

27 September 2010
EMA/660316/2010

EMA / FDA joint GMP inspection pilot programme

Terms of reference and procedures for participating authorities (manufacturers of medicinal products)

1. Background

The majority of national regulatory authorities are obliged by law to have systems in place to verify the GMP status of medicinal product manufacturers whose products are marketed in their territory. Most “developed” regulatory authorities ensure that these manufacturers in their territory are subject to routine GMP inspections. However, different approaches are taken to supervision of the manufacture of medicinal products outside a national territory. The international industry associations have also raised the issue of international duplication of inspection and associated resources on a number of occasions. According to industry sources, the United States Food and Drug Administration (FDA) and the European Union (EU) are the most active regulators inspecting outside their respective territories.

The objective of the paper is to outline a proposal for joint inspections between FDA/Center for Drug Evaluation and Research (CDER) and EU National Regulatory Authorities. The basic idea is that companies requiring either pre- or post-approval inspections may contact the FDA/CDER and/or EMA to express interest in a joint inspection. Based on the information received and the common areas of interest, both authorities may decide to perform a joint inspection in accordance with the principles and procedures outlined below.

2. Objective

The overall objective is to see whether greater international collaboration can help to better distribute inspectional capacity, allowing more sites to be monitored with the opportunity to optimize resources and better assess inspectional needs.

The purpose of this paper is to outline common principles and terms of reference for agreement between FDA and EU National Regulatory Authorities (under the coordination of the EMA) for joint inspections, taking into account risk based approaches, building on similar GMP standards and mutual confidence between international regulators.

This project is restricted to inspections of manufacturers of human medicinal (finished drug) products which come under the authority of FDA’s Center for Drug Evaluation and Research and the centralised marketing authorisation process in the European Union.



3. Principles

- 3.1. The scope of these activities is collaboration on joint GMP inspections of manufacturers of human medicinal (finished drug) products, which are of common interest to both parties. It is recommended for pre- and post-approval inspections
- 3.2. Exchange of information on human medicinal products, manufacturing sites, inspection reports and other detailed information shall be subject to specific confidentiality agreements with both authorities and companies concerned, as necessary
- 3.3. Both authorities are responsible for ensuring that appropriate confidentiality arrangements are in place to allow them to conduct the activities covered by this paper. All participating companies are expected to permit unrestricted and comprehensive exchange of information between authorities.
- 3.4. The normal rules for national/regional coordination of inspections will apply, e.g. in the EU, the EMA coordinates inspections involving the different EU Member States.
- 3.5. The national/regional rules for inspection fees, if any, apply for authorities participating in any joint inspection.
- 3.6. Following close-out of the inspection, each involved authority is responsible for administrative or enforcement actions at national/regional level, e.g. database entry, issuance/update of certificates/licences reports.
- 3.7. Each authority reserves the right to perform its "own" inspection. However, the regulatory authorities will communicate on any deficiencies (or a negative inspection result) found. This will ensure a common understanding of the underlying facts and may assist in efforts to try to achieve a joint conclusion.

4. Procedure

- 4.1. Both authorities identify a contact point specifically for joint inspection coordination purposes.
- 4.2. The contact points share information on manufacturing sites that have expressed interest in the performance of a joint FDA/EMA inspection.
- 4.3. The company or its representatives (e.g. Marketing Authorisation Applicant or Sponsor) provides a contact point and available information on the manufacturing site to be inspected, covering at least:
 - i. Human medicinal product name(s), strength, pharmaceutical form
 - ii. Drug Application Number (also include Supplement number, if applicable)
 - iii. Application Submission Date
 - iv. AS/API name(s)
 - v. (if available) Site Master File
 - vi. Manufacturing process description (a flow-chart as a minimum)

- vii. Specific facilities and operations at the subject site connected with the submission triggering the inspection
- 4.4. The inspection coordination contacts set up a teleconference to agree that a joint FDA/EMA inspection is warranted, determine timelines and identify the inspection team.
- 4.5. The inspection coordination contacts will together decide who the leading inspection authority will be, taking into account the following:
 - a. For manufacturing sites in the USA or EU; the lead inspector will be the authority of the country where the manufacturing site is located.
 - b. For manufacturing sites outside the respective territories: the lead inspector will be allocated on a case-by-case basis taking into account these points : the legal requirements for the inspection, the inspection history of the site and the number of concerned human medicinal products in each area (i.e. USA and EU).
- 4.6. The lead inspector has the following duties:
 - a. Setting a reporting deadline in agreement with all team members taking into account any specific deadlines linked to on-going submissions or procedures;
 - b. Technical preparation of the inspection with the inspectee in liaison with the other inspectors of the team;
 - c. Establishing a draft inspection plan in cooperation with the involved authorities and arranging for a pre-inspectional preparation meeting;
 - d. Leading the conduct of the inspection on site;
 - e. Communication between the inspectee and the inspection team;
 - f. Facilitate the discussion for all the findings/observations jointly agreed with the inspection team
- 4.7. With few exceptions, the inspection team's findings/observations and the preliminary inspectional findings should be jointly agreed on site. Where applicable, according to the procedures of either party, the inspection team may provide the inspectee with a written list of observations (e.g., FDA Form 483) at the conclusion of the inspection. If agreement is not reached at this step see 4.13.
- 4.8. Taking into account any applicable national/regional procedures, each regulatory authority should send/provide their final list of deficiencies to the inspectee. The inspectee should comment within each regulatory authority's applicable timeframe.
- 4.9. On receipt of responses of findings/observations, the participating authorities should discuss the responses and any action plan proposed by the inspectee taking into account applicable national/regional procedures. If agreement is not reached at this step see 4.13.
- 4.10. Unless otherwise agreed, separate final inspection reports (in English) in accordance with regional requirements will be prepared to close out the inspection process, by each of the two parties involved in the inspection team. In some cases during this pilot, attempts may be made to write a joint report and/or follow a uniform report format.
- 4.11. In the case of a negative inspection result, the inspecting authorities will liaise with each other to ensure a common understanding and if possible an agreed conclusion before closing out the inspection and review process. If agreement is not reached at this step see 4.13.

- 4.12. Each participating authority is responsible for any follow-up actions according to their own regulations and procedures.
- 4.13. In the unlikely event of a major disagreement on the conclusion of the inspection, both authorities should proceed separately and conclude the inspection in accordance with their own national procedures.
- 4.14. Any joint follow-up inspection should be organised as outlined in this procedure.

5. Flow-chart

