SMG 2830.2

FDA STAFF MANUAL GUIDES, VOLUME III - GENERAL ADMINISTRATION

AGREEMENTS WITH OTHER GOVERNMENT AGENCIES

ARRANGEMENT WITH FOREIGN GOVERNMENTS: MOUs, CONFIDENTIALITY COMMITTMENTS

INTERNAL GUIDANCE FOR SITE AUDITS OF AGENCY COMPONENTS RELATIVE TO INTERNATIONAL AGREEMENTS OR OTHER CIRCUMSTANCES

Transmittal Number 01-16 -- Date: 01/24/2001

1. PURPOSE

To provide guidance to FDA staff and organizational components that will be involved in scheduling and hosting a site visit for the purpose of auditing the capabilities of an aspect of FDA's regulatory system so that such audits may be conducted in the most appropriate and effective manner.

2. POLICY

In recent years, FDA has become a participant in several international agreements with foreign governments which involve the evaluation of the equivalence of the respective regulatory systems in providing adequate (as determined by the importing country) public health protection. Thus, when an assessment of equivalence is reached, FDA and the counterpart foreign regulatory agency may agree to rely on each other's regulatory activities, e.g. inspections.

In addition, there may be instances where FDA agrees less formally to cooperate with a foreign regulatory agency wishing to audit our system.

Beyond the scope of the bilateral agreements or cooperative arrangements, there are general obligations regarding equivalence in both the World Trade Organization Agreement (WTO) and the North American Free Trade Agreement (NAFTA). These obligations are set out in Appendix A to this Guidance.

Under an equivalence agreement, a foreign country's regulators may evaluate FDA to determine whether FDA's regulatory system is equivalent to its system based on its criteria. The agreement may include jointly agreed criteria for equivalence determination. An equivalence assessment may cover: 1) the adequacy of existing regulations, 2) the ability of the inspectional method to evaluate compliance to those regulations, 3) the regulatory body's internal policies and procedures to effectively manage the inspectional system, and 4) the enforcement system that ensures compliance with the regulations.

It is essential that FDA components understand this process and prepare to be evaluated under these agreements. The texts of the international agreements cited above are found on the Website of the U.S. Trade Representative (www.ustr.gov) and specific FDA agreements may be found in the FDA International Cooperative Agreements Manual (November 1996), obtainable from the Division of Compliance Policy, Office of Enforcement. Text of agreements since the latest publication of the Manual can be obtained from the International Agreements Staff, Office of International and Constituent Relations.

3. DEFINITIONS

A. Audit: An evaluation of a regulatory system, or an aspect of the system (e.g., regulation of GMPs) to determine whether it provides a level of health protection equivalent to the system applied by the regulatory system of the auditor's government. Such an evaluation involves the auditor assessing the plans and actions of the auditee's regulators, and the interactions between the auditee's regulators and regulated firms, primarily through review of regulator's records or observing inspections, rather than inspecting firms for regulatory compliance.

B. Audit plan: The agreed upon scope and parameters under which the visiting audit team will conduct the audit.

C. Contact person: The person named as the FDA contact point in the agreement under which the audit will be conducted. Or, if an agreement involves agencies in addition to FDA, and the contact point named in the agreement is not in FDA, an FDA contact point should be identified. If there is no formal agreement covering the audit, it is still important to identify an FDA contact point.

D. FDA component: Any organization within FDA that will be subject to a site visit from a visiting audit team in order to evaluate FDA's regulatory system. This includes a field office, laboratory, or a headquarters unit.

E. FDA team: The FDA staff responsible for preparing for the audit and interacting with the visiting audit team. Refer to "Formation of the FDA Team" on page 5.

F. Site coordinator: The person designated as responsible for organizing the preparation of a particular component for the assessment by the visiting audit team.

G. Site team: The site coordinator and staff of a particular component designated to prepare for and, as necessary, participate in the site audit.

H. Visiting audit team: Representatives of a foreign government responsible for auditing an aspect(s) of FDA's regulatory system.

4. ADVANCE COORDINATION

A. Notice of an Audit Visit

For each equivalence agreement to which FDA is a party, or to each audit intended to move toward such an agreement, FDA has identified a designated contact person (Appendix B). Foreign governments should initiate all site visits through this contact person. It will be this persons responsibility to notify the Office of International Programs (OIP)/Office of International and Constituent Relations (OICR), ORA, and any affected Centers regarding the requested visit. If FDA has agreed to cooperate with an audit by a foreign regulatory agency, even though there is no formal agreement, a contact person will be designated and this guidance document is applicable.

If representatives of another government communicate directly with a FDA component (e.g. District Office or Laboratory) requesting a site visit, that component should immediately notify OIP. OIP will work with the appropriate FDA contact person, Center, and ORA to ensure that a visit is organized through proper channels.

B. Formation of the FDA Team

The composition of the FDA team will vary according to the product involved and the questions or issues raised in the request for the audit, since audits will generally be subject matter specific, e.g. pharmaceutical GMPs, dairy products, or seafood. The identified contact person will coordinate the identification of relevant FDA staff to participate. A typical

FDA team will include representatives from ORA, the relevant Center(s), a site coordinator from each component to be visited, and technical specialists, as appropriate. OIP will provide advice as needed on issues of protocol, obligations under the relevant agreement, international relations or other relevant international issues with regard to the auditing party.

The leader of the FDA team will be an individual of sufficient seniority to speak with authority during meetings with the auditors, seeking guidance as necessary from senior FDA management. The team leader may be the person designated as the contact point for the agreement, if a relevant agreement exists, or another leader designated, e.g., by the Associate Commissioner for Regulatory Affairs (ACRA) or Center Director after consultation with the OIP. Under some circumstances, e.g., the agreement includes multiple product areas but the audit is product specific, a product expert may be identified as the appropriate team leader.

C. Audit Plan

It is the responsibility of the team leader to negotiate a mutually agreed audit plan for the specific audit to be conducted. The agreement may include a general audit plan or protocol, and the details of the specific audit will need to be negotiated. Issues that must be agreed to in advance, [usually a minimum of 60 days prior to the start of the audit - CFSAN] if not included in the agreement or if no relevant agreement exists, include:

- the subject matter scope of the audit relative to the agreement, e.g., all aspects of the agreement versus a subset of the agreement scope; if no agreement exists the scope of the audit plan must be mutually agreed;
- the objectives of the audit;
- the parameters of the system that will be evaluated to verify that the goals of the agreement are being met;
- reference documents to be used as evaluation criteria, e.g., international standards, agreement texts
- members of the FDA and visiting audit teams and their roles;
- languages to be used during the audit and in reports and arrangements for interpretation and translation as required;
- organizational components to be audited;
- dates and places where audits will be conducted;

- records and other evidentiary materials to be furnished to auditors;
- confidentiality agreements; and
- complete schedule of meetings (including opening and close-out meetings), audit activities, and report procedures (must provide for FDA to receive a copy of the report).

It is anticipated that the visiting audit team will propose an audit plan at the time of, or shortly after, the first contact regarding the audit. This proposal may or may not address all the items listed above. It is the responsibility of the team leader to ensure that all aspects of the final plan meet FDA needs. The team leader is responsible for ensuring that all of the above items are in the final audit plan.

D. Access to Documents

In general, it will be in FDA's interest to make requested documents available to the visiting audit team. FDA regulations provide for the sharing of commercial confidential information with foreign government officials if they agree not to disclose it. FDA regulations and procedures (21 CFR 20.89 and Regulatory Procedures Manual Chapter 8, Information Disclosure, Subchapter: Sharing Non-Public Information with Foreign Government Officials (www.fda.gov)) specify a mechanism for sharing information and provide for a nondisclosure form to be signed by the person who will be given access to such information. In some instances, a manufacturer or other owner of proprietary information needs to consent to its disclosure. When the FDA contact anticipates that the visiting audit team will request access to documents that are either confidential commercial information or non-public FDA internal documents, the FDA contact will request that a nondisclosure form be signed in advance or at the latest at the beginning of the opening meeting. This should be discussed with the foreign government contact during the planning of the visit, and the contact person should be responsible for ensuring that the visiting audit team understands and agrees to this requirement. RPM Exhibit 8-20 includes samples of confidentiality commitment documents. Center/ORA designated decision-makers for disclosures are also identified in the RPM. Copies of the signed nondisclosure forms should be made available to the site coordinator of any site to be visited.

E. Funding

There is no central funding mechanism for equivalence activities, including audits. Staff time and travel expenses will be provided by the team members' organizations. If FDA is faced with an overwhelming number of

requests for audits, priorities will be established by senior agency management. The OIP will facilitate the priority setting process.

F. Site Selection and Scheduling

The team leader will be responsible for negotiating the audit plan, including the times and places for audit site visits, with input from other team members and especially from components that are candidates to be visited, and with concurrence of the ACRA and Center Directors or their designees. To the extent possible, the visits will be arranged to be convenient for FDA. It must be recognized, however, that the other country's evaluators may be more comfortable with sites they have selected, either because certain regulatory activities are conducted there, or because they wish to make random selections. Workload considerations, or the preference of the director of the component not to be the subject of an audit visit, is not sufficient justification for refusing to host a visit. FDA needs to be mindful that it may need to conduct its own audits in the other country and will need the cooperation of the other country in order to do so.

To permit the maximum possible lead/preparation time, the contact person will ensure that the organizational Director is notified as early as possible that they are candidates for a site visit or that they have been selected for a site visit.

G. Federal-State, other Agency, or Partnership Relations

There may be occasions when the program to be audited involves shared responsibility between FDA and state governments, other agencies, or other partners. While FDA cannot require these partners to submit their programs to audits by foreign countries' regulators, it will be appropriate for FDA staff to actively facilitate the cooperation of such partners as a means to achieve the objectives of the proposed audit. The FDA team leader should take the initiative in working with such partners. In cases where partners are relevant state offices, the appropriate ORA District Office should work with the Team Leader to coordinate such cooperation. Sharing this Guidance with partners for their use in preparation for the audit may be appropriate.

5. AREAS OF RESPONSIBILITY

A. Preparatory Steps

FDA personnel are more accustomed to evaluating others, particularly the industry compliance to FDA requirements, than to being evaluated by those outside their chains of command. Therefore, it is imperative that the

site visit be well planned and that FDA staff be prepared for this role reversal, to ensure the success of these visits.

Upon receiving notice of a pending site visit, the Director of the component shall appoint a site coordinator. If possible, the site coordinator should be familiar with the relevant agreement(s) and understand the importance and purpose of the equivalence audits. The site coordinator will work with the team leader, the contact person (if different than the team leader) and other FDA team members during the negotiation of the scheduling and scope of the audit for that specific site. Clarifying the scope of the program to be examined and the specific items of interest to the auditors at the earliest possible time in the form of an audit plan, agreed upon by both FDA and the visiting audit team, will permit the component to prepare for a smooth and informative visit.

Once the scope of the audit is defined, the site coordinator is responsible for identifying the activities/staff members to be involved in the evaluation. All staff who may have any contact with the evaluators must be briefed by the site coordinator on the pending visit, its significance to the agency, the industry, or the U.S. government. It is essential that all FDA staff understand that there can be repercussions beyond FDA's own programs if the visit is not conducted in a professional and forthcoming manner.

Criteria for determining who should accompany the auditors throughout the visit should include not only subject matter expertise, but also communications skills and organizational rank comparable to the senior member of the visiting audit team. Attendance by an FDA official with relevant foreign language skills may be useful and should be considered, as necessary.

The site coordinator should organize a site team, as necessary, to cover the major elements of the audit plan. Because it is in FDA's interest to be prepared for the audit and have it reflect well on our program, the site team, in conjunction with the FDA team should determine whether to evaluate their respective component or subcomponents in advance, using the parameters of the audit plan, and identifying facilities, programs, written procedures, and other records that will demonstrate the effectiveness of FDA's system. Each site team should review all materials that may be subjects of review by the evaluators to verify that they are complete, up-to-date, and that all records are consistent with Agency procedures. If these activities have been subject to self-audit under an agency quality assurance program, results of the most recent audit should be reviewed. Correction of any deficiencies found in the self-audit should be verified by the site team. An ORA headquarters unit may schedule and conduct an on-site audit in advance of the foreign audit. The purpose of this visit will be assisting to prepare for a successful audit by a foreign

audit team. Although, it is not appropriate to show records of internal audits to the visiting audit team, results of internal audits should be shared with the FDA team. Any deficiencies or weaknesses identified by the site teams should be reported to the site coordinator and to the Director of the component.

If corrections are not feasible, a scenario should be developed for responding when the visiting audit team identifies a deficiency or weakness in an FDA program. FDA staff are not obligated to point out weaknesses to the visiting audit team. The FDA team and the site team must be fully informed of all such deficiencies and FDA's response. The site coordinator will be responsible for assuring that all relevant staff in the component are familiar with the potential issues that may arise, and determining, in cooperation with the FDA team, who would be the appropriate spokesperson for each issue.

B. Structure of the Visit

Audit visits, whether to a single site or a series of sites, begin with a formal opening meeting. The site of the opening meeting for the overall audit should be determined by the team leader during the planning for the visit. If the auditors plan to visit sites other than the one where the initial meeting is held, participants from the other sites should participate in the opening meeting, either in person or by teleconference. The purpose of this meeting is to confirm the Agency's understanding of the auditors' expectations, the scope of the evaluation, as set forth in the agreed audit plan, to answer any questions that arise, and to set the tone of the proceedings. Additional opening meetings may also be appropriate at each site.

The opening meeting should be used to clarify procedures to be followed and to confirm logistical plans. It is also the appropriate time to remind the visiting audit team that FDA expects to have a close-out meeting, as specified in the audit plan, at the end of the audit to discuss the general and/or specific findings of the visiting audit team.

Effort should be exerted to maintain a collegial, cooperative tone throughout the evaluation. Communication throughout the process is key to identifying and clarifying any misunderstandings or misinterpretations of information as they occur.

C. Close Out Meeting

The audit should conclude with a formal close-out meeting, to discuss the evaluators' findings. This provides another opportunity for clarifying any

misperceptions or misunderstandings concerning FDA's program. Attendance at this meeting may include all members of the FDA team.

The audit plan should include the time and location for the close out meeting. Comments from the visiting audit team should be requested at the meeting. The audit plan should include an agreement that the FDA will receive a draft copy of the visiting audit team's formal report, and this agreement should be confirmed during the close-out meeting.

6. REPORTING

At the conclusion of each site visit, each site coordinator should prepare a summary of the visit and include the observations of the audit participants, both observations made by FDA participants and any comments of the visiting audit team. The summary should be provided by the site coordinator to the team leader and FDA contact point (if different from the team leader) for information. If non-FDA sites were visited, the FDA contact point will with work with the site to prepare an appropriate summary. A copy of the summary should be provided to all team members and OIP. These summaries should be regarded as drafts, not releasable without approval of the Director, OIP.

As discussed above, the audit plan should include an agreement that FDA will receive a copy of the formal report of the visiting audit team. FDA should request a draft copy of the report to correct any technical errors, etc., prior to its finalization. The FDA contact point will coordinate FDA comments on the draft and final report of the visiting audit team.

FDA Staff Manual Guide 2830.2 Attachment A

APPENDIX A

In the **WTO Agreement on Technical Barriers to Trade**, equivalence is addressed as follows:

> 2.7 Members shall give positive consideration to accepting as equivalent technical regulations of other Members, even if these regulations differ from their own, provided they are satisfied that these regulations adequately fulfil the objectives of their own regulations.

A related concept, mutual recognition of conformity assessment procedures, is also addressed:

> 6.1 Without prejudice to the provisions of Article 6, paragraphs 3 and 4, Members shall ensure, whenever possible, that results of conformity assessment procedures in other Members are accepted, even when those procedures differ from their own, provided they are satisfied that those procedures offer an assurance of conformity with applicable technical regulations or standards equivalent to their own procedure .....
>
> 6.3 Members are encouraged, at the request of other members, to be willing to enter into negotiations for the conclusion of agreements for the mutual recognition of results of each other's conformity assessment procedures
>
> The WTO Agreement on the Application of Sanitary and Phytosanitary Measures also addresses equivalence:
>
> 14. Members shall accept the sanitary or phytosanitary measures of other Members as equivalent, even if these measures differ from their own or from those used by the other Members trading in the same product, if the exporting Member objectively demonstrates to the importing Member that its measures achieve the importing Member's appropriate level of sanitary or phytosanitary protection. For this purpose, reasonable access shall be given, upon request, to the importing Member for inspecting, testing and other relevant procedures.

The **NAFTA Part Three: Technical Barriers to Trade, Chapter 9, Standards-Related Measures (SRM)** addresses equivalence and conformity assessment as follows:

> Article 906: Compatibility and Equivalence, para. 4. Each importing Party shall treat a technical regulation adopted or maintained by an exporting

> Party as equivalent to its own where the exporting Party, in cooperation with the importing Party, demonstrates to the satisfaction of the importing Party that its technical regulation adequately fulfills the importing Party's legitimate objectives.
>
> Para. 6: Each Party shall, wherever possible, accept the results of a conformity assessment procedure conducted in the territory of another Party, provided that it is satisfied that the procedure offers an assurance, equivalent to that provided by a procedure it conducts or a procedure conducted in its territory the results of which it accepts, that the relevant good or service complies with the applicable technical regulation or standard adopted or maintained in the Party's territory.

The NAFTA Chapter 7, Section B - Sanitary and Phytosanitary Measures includes Article 714: Equivalence:

> 1. Without reducing the level of protection of human, animal or plant life or health, the Parties shall, to the greatest extent practicable and in accordance with this Section, pursue equivalence of their respective sanitary and phytosanitary measures.
>
> 2. Each importing Party:
>
> > (A) shall treat a sanitary or phytosanitary measure adopted or maintained by an exporting Party as equivalent to its own where the exporting Party, in cooperation with the importing Party, provides to the importing Party scientific evidence or other information, in accordance with risk assessment methodologies agreed on by those Parties, to demonstrate objectively, subject to subparagraph (b), the exporting Party's measure achieves the importing Party's appropriate level of protection.

APPENDIX B

Agreements That May Be the Basis for FDA Programs Being Audited

Number	Country	Sponsor & Contact	Title	Effect Date	Term Date
EOL	Australia	CDRH Gill	Insp Info on Med Dev GMP (EOLs)	2/17/93	Indef
225-75-2027 CPG	Canada	CDER Molzon	GMPs Exchange of Drug Plan Inspection Info.	10/1/73	Indef
225-75-6001	Canada	CDRH Leggett	Exchange Info. on Compliance Prgm. Efforts	12/16/74	Indef.
225-79-8400 CPG	Canada	ORA Haggard	GLPs Phase I/Non-Clinical Labs	5/10/79	Indef.
MRA	European Union	CDRH Stigi & CDER Famulare	Mutual Acceptance of device, drug and biological inspection reports	5/18/98	Indef.
225-86-8400 CPG	France	ORA Haggard	GLPs Phase II Info. Exchange of Toxicological Labs	3/18/86	Indef.
225-89-4001 CPG	Germany	ORA Haggard	GLPs Phase II (Joint with EPA)	12/23/88	Indef.
225-89-4000 CPG	Italy	ORA Haggard	GLPs Phase II	12/19/89	Indef
Note Verbal	Japan	ORA Haggard	GLPs	4/15/83	Indef.
225-89-4003 CPG	Netherlands	ORA Haggard	GLPs Phase II	12/20/88	Indef.
225-96-2004	New Zealand	CFSAN Spiller	Fish & Fishery Products	12/20/95	12/20/00
225-79-4011 CPG	Sweden	ORA Haggard	GLPs Phase I/Non-clinical Labs	5/25/79	Indef.
225-79-4057 CPG	Sweden	CDER Williams	Upgrade Quality of Drugs in Int'l Commerce	10/17/72	Indef.
225-75-4058 CPG	Switzerland	ORA Pierce	Inpsection of Production of Swiss Drugs	10/28/68	Indef.
225-85-8401 CPG	Switzerland	ORA Haggard	GLPs Phase II Exchange Info.	4/29/85	Indef.
225-86-6000 CPG	United Kingdom	CDRH Gill	Mutual Recognition of Medical Device Inspections	6/6/86	Indef.