

Mutual Recognition Agreement / Frequently Asked Questions and Answers

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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 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 following is a link to the 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 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 United States and European Union.

Prior to implementing the MRA, the European Union 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 European Union 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: Is the Mutual Recognition Agreement with the entire European Union or with individual countries?

A3: The Mutual Recognition Agreement is between the United States and the European Union. However, the FDA completed assessments of 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' regulatory authorities were completed by 11 July 2019.

Q4: What does the FDA mean by the term "capable"?

A4: 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.

Q5: How has the FDA determined a regulatory authority’s capability in the EU?

A5: 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. These audits are meant to ensure consistency across all the EU country by assessing each regulatory authority’s processes, workforce skills and compliance with EU laws and, in particular, relevant guidelines.

The FDA’s capability assessment 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 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 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.

Q6: Has the European Union evaluated the FDA?

A6: 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 European Union officials also observed the FDA conducting an inspection as part of its evaluation. The EU assessment of the FDA was formally concluded in July 2017.

Q7: Do countries in the European Union share GMP surveillance inspection reports with the FDA and vice versa?

A7: 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

Q8: Does this Mutual Recognition Agreement mean that FDA inspectors will never inspect in the European Union?

A8: No. Both the FDA and the European Union 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.

Q9: What percentage of drug manufacturing facility inspections is relied upon under this Mutual Recognition Agreement?

A9: 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.

Q10: 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?

A10: No. The FDA and European Union 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 European Union have different legal systems and enforcement tools and can take different enforcement actions.

Q11: Do agreements like this exist in other areas besides drugs?

A11: Yes. The 2017 Pharmaceutical Annex is one among several annexes associated with the U.S.-EU MRA. Other annexes associated with the U.S.-EU MRA include the Telecommunication Equipment, Electromagnetic Compatibility (EMC), Electrical Safety, Recreational Craft, and Medical Devices.

Similar agreements include the Customs-Trade Partnership Against Terrorism Mutual Recognition Agreement, which allows the exchange of information and recognizes the compatibility of respective supply chain security programs, and the Aviation Safety Agreement between the United States and the European Community. This agreement minimizes duplication of efforts and increases efficiencies by promoting reciprocal acceptance of safety compliance findings and safety equipment approvals for aircraft.

Q12: How will resources saved from EU drug manufacturing facility surveillance inspections be used?

A12: 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 European Union to other areas of higher risk.

Q13: Are pre-approval inspections included under the Mutual Recognition Agreement?

A13: As of July 2019, both the FDA and European Union have been actively engaged in evaluating how best to implement the US-EU MRA for consideration of pre-approval inspections (PAIs). This evaluation is ongoing and in December 2019 both FDA and European Union agreed and have been engaged in jointly developing a PAI capability assessment workplan for mutual recognition of and reliance on each other's expertise for PAI coverage of manufacturing facilities named or referenced in marketing applications (e.g., NDA, ANDAs, BLAs).

In general, the PAI capability assessment workplan under development includes, but is not limited in scope to, the following points of consideration: Capability assessment level (EU centralized vs. individual member state); inclusion and exclusion criteria for application types (e.g., original NDA, ANDA, BLA and supplements), product and manufacturing process specific risks (e.g., unique operations and associated control strategies), manufacturing facility specific risks (e.g., existing vs. new, drug substance (chemical, biotech), drug product, or both), and PAI coverage scope; fellowships with subject matter experts (application assessors) and investigators for joint inspections; protocol for preparation, execution, communication, conclusion and documentation for both independent or joint inspections by FDA and/or EU; milestones and timelines for completion and execution of the workplan.

Efforts are currently underway to complete and finalize the U.S.-EU joint workplan for the PAI capability assessment; however, the work planned and under way is encountering unavoidable delays due to both increased regulator workload and restrictions on activities on both EU and FDA staff during the current COVID-19 pandemic. We plan to update this information periodically as certain milestones under the workplan are reached.

Q14. 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?

A14. Article 8.3 provides the FDA and European Union the option to rely on inspection reports issued by a recognized authority for manufacturing facilities located outside our respective territories. Therefore, the FDA and European Union have the option to rely on inspection reports issued by a recognized authority for manufacturing facilities located outside our respective territories.

The initial capability assessments did not specifically address this, so it will be important for us to understand any variation between approaches to domestic and 3rd country inspections before we can consider relying on inspection reports in 3rd countries. As of July 2020, both the FDA and the EU are exchanging information to better understand if any significant differences exist.

Additional information can be found on:

[United States - European Union Amended Sectoral Annex for Pharmaceutical Good Manufacturing Practices \(GMPs\)](#)

Q15: Now that the U.S.-European Union (EU) Mutual Recognition Agreement is in effect, what would happen if the United States and a recognized (i.e., capable) EU regulatory authority had different outcomes after inspecting the same facility?

A15: Although the FDA and recognized authorities from the European Union 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.

Q16: 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?

A16: 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.

Q17: Does the European Union (EU) have an equivalent to the FDA Warning Letter?

A17: No. In the European Union, 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.

Q18: Is the FDA planning to have a mutual recognition agreement with Canada (Health Canada)?

A18: The U.S.-EU Mutual Recognition Agreement is a landmark achievement. At this time, FDA is focused on working closely with our EU partners on the continued implementation of the measure.

Q19: Does the MRA cover veterinary products?

A19: The scope of the Amended Sectoral Annex covers a broad range of human drugs and biologics as well as veterinary drugs regulated by FDA (at this time, the agreement does not cover veterinary biologics regulated by the United States Department of Agriculture); however, with respect to veterinary products the agreement will not be implemented until the FDA and EU determine the mutually agreed upon criteria required to fully operationalize the MRA for veterinary products. For more information, see [FDA's March 2020 CVM Update](#).

Q 20: Will the process for determining inspection capability for animal drugs be the same as what was done for human drug products?

A 20: Yes, the MRA assessment process for animal drugs closely mirrors the process used for human drug products.

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