these inspections will inform potential GMP application driven actions, e.g., enforcement actions, requested changes to an approved application, and modification to an application's change reporting

strategies. FDA utilizes risk-based strategy and approach to determine a need for a pre-approval or a post-approval inspection and its associated inspectional coverage.

FDA's intent is to enable sharing of GMP surveillance inspections and application-based inspections information. However, the sharing and use of application-based inspections would occur only after FDA and our MRA partner's review and thorough understanding of each other's pre-approval and post-approval inspection programs. FDA will leverage inspection information, including inspection reports, shared by MRA partners on surveillance inspections, to help FDA inform a risk-based decision on a need of a pre-approval or post-approval inspection.

Q15: Does this agreement mean that the FDA will recognize inspections completed by regulatory authorities under the agreement only in their respective countries or will the FDA recognize inspections by capable authorities regardless of the location? For example, would the FDA recognize an inspection done in India or China by a recognized member state?

A15: Article 8.3 provides the FDA and EU the option to rely on inspection reports issued by a recognized authority for manufacturing facilities located outside our respective territories. Therefore, the FDA and EU have the option to rely on inspection reports issued by a recognized authority for manufacturing facilities located outside our respective territories.

Q16: What would happen if the United States and a recognized (i.e., capable) EU regulatory authority had different outcomes after inspecting the same facility?
A16: Although the FDA and recognized authorities from the EU use essentially harmonized quality standards and the same underlying principles of current good manufacturing practices, it is important to note that inspections are a snapshot in time. It is the responsibility of the investigators/inspectors to only note what they see during the course of the inspection at a particular time. Therefore, observations made by one investigator/inspector at a given time may not be observed by another investigator/inspector at a different time. In other words, every inspection will have its own set of observations that may or may not overlap.

The MRA fosters collaborative efforts between trusted regulators to engage in discussions related to inspectional findings and outcomes. These discussions provide a platform for regulators to examine and ask questions about each other's inspectional processes to better understand each other's regulatory and enforcement frameworks. Open dialogue and collaboration between regulators will help determine the reasons why their inspections resulted in different outcomes. This information allows the regulators to learn from each other's best practices and update their collective standards and inspectional processes, as appropriate.

Q17: How does FDA ensure that only quality products enter the United States when it accepts a capable European Union (EU) regulatory authority's inspection report?
A17: The FDA undertakes a rigorous process to formally recognize an EU regulatory authority. The FDA has developed a robust assessment method and decision-making tools to determine if an authority is capable of conducting drug manufacturing facility inspections according to our standards. The FDA's assessment of each authority individually ensures that any variations between authorities are evaluated for compliance with our standards.

Under the amended Pharmaceutical Annex to the 1998 U.S.-EU Mutual Recognition Agreement, the FDA will request inspection reports from capable partners. This will enable FDA experts to directly engage the regulatory authority's inspectors in a discussion about a specific drug manufacturing facility. An added benefit of collaborating with other regulators is that we can leverage expertise, learn from each other and update our collective standards, as appropriate.

The MRA allows the FDA to obtain inspectional information we would otherwise not have and along with other FDA data, bolster the FDA's understanding of the potential risk of the products being made at a manufacturing facility. Additionally, we maintain the right to conduct our own inspection if warranted.

Q18: Does the European Union (EU) have an equivalent to the FDA Warning Letter?
A18: No. In the EU, if the outcome of an inspection is that a drug manufacturer (either internal or external to the EU) does not comply with the principles of Good Manufacturing Practices, a statement of non-compliance may be issued. Statements of non- compliance contain information on the nature of the non-compliance and the actions taken or proposed by the issuing authority in order to protect public health. These statements aim to establish a coordinated and harmonized response by the network of EU regulatory authorities for medicines.

A statement of non-compliance means that the products manufactured in the facility are no longer marketable in the EU whereas an FDA Warning Letter is not an enforcement action but an advisory notice informing the regulated industry about violations the FDA documented during an inspection or investigation.

Q19: Is the FDA planning to have a mutual recognition agreement with other countries?
A19: On January 12, 2023, the FDA signed an MRA with Switzerland which covers both human and animal drugs. Before this MRA enters into force, the FDA must determine whether Switzerland is capable of conducting inspections that meet U.S. requirements, and the Swiss Agency for Therapeutic Products (Swissmedic), must make a similar determination with respect to the FDA meeting Swiss requirements. Before the United Kingdom left the EU, it was part of the US-EU MRA. As a result of Brexit, an MRA with the UK entered into force on January 1, 2021. This MRA covers both human and animal drugs.

Q20: Has the process for determining inspection capability for animal drugs been the same as what was done for human drug products?
A20: Yes, the MRA assessment process for animal drugs mirrors the process used for human drug products.

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