SMG 9121

FDA Staff Manual Guides, Volume IV – Agency Program Directives

General or Multidiscipline - Business Practices and Agreements

Framework for Mutual Recognition Agreements and Arrangements Relating to Drugs

Effective Date: 02/13/2023

1. Purpose

This guide establishes a framework for FDA engagement, processes, and considerations with foreign regulatory authorities on matters related to mutual recognition agreements or arrangements for human and animal drug[1] oversight.

2. Policy

Several sections of the Federal Food, Drug, and Cosmetic Act (FD&C Act) authorize FDA to enter into arrangements (including agreements) with foreign regulatory authorities, including mutual recognition agreements relating to drugs. These

[1] As defined under section 201(g) of the Federal Food Drug and Cosmetic Act, subject to any agreement-specific exclusions.

arrangements can be established for a variety of purposes, including ensuring that adequate and effective means are available for determining whether foreign drugs should be refused admission, (FD&C Act § 510(i)), harmonizing regulatory requirements and participating in mutual recognition agreements, (FD&C Act § 803(c)), and reducing the burden of regulation, and achieving appropriate reciprocal arrangements, (FD&C Act § 1003(b)(3)), among others. In addition, FDA is explicitly authorized to enter into arrangements to recognize the inspection of foreign drug establishments to facilitate risk-based inspections (FD&C Act § 809(a)(1)) if the foreign agency has the capability of conducting inspections that meet the applicable requirements of the FD&C Act (FD&C Act 809(a)(2)). Further, FDA may use the results of foreign drug inspections performed by foreign governments under such arrangements as evidence of compliance with section 501(a)(2)(B) or section 801(r), or for any other purposes as determined appropriate by FDA (FD&C Act 809(b)).

3. Scope

Activities relating to drugs, including biological drugs, conducted under this framework include potential foreign regulatory partner identification; agreement negotiation; capability assessment and determination; and implementation and maintenance of the agreement, including reassessments. Processes, policies, and procedures specific to each Center and Office should be developed by them, in alignment with this SMG.

4. Responsibilities

4.1. Office of Global Policy and Strategy (OGPS)

A. Leverages existing relationships with foreign regulatory authorities with similar public health priorities to identify potential mutual recognition partners.

B. Assesses conflict of interest frameworks to determine whether they provide a similar level of protection to those of the United States.

D Serves as the primary point of contact with U.S. interagency counterparts and foreign government entities to facilitate negotiations and finalize agreement terms.

E Ensures FDA’s program interests are adequately represented during negotiations and final mutual recognition agreement or arrangement.

F. Ensures appropriate information exchange arrangements regarding sharing non-public information, are in place and timing supports initial assessment and implementation activities.

G. After or in tandem with agreement negotiations, leads collaborative effort with the Centers, Office of Regulatory Affairs (ORA), Office of Ethics and Integrity,

and the Office of Chief Counsel (OCC), to plan and facilitate initial capability assessments of potential MRA partners.

H. Leads initial capability assessment of foreign regulatory authority.

I. Leads liaison activities and communications with foreign regulatory authority on initial assessment timelines.

J. Participates in ongoing assessment activities and decision making.

K Maintains internal and external websites on impacting MRA activities and status, including confidentiality commitments with foreign regulatory authorities.

L. Establishes and maintains procedures to ensure MRA implementation and maintenance are consistently applied across FDA and across agreements, whenever appropriate.

4.2. Office of Regulatory Affairs (ORA)

A. In accordance with an MRA, develops and executes an audit strategy in collaboration with OGPS and impacted product center(s).

B. Provides expertise in developing (1) mutual recognition agreements and arrangements, and (2) the assessment program, which is a standard program developed to verify the implementation of an authority's legislation, regulations, product approval and good manufacturing practices (GMP) activities to ensure they meet agreed upon standards.

C. Participates in conducting capability assessments and in making capability evaluations and determinations.

D. Leads capability reassessments in collaboration with the Centers, components of the Office of the Commissioner (OC), and OCC.

   1. Plans and executes the capability reassessment, including determining whether it should include a new inspection audit.

   2. Leads liaison activities and communications with recognized regulatory authority on re-assessment timelines.

E. Participates in ongoing assessment activities and decision making.

F. Establishes and maintains ORA-specific procedures relating to MRA implementation and maintenance consistent with procedures established throughout FDA.

4.3. Center program and other related subject matter experts

A. Collaborates with ORA and other agency components on the assessment and reassessment process, decision making, and MRA implementation.

B. Provides expertise in developing agreements as requested by OGPS.

C. Participates in initial assessments and in making capability evaluations and determinations.

D. Participates in ongoing assessment activities and decision-making.

E. Establishes and maintains Center-specific procedures relevant to MRA implementation and maintenance consistent with procedures established throughout FDA.

4.4. Teams Related to Capability Assessment

A. Audit Team - Conducts the on-site assessment of the regulatory authority, including observing inspections of drug manufacturing facilities

B. Primary Assessment Team

1. Includes on-site audit team as well as SMEs from various offices

2. Reviews assessment package provided by the foreign regulatory authority as well as audit team assessments of the regulatory authority and provides recommendations to Secondary Assessment Team

C. Secondary Assessment Team

1. Based on MRA partner's regulatory framework and the FDA-established capability assessment process, determines country-specific evaluation process and criteria, including:

    a. Assessment milestones and timelines
    b. Additional documents to be exchanged
    c. Audit and assessment focus areas

2. Reviews assessment findings and recommendations provided by Primary Assessment Team; and

3. Makes capability determination and identifies reassessment criteria and submits for ratifier consideration.

D. FDA MRA Leadership

1. Comprised of the Commissioner, Office of the Chief Counsel, the Associate Commissioner for Global Policy and Strategy, the Associate Commissioner for Regulatory Affairs and relevant Center Directors or designees.

2. Ratifies the capability determination of the secondary assessment team.

4.5. MRA Governance Subcommittee

A. Provides continuity of oversight as well as guidance and direction regarding activities conducted under this SMG when needed.

B. Ensures relevant stakeholders are informed regarding activities conducted under this SMG by overseeing communications and strategies intended for internal and external audiences.

4.6. MRA Implementation Sub-Group

A. Defines and standardizes FDA processes and procedures to implement MRA provisions.

B. Identifies and resolves roadblocks to implementation.

C. Monitors implementation to identify issues/patterns that require mid-course adjustments.

D. Oversees defined MRA maintenance activities.

5. Process for Capability Determination

5.1. Potential Partner Identification

A. OGPS, in collaboration and alignment with Centers and ORA, will consider the following factors, *inter alia*, when identifying potential MRA partners:

1. Existing regulatory relationship with FDA

2. Benefit to FDA's public health mission

3. Maturity of regulatory framework to provide appropriate oversight of manufacturing facilities

4. Code of ethics and standards of conduct; and

5. Program interests of ORA and drug product centers including establishment inventory and logistical considerations.

5.2. Conflict-of-Interest Evaluation

A. OGPS, in collaboration with FDA's Office of Ethics, will review the foreign regulatory authority's conflict of interest framework to ensure comparable impartiality protections are in place.

5.3. Negotiations

A. OGPS serves as the lead in all internal and external discussions related to agreement negotiation, including:

1. Collaborating and aligning with Centers and ORA to assess the value of MRA partnership, identifying scope, and determining FDA's terms of agreement.

2. Serving as FDA point of contact during negotiations and liaising with interagency counterparts to advocate for and negotiate FDA's position; and

3. Communicating to appropriate agency components the commitments and conditions of the finalized agreement to ensure a full understanding and enable successful implementation. Communications should include scope, commodities, types of inspections, key milestones, and any limitations or exceptions and other items of mutual interest.

5.4. Initial Capability Assessment

A. General considerations

1. As described in the applicable provisions of the relevant MRA, in evaluating the capability of the foreign regulatory authority to conduct inspections for which inspectional findings will be shared and considered for regulatory purposes, the assessment teams will consider whether the foreign regulatory authority:

a. Has the legal and regulatory authority to conduct inspections against a suitable standard for GMPs

b. Maintains appropriate oversight of manufacturing facilities within its jurisdiction

c. Has and uses sufficient resources

d. Employs trained and qualified inspectors with the skills and knowledge to identify manufacturing practices that may lead to patient harm

e. Has the tools necessary to take action to protect the public from harm due to poor quality drugs; and

f. Generates inspection reports with sufficient detail of the areas that were critically assessed during the inspection to support regulatory decision-making.

B. Preparation for Initial Capability Assessment

1. OGPS will:

a. Share the final signed agreement with ORA and any impacted product center(s), and with other OC components, such as OCC as appropriate

b. Convene a meeting to explain the agreement, including information about the scope and legal basis for the agreement

c. Establish Primary and Secondary Assessment Teams comprised of subject matter experts from ORA and impacted Center(s)

d. Facilitate FDA's initial capability assessment with experts from ORA and Centers

e. Along with ORA, liaise with government counterparts on assessment-related activities, including initiating communication with the partnering authority to establish a timeline for assessment

f. With input and expertise from ORA and Centers, lead the review of the legislative and regulatory framework of the foreign authority to ensure that appropriate jurisdiction and oversight over commodities exists; and

g. Engage the FDA Office of Ethics and Integrity and provide an initial analysis and recommendation to facilitate its review of the foreign authority's code of ethics and standards of conduct as comparable to FDA requirements and practices.

2. ORA will:

a. Liaise with foreign regulatory authority to facilitate onsite audit logistics including audit schedule, the number of observed inspections needed, and the size of onsite audit team

b. Collaborate with impacted Center(s) to establish criteria for audit team participation, which should be based on knowledge and experience, consistent with the criteria outlined in current Pharmaceutical Inspection Co-operation Scheme (PIC/S) Joint Reassessment Program (JRP) procedures, except on a case-by-case basis

c. Establish the FDA audit team and audit strategy in collaboration with impacted Center(s)

d. Lead FDA's audit of the foreign regulatory authority in collaboration with impacted Center(s); and

e. Collaborate with the impacted Center(s) to document findings and outcome of audit.

C. Capability Assessment

1. The Primary Assessment Team makes an initial recommendation to the Secondary Assessment Team.

2. The Secondary Assessment Team will provide final recommendations and MRA Reference Date to FDA Leadership or designee.

a. The MRA Reference Date criteria are as follows:

(1) Capability determination by FDA assessment teams and ratifiers

(2) FDA's audit completion date or the date in which all corrective actions/preventive actions (CAPA) were implemented, whichever is later; and

(3) Conflict of Interest (COI) acceptability date, which is determined by the date on which all COI provisions are implemented.

3. FDA Leadership or designee reviews capability assessment package and provides concurrence with Secondary Assessment Team recommendations.

4. OGPS provides notification of capability determination to MRA partner.

D. Implementation and Maintenance

1. The MRA Implementation Sub-group activities will be co-led by ORA and the Center most relevant to the MRA, with participating representatives from all impacted Centers and OGPS.

E. Reassessment of Capable Authorities

1. ORA will lead the re-assessment of capable authorities in collaboration with impacted Center(s).

2. Capability determinations should be reassessed at least every 5 years, as defined in the capability decision.

3. A re-assessment may be conducted in less than 5 years if warranted for any reason. Whenever possible, easily resolved issues – or significant, isolated challenges – should not be deferred until the regularly scheduled reassessment.

4. Reassessment should be conducted according to the FDA's assessment tool(s) and may include an audit, if necessary, and consideration of data from inspection reports received and reviewed during the interim period. Analysis may also be informed by experience acquired in implementing the MRA.

6. Budget and Resources

A. Each affected Center, ORA, and other impacted FDA components (e.g., OCC) is responsible for providing the staff and other resources necessary to carry out assessment and reassessment activities described in this SMG.

7. Suspension of Capability Decision

A. FDA may recommend the suspension of a capability decision under this SMG under the terms and the applicable MRA.

8. Effective Date

The effective date of this guide is February 13, 2023.

9. Document History – SMG 9121, "Framework for Mutual Recognition Agreements and Arrangements Relating to Drugs"

Status (I, R, C)	Date Approved	Location of Change History	Contact	Approving Official
Initial	01/10/2023	N/A	ORA/Office of Medical Product and Tobacco Operations	Elizabeth Miller, Assistant Commissioner for Operations