



European Medicines Agency



US Food and Drug Administration

London, 29 July 2009  
Doc. Ref. EMEA/INS/GCP/538414/2008  
FDA Mod. 20 August 2009

## EMEA-FDA GCP Initiative

### Terms of engagement and procedures for participating authorities

Pilot Phase (18 months): Start date 01 September 2009

#### 1. Background

International regulatory authorities have systems in place to verify compliance with provisions of good clinical practice (GCP), and therefore to inspect the conduct of clinical trial(s), in particular those included in Marketing Authorisation Applications (MAAs) submitted to the European Medicines Agency (EMA) and/or New Drug Applications (NDAs)/Biologics License Applications (BLAs) submitted to the US Food and Drug Administration (FDA). Clinical investigator trial sites and sponsor/contract research organization (CRO) sites are most often subject to GCP inspections. Occasionally, other sites, including laboratories or central technical facilities used for analyses in the clinical trial, may also be selected for inspection. US and European Union (EU) regulatory authorities ensure that clinical trials conducted in their territory are subject to routine or targeted GCP inspections in the context of investigational new drug/biologic applications or as part of an MAA or NDA/BLA.

Thus far, the EMA and FDA have jointly signed a Confidentiality Arrangement (in effect through 2010) that facilitates the sharing of 1) advance drafts of legislation and/or regulatory guidance documents; 2) information related to the authorization and supervision of medicinal products; and 3) information, including inspection reports, about good clinical practice (GCP) inspections for specific products.

The clinical development of medicines is a global undertaking. In most cases the same clinical trials are used to support MAAs to the EMA and NDAs to the US FDA. Subjects participating in the pivotal clinical trials in these MAAs/NDAs are often recruited in Europe and the USA. Regulators in the US and EU must ensure that clinical trials, both in their own territories and in other regions of the world, have been conducted in an ethical manner, have been carried out in accordance with the investigation plan, and have data that have been correctly reported. The increasing globalization of large scale and complex clinical trials, coupled with the limited size of available inspection resources, means that only a sample of sites and studies can ever be inspected. If regulators can work in a collaborative and synergistic manner in carrying out GCP inspections and implement information exchanges then GCP inspection resources can be used more efficiently.

This document outlines a process which focuses on enhanced and systematic GCP-related information exchanges between EMA and FDA combined with collaboration in the conduct of GCP inspections of clinical trials included in MAAs and NDAs/BLAs submitted to EMA and FDA, respectively.

This initiative will be carried out in the framework of the Confidentiality arrangements established between the European Commission, the EMA and the US FDA and will commence with an 18-month pilot phase which will consider only a subset of regulated products, specifically, those regulated

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK  
Tel. (44-20) 74 18 84 00 Fax (44-20)

E-mail: [mail@emea.europa.eu](mailto:mail@emea.europa.eu) <http://www.emea.europa.eu>

© European Medicines Agency, 2009. Reproduction is authorised provided the source is acknowledged

by the Center for Drug Evaluation and Research (CDER) in the US FDA and by EMEA for the centralized procedure in EU. The pilot initiative will focus on those applications pertaining to new drug applications (including orphan and pediatric drugs) and on inspections of sites located in the US and EU. The initiative will not include generic drug applications during the pilot program. This is without prejudice to other ongoing collaborative work on inspections.

Performance indicators have also been defined to measure progress toward the goals outlined in this document. Based on these indicators, a joint assessment on the pilot phase will be made by the EMEA and FDA after 18 months. This process will then be amended as needed (e.g. to widen the subset of regulated products, inclusion of generic applications, inspection of sites outside the EU and US, etc.).

Participation in joint or observed inspections is voluntary for EU and FDA inspectors, and subject to their availability and possibility of the inspectors of EU member states and of US FDA to participate on each occasion. Part of the objective of the pilot phase is to identify difficulties that may arise and to explore how these can be resolved.

## **2. Objectives**

### **2.1 To Conduct Periodic Information Exchanges on GCP-Related Activities**

- a. To streamline the sharing of information relevant to GCP inspection planning so that the selection of studies and sites is well informed, and inspection coverage is improved.
- b. To exchange GCP-related information contained in applications for scientific advice, orphan medicines designation, pediatric investigational plans, marketing authorization or post-authorization activities of significant public health interest.
- c. To communicate effectively and in a timely manner on inspection outcomes (negative and positive) and their potential impact, where the clinical trials and/or inspected sites/organizations are of common interest.

### **2.2 To Conduct Collaborative GCP Inspections**

- a. To build mutual understanding of, and confidence in, the GCP inspection processes utilized by the EU/EMEA and FDA – through the sharing of information, experience and inspection procedures, and cooperation in the conduct of inspections.
- b. To improve effectiveness of inspections by sharing best-practice knowledge in order to enhance inspection techniques and processes.

### **2.3 To Share Information on Interpretation of GCP**

- a. To keep each other informed of GCP-related legislation, regulatory guidance documents, position papers, and policy documents that might be in draft or finalized form.
- b. To identify and act on areas where greater convergence could be achieved to the benefit of the clinical research process.

## **3. Principles**

- 3.1 The scope of these activities is the sharing of information and collaboration on GCP inspection of sites (clinical investigators, sponsors, CROs, laboratories, etc.) in relation to

pivotal clinical trial(s) included in applications for marketing approval to EMEA and/or FDA.

- 3.2 All information exchange (e.g., inspection reports and/or more detailed planning information) and collaborative work in relation to this initiative will be carried out in the framework of the Confidentiality arrangements established between the European Commission, the EMEA and the US FDA.
- 3.3 Exchange of confidential information should be done via Eudralink as appropriate.
- 3.4 Where an NDA/BLA and/or MAA are of common interest, EMEA and FDA agree to the following actions:
  - a. They will identify those applications which may benefit from GCP inspection collaboration (i.e., synchronized timing of dual submissions, those submissions whose review procedures specific to FDA or EMEA have overlap on the review clock, or just applications to be inspected by one of the parties and hence useful for observational inspections regardless of the submission timeframe) and will determine the GCP inspection collaboration strategy (see Section 4.2). This may involve requesting sponsor willingness to coordinate activities.
  - b. They will exchange information available to them and contained in applications.
  - c. They will endeavour to coordinate risk-based site selection activities related to GCP planned inspections, and to the extent possible based on current regulations and laws and as outlined in the Confidentiality Arrangement established between the EC, EMEA, and US FDA (Section 3.3), share the observations and results of any inspections carried out previously by FDA or EU inspectors on behalf of EMEA, in planning their inspection activity covered within the scope of this project.
- 3.5 The reference GCP standard for the inspections will be ICH Topic E6: Guideline for Good Clinical Practice, the Clinical Trial Directive 2001/20/EC for the EMEA, and Title 21 CFR Parts 11/50/54/56//58/312 and 314 for the FDA.
- 3.6 With respect to EMEA requested EU GCP inspections, the normal rules for national/regional coordination of inspections will apply. The national/regional rules for inspection fees should apply for each authority participating in any inspection.
- 3.7 Each authority (EMEA or FDA) reserves the right to perform its own inspection(s). EMEA and FDA recognize that each regulatory authority may conduct additional GCP inspections at anytime based on application issues and findings, and observations of ongoing or completed GCP inspections. They will strive to inform each other of such intent.
- 3.8 EMEA or FDA may request to the other inspecting regulatory authority that they expand the scope of their planned or ongoing inspection to cover additional areas of common interest.
- 3.9 Following close out of any inspection, each involved authority is responsible for administrative or enforcement actions within its own regulatory framework.

#### **4. Procedures**

##### **4.1 Exchange of information**

The following procedures should be followed for the conduct of periodic information exchange on GCP-related information:

- a. The FDA Office of International Programs (OIP) in the Office of the Commissioner is the FDA's lead for all international commitments, arrangements, and agreements. The equivalent lead in the EMEA is the International Liaison Officer (ILO). Information shared under these arrangements must flow through the respective international offices (OIP and ILO) as the entry site for requests for information and subsequently as the distribution point for the information provided. In the process the international offices will track the information requested/provided and provide the necessary clearances for the sharing of information.
- b. EMEA and FDA will identify a contact point(s) specifically for GCP-related information exchange. These contact points will be the recipients of the exchanged information as identified for the respective agency or designee and will be specified outside of the scope of this document.
- c. The EMEA and FDA contact points will exchange GCP-related information on MAA and NDA/BLA submissions and GCP inspection information within the parameters defined by confidentiality arrangements and within each regulatory authority's statutory and regulatory framework via:
  - i. Periodic exchange of prescribed information at least quarterly using templates.
  - ii. Routine monthly teleconferences
  - iii. Ad hoc exchange via teleconference or other means (e-mail, etc.)
- d. Ad hoc requests for information will be at the discretion of either the EMEA or FDA and communicated via e-mail, Eudralink or telephone. Requests must include a timeline for response to the request and alternative options if the timeline is not feasible. Ad hoc exchange of GCP related information may include the following:
  - i. Inspection assignments/scope
  - ii. Inspection reports or summaries of critical or relevant findings
  - iii. Inspection outcome and basis (preliminary and/or final)
  - iv. Outcome of the assessment of the application
  - v. Third party complaints (including those from other regulatory agencies)
  - vi. Other information that may be applicable to any application (e.g., change of ownership, mergers)
  - vii. GCP issues related to policy or procedure

EMEA and FDA agree to send information to the contact points outlined in Section 4.1.b.

#### 4.2 Collaborative GCP Inspections

The following four different types of collaborative inspections have been identified:

- a. Observational GCP inspections
  - i. Definition: Either EU/EMEA or FDA inspectors conduct a GCP inspection in the other's territory, but not both, with observers from the non-inspecting authority (the authority of the country where the site is located, EU/EMEA or FDA) present during the inspection.
  - ii. Purpose: To learn about the similarities and differences in inspection process and procedures between the EU/EMEA inspectors and the FDA. The intention of this inspection approach is to build confidence and gain insight into the inspection techniques applied by each Agency. This will facilitate a better understanding of how to interpret the findings reported by inspectors from each Agency.
- b. Sequential GCP inspections

- i. Definition: When the MAA or NDA/BLA do not overlap sufficiently but the agency receiving the application first, and therefore initiating the GCP inspection, supports the planning of the inspection by the second agency.
  - ii. Purpose: To increase transparency and visibility of inspections performed by participating authorities. To exchange information for scientific/enforcement advice to enhance public health interest.
- c. Joint GCP inspections
  - i. Definition: Both EMEA/EU and FDA inspectors are on site at the same time or at an overlapping time period conducting an inspection. EMEA/EU inspectors and FDA inspectors will follow their respective Agency's process and procedures for performing inspections and will produce an independent/separate inspection report in accordance with their respective Agency's policy and procedures.
  - ii. Purpose: To conduct an inspection under the jurisdiction of both the FDA and EMEA and to learn about the similarities and differences in inspection process and procedures between the EMEA/EU and the FDA. The intention of this inspection approach is to build confidence and gain insight into the inspection techniques applied by each Agency. This will facilitate a better understanding of how to interpret the findings reported by inspectors from each Agency.
- d. Parallel GCP inspections
  - i. Definition: EMEA/EU and FDA inspectors conduct separate GCP inspections at different sites, in support of the same MAA or NDA/BLA interest.
  - ii. Purpose: To increase the number of sites for which inspection information is available without increasing the number of actual inspections performed by each Agency. The intent of this collaborative inspection approach is to leverage inspection resources.

The following procedure should be followed when coordinating the Conduct of Collaborative GCP Inspections:

- a. EMEA and FDA will identify a contact point(s) specifically for GCP inspection planning purposes (see Section 4.1.b).
- b. The EMEA and FDA will identify applications of common interest (MAAs and NDAs/BLAs) and exchange GCP inspection strategies specific to FDA and EMEA, including each other's risk-based site selection of clinical investigators, Sponsor/Applicants, CROs, laboratories, etc. They will identify those entities that they have previously inspected and if they have an interest in the entity for some other reason.
- c. For each application of common interest, EMEA and FDA will decide whether collaboration on GCP inspection is proposed (yes or no), and if yes, which type of collaborative (joint, parallel, sequential or observational) GCP inspection, under the four scenarios, is appropriate.

In general, observational and sequential inspections are designed to enhance each regulatory authority's inspectional procedures and encourage the exchange of inspectional information. These inspections will be the first type of inspections utilized as an efficient method for each regulatory authority to learn more about each party's inspectional approaches. Joint and parallel inspections are more advanced inspectional types which may be selected after the EMEA and FDA have had the opportunity to better understand each others' inspectional approaches.

Each party will discuss and mutually agree to the type of inspection needed for specific applications.

#### 4.2.1 Observational GCP Inspection Process

- a. The EMEA and FDA will exchange available information on the clinical trial(s)/related applications/specific site(s) to be inspected following the procedures in Section 4.1.
- b. FDA inspectors or EU inspectors (from the Member State) may decide to participate as a GCP inspection observer in an FDA or EMEA inspection, respectively, identified during the exchange of information. Sites inspected may be of interest to the EMEA or FDA or both.
- c. The GCP regulatory authority (EMEA or FDA) will develop, issue inspection assignments/scope, and conduct the GCP inspection in accordance with their procedures.
- d. If the lead inspector and inspected entity are agreeable, an inspector from the non-inspecting authority (EU or FDA) will first sign a confidentiality agreement with the inspecting GCP regulatory authority relevant to the observational inspection, and be present to observe the conduct of the GCP inspection.
- e. The GCP inspector of the inspecting authority will prepare the inspection report.
- f. The EMEA and FDA will be responsible for any follow-up actions based on recommendations from the inspectors, in the context of the marketing authorisation.
- g. Inspection outcome and any follow-up information may be shared following the procedures outlined in Section 4.1 of this document.
- h. The observer will prepare (in English) a summary of similarities and differences between the conduct of the inspection observed and the process used in his or her regulatory agency, with the input from the GCP inspector of the inspecting authority. This summary should not refer to product or company information in any specific way. It is a report of the inspection process and not a means of communicating issues in relation to a product or site.
- i. The GCP observer's summary will be provided to the EMEA and FDA GCP-related point of contact for information exchange (Section 4.1) within 30 days of completion of the GCP inspection.
- j. Each regulatory authority (FDA and EMEA via the EMEA GCP Inspectors Working Group) may review and consider the observer's summary in order to optimize their respective GCP inspection programs in accordance with their respective procedures and regulations.
- k. Each regulatory authority (FDA and EMEA, including the EMEA GCP Inspectors Working Group) may discuss the observer's summary using the procedures in Section 4.1.

#### 4.2.2 Sequential GCP inspection Process

- a. The EMEA and FDA will exchange available information on the clinical trial(s)/related applications/specific site(s) to inspect following the procedures in Section 4.1.
- b. EMEA or FDA will identify an application submitted to both agencies in a different timeframe.

- c. The first GCP regulatory authority receiving the application (EMA or FDA) will perform a GCP inspection.
- d. The first GCP regulatory authority will share, upon request from the second GCP regulatory authority, the inspection outcome and other relevant information following the procedures outlined in Section 4.1 of this document.
- e. The second GCP regulatory authority (EMA or FDA) will receive the same application and will decide whether to conduct GCP inspections. The second GCP regulatory authority may seek the support of the first authority for planning such inspection.
- f. The second GCP regulatory authority receiving the application (EMA or FDA) will, if previously decided, perform a GCP inspection.
- g. The second GCP regulatory authority will share, upon request from the first GCP regulatory authority, the inspection outcome and other relevant information following the procedures outlined in Section 4.1 of this document.

#### 4.2.3 Joint GCP Inspection Process

- a. The EMA and FDA will exchange available information on the clinical trial(s)/related applications/specific site(s) to inspect following the procedures in Section 4.1.
- b. The EMA and FDA will agree on the scope, sites for inspection, and timelines for the inspection.
- c. EMA and FDA will develop and issue inspection assignments/scope in accordance with their respective procedures.
- d. The inspection planning contacts from EMA and FDA will coordinate to develop an inspection strategy, taking into consideration where most of the sites to be inspected are located (i.e., in EU or US) or other criteria to be agreed to by both parties. The specific issues to be coordinated include but are not limited to the following:
  - i. Notification requirements of the inspection(s) to the sites and applicant, as appropriate.
  - ii. Reporting deadlines requirements to be in agreement with all GCP inspectors taking into account any specific deadlines linked to on-going applications or procedures.
  - iii. Coordination of the conduct of the inspection at all sites.
  - iv. Communication with the applicant and EMA and FDA contact points.
- e. The EU and FDA inspectors will conduct and communicate inspection findings to the inspected entity in accordance with their national/regional procedures.
- f. Separate final inspection reports (in English) will be prepared by each of the authorities conducting the inspection in accordance with their national/regional procedures.
- g. The EMA and FDA will be responsible for any follow-up actions based on recommendations from the inspectors.
- h. Inspection outcome and any follow-up information may be shared following the procedures outlined in Section 4.1 of this document.

#### 4.2.4 Parallel GCP Inspection Process

- a. The EMEA and FDA will exchange available information on the clinical trial(s)/related applications/specific site(s) to inspect following the procedures in Section 4.1.
- b. EMEA and FDA will select sites that do not overlap for their respective inspections.
- c. EMEA and FDA will develop and issue inspection assignments/scope in accordance with their respective national/regional procedures.
- d. Independent site inspections will be carried out by the EU/EMEA and FDA in accordance with their national/regional procedures.
- e. See Section 4.2.3 f-h.

#### 4.3 GCP Policy and Program: Development and Harmonization

The EMEA and FDA will try to keep each other informed of proposed and new policy, and will try to identify and act on areas where greater convergence could be achieved to the benefit of the clinical research process. The following communication and training opportunities will be used to facilitate sharing of GCP policy and practices:

- a. Through the exchange-of-information process as outlined in Section 4.1
- b. Through the participation in the annual EMEA GCP Inspectors Working Group training course/other training courses and equivalent participation by EMEA/European inspectors in FDA training activities.
- c. Through the involvement of the FDA by teleconference in the EMEA GCP Inspectors Working Group Meeting, “GCP Interpretation” agenda point and equivalent participation by EMEA/European inspectors in relevant FDA meetings.
- d. During the participation of both parties in international conferences
- e. Through visits and/or exchanges of EMEA or FDA personnel to the other regulatory authority.

## **REFERENCES**

Extension of Confidentiality Arrangement between United States Food and Drug Administration and the European Commission Enterprise and Industry Directorate-General, and the European Medicines Agency to Exchange Regulatory Information; signed September 2005 (in effect until September 2010)

United States Freedom of Information Act, U.S.C. 552(b)(4)

European Commission Regulation # 1049/2001

U.S. Food, Drug and Cosmetic Act, with all amendments

## 5. Flow-chart: GCP Initiative

