

Joint EMA-FDA
GCP Inspections:

A Comparison between the FDA and European Inspection Process



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The European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) Good Clinical Practice (GCP) initiative, which began an 18-month pilot phase on 1 September 2009 targets investigator sites, sponsors, and contract research organizations (CROs) who are based in either the US or the European Union (EU). This joint inspection process is still in its infancy with only a handful of organizations and sites involved. These collaborative international GCP inspections come under the scope of the confidentiality arrangements between the European Commission, the EMA, and the FDA. The initiative aims to include the sharing of information on inspection planning, policy and outcomes, and the conduct of collaborative inspections. This is all part of the recognition that clinical trials are becoming increasingly global, with similar numbers of patients now being recruited into studies in North America, Europe and the rest of the world. The same trials are being used to support Marketing Authorization Applications (MAAs) in the EU and New Drug Applications (NDAs) or Biologics License Applications (BLAs) in the US, often as parallel

assessments. Regulations in the US and Europe have similar aims to ensure that trials are being run according to ethical principles, patients are safe and well cared for, the study is run according to the protocol, and that data is recorded accurately. Inspectorates have limited resources, and inspections frequently overlap at both the site and sponsor/CRO level. These resources can be used more effectively, and joint inspections or sharing of inspection findings could be desirable for all. However, this partnership is still in its early stages and there are certain subtle differences between the way in which the two agencies operate, request documents, and present findings which are apparent from the beginning of the inspection to the end of the process.

In 2005, the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA) made a commitment to cooperate. This was extended in 2010 by the “FDA-MHRA Confidentiality Commitment.” Per the Confidentiality Agreement, the FDA may disclose otherwise nonpublic information to the MHRA regarding FDA-regulated products as part of cooperative law enforcement or cooperative regulatory activities.

In this context the term “medicinal products for human use” excludes all medicinal products subject to evaluation or authorized by the European Medicines Agency (EMA) under the centralized procedure as well as medicinal products authorized at the national level by European Union Member States that are subject to official European Union arbitration and referrals.

Regulatory Requirements

When the FDA conducts inspections, they follow the written Compliance Program 7348.810 Bioresearch Monitoring for Sponsor, CROs and Monitors and Compliance Program 7348.811 for Inspection of Clinical Investigators. It is important to note that Clinical investigator inspections are product specific, ie, human drugs and biologics or medical devices and investigators must apply the appropriate FDA regulations to these areas. In contrast, when inspections of sponsors, CROs, and monitors are performed, FDA will compare the practices and procedures conducted by the inspected party against the commitments made in the FDA application. Additionally there are two agency-wide Bioresearch Monitoring Compliance Programs. Regulations that govern the proper conduct of clinical studies establish

specific responsibilities of sponsors for ensuring (1) the proper conduct of clinical studies for submission to the FDA and (2) the protection of the rights and welfare of subjects of clinical studies; these specific regulations are found in 21 CFR 312 (Investigational New Drug Application) and 21 CFR 812 (Investigational Device Exemption).

European oversight falls to the GCP Inspection Services Group of the EMA. Their inspectors use the Joint Audit Programme to ensure conformity among Member States throughout the inspection process and to make sure trials stay in accordance with mutual recognition agreements among European countries. Requirements for the conduct of clinical trials in the EU, including GCP and good manufacturing practice (GMP) and inspections of these, have been implemented in the Clinical Trial Directive (Directive 2001/20/EC) and the GCP Directive (Directive 2005/28/EC) and related guidance documents. Volume 10, Clinical Trials, of the Rules Governing Medicinal Products in the European Union, brings together information on clinical trial authorization, safety monitoring, GCP inspections, and GCP and GMP requirements for clinical trials in the European Economic Area (EEA). Clinical trials included in MAA in the EEA are required to be conducted in accordance with GCP (Directive 2001/83/EC Annex I, as amended by Directive 2003/63/EC) and the ethical standards of Directive 2001/20/EC.

The EMA is also responsible for coordinating any inspection requested by the Committee for Medicinal Products for Human Use (CHMP).

The EU adopted the ICH-GCP guideline in July 1996. ICH developed unified standards for Europe, the US, and Japan; this is still considered the cornerstone for clinical research across the three regions and was one of the first and greatest steps to harmonization.

An Overview of the Inspection Process

The EMA-FDA joint inspection process commences with selection of suitable MAA holders and sites to inspect. During the EMA-FDA GCP initiative pilot phase, only a subset of regulated products will be inspected, specifically those regulated by the Center for Drug Evaluation and Research (CDER) in the US and by the centralized procedure in the EU. Inspection objectives are defined, and Member States in the EU volunteer to participate. Lead and reporting inspectors are then defined. Currently, only routine inspections are being targeted as part of this pilot process.

The Inspection Notification Process

During an FDA inspection of a sponsor or CRO, prior notification is not usually given unless specified by the related FDA Center (ie, Center for Drug Evaluation and Research [CDER]), and all expenses for the FDA related to the inspection are covered by the FDA. Each inspection will consist of a comparison of the practices and procedures of sponsors, CROs, and monitors to the commitments made in the application for investigational exemption (including 510[k]) and applicable regulations and guidelines as instructed by the report formats in the attachments.

In comparison, the holders of the MAA for the EMA submission are required not only to cover all of the inspector's expenses but also to make

all necessary travel arrangements. With respect to EMA-requested EU GCP inspections, the normal rules for national/regional coordination of inspections apply. The national/regional rules for inspection fees apply for each authority participating in any inspection.

Formal notification is made by the inspectorates of the local regions. For example in Germany, notification from the EMA could come from BfArM inspectors (Federal Institute for Drugs and Medical Devices). Notification can vary; it may be via a facsimile for primary notification of an upcoming inspection with postal mail or email for follow-up.

With most FDA inspections of sponsors and/or CROs, there is no letter sent ahead of the inspection specifying the areas that the FDA will review in regard to the submission. However, with the EMA, it is typical that they do send a letter specifying the dates/times of the inspection as well as the areas that they want to audit and documents that they expect to have made readily available.

The Opening Meeting

Before the FDA inspector(s) begin an inspection, they are required to present their credentials and issue the original signed FDA-482 form, Notice of Inspection, to the most responsible person at the firm that is being inspected. In comparison, there is no formal documentation issued during the beginning of the inspection by the European inspectors. Instead, an opening discussion is held on the purpose of the inspection, expectations for the inspection, and verbal discussion of documents or people they need available.

When working together, the EMA and FDA conduct joint opening and

closing meetings. The questioning process is conducted in partnership. If an observational inspection is being conducted by the FDA, the EMA inspectors take the lead and ask all the questions, leaving the FDA inspector to take notes.

EU inspectors commonly work in teams of two or three inspectors who are taken from two of the Member States, whereas the FDA inspectors often work alone.

During the Inspection

The European inspectors maintain a formal tracking log of all documents requested and received. This document is given to the firm being inspected to ensure that all requests are appropriately documented and followed up. In comparison, FDA only makes formal verbal requests for documents, unless they are requesting copies of the firm's internal audit reports (which require center clearance/concurrence, as to request this on an ongoing basis would defeat the purpose of firm's conducting and maintaining an effective internal auditing program). The reason that a written request for records is not typically made is per Section 703 of the Federal Food Drug and Cosmetic Act, evidence obtained in response to specific written request cannot be used in criminal prosecution of the person from whom obtained. Normally this option, with FDA Supervisory Approval, may be exercised when the importance of the evidence is crucial to protecting public health.

Both the FDA and the European inspectors typically walk through the firm's facility and ask questions to confirm and evaluate that equipment, resources/personnel, and overall facility are appropriate to the work being conducted. During this process, procedures

and other supporting documents may be requested, ie, validation and temperature controls/records for the Information Technology (IT) server room or security access to the IT server, central archive or project security levels/access for those involved in support of the application (data entry, database build, edit check testing, programming, and writing of the clinical study report).

Neither the FDA nor the European inspectors are required to sign any company-requested documents. In the FDA's Investigator Operational Manual (IOM), instructions are provided to the FDA inspectors not to sign any non-FDA forms, but they are required to report these requests in their written Establishment Inspection Report (EIR). The EMA operates in the same manner as the FDA in this area.

The Closeout Meeting

Prior to departing the firm, the FDA inspectors are required to present/ issue the most responsible individual of the firm an FDA-483, a List of Objectionable Conditions, in writing, if any significant objectionable conditions, relating to products and/ or processes or other violations of the FD&C Act and related Acts, were observed during the inspection. These observations are based on the FDA investigator's "judgment" that conditions or practices observed indicate failure to adhere to the regulations and are ranked in order of significance. The FDA is required to only list observations which are significant and correlate to regulated products or processes being inspected. If an observation was made during a prior inspection that has not been corrected or is recurring, it can be noted on the FDA-483. Observations which are considered of questionable significance are required to be

discussed and described in the EIR, but not listed on the FDA-483.

When FDA issues the FDA-483, they include the following statements per their IOM guidance to ensure that the firm understands that this is the FDA inspector's judgment which could change based on final agency interpretation: "This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above."

In addition to the above information, the FDA also adds the following language when issuing medical device FDA-483s: "The observations noted in this form FDA 483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self audits to identify and correct any and all violations of the quality system requirements."

In comparison, European inspectors do not issue their list of objectionable findings at the close of the inspection, but instead discuss the findings verbally in the closeout meeting. The EMA provides an inspection report for each site inspected as well as an Integrated Inspection Report (IIR). The audit reports are issued in English. For site inspections, the investigator

and the sponsor are copied on the report, whereas for CRO/sponsor inspections only the auditees are copied.

When the FDA issues the EIR, besides covering the significant objectionable conditions, they also dedicate a section of the report to document the Non-Reportable observations under the “General Discussion with Management” section of the report. These objectionable conditions cover observations of significant deviations from specific laws and/or regulations, non-reportable items, items of questionable significance which have been deemed not to merit inclusion on the FDA 483 and observations which deviate from official published guidance (not regulations). These items are included since they warrant discussion with management.

Regulatory Classification of Inspectional Findings

The FDA Center has the final classification authority for all Bioresearch Monitoring Program inspection reports. The Center will provide to the FDA district office copies of all final classifications. The FDA’s system of classification includes the following:

1. NAI - No objectionable conditions or practices were found during an inspection (or the objectionable conditions found do not justify further regulatory action)
2. VAI - Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action
3. OAI - Regulatory and/or administrative actions will be recommended

FDA LEGAL AUTHORITY ACTIONS FOR SPONSORS, MONITORS, AND CROS	EU LEGAL AUTHORITY ACTIONS
<ol style="list-style-type: none"> 1. Warning and Untitled Letters 2. Re-inspection 3. Termination of an exemption (IND, IDE, INAD) 4. Refusal to approve or license 5. Withdrawal of approval (PMA, NDA, NADA) 6. Determination of not substantially equivalent or rescission of a 510(k) for devices 7. Implementation of the Application Integrity Policy 8. Initiation of stock recovery 9. Seizure of test articles 10. Injunction 11. Prosecution under the FFDCA and other Federal statutes, ie, 18 USC 2, 371, 1001, and 1341. 12. Referral of pertinent matters with headquarters’ concurrence to other Federal, state, and local agencies for such action as that agency deems appropriate. <p style="font-size: small; margin-top: 10px;"><i>For Clinical Investigators, there are additional Administrative/Civil/Criminal Actions that can be invoked as well as other legal sanctions under the FFDCA and/or Title 18, United States Code that are not listed as part of this article.</i></p>	<p>EU GCP inspections are conducted by EU Member State inspectors. The EMA does not have a role of enforcement like the FDA. Any enforcement actions are the responsibility of the individual Member States concerned and are subject to each country's local laws and regulations. For example in the UK, MHRA can issue warnings and alerts. They can also prosecute when regulations have been breached. UK courts can impose fines and prison sentences when the law has been broken. The MHRA can also withdraw any unlicensed or illegal products from the market.</p>

Table 1. Comparison of FDA and EU Legal Authority Actions

In Europe, findings are generally presented as critical, major, minor, or other. There is some variation in how inspection findings are presented depending on the Member State. In some cases, “recommendations” can be made; however, these do not require a response from the auditee. The MHRA has a well defined classification system for GCP inspection findings. They grade their findings as critical, major, or other. A critical finding is “where evidence exists that significant and unjustified departure(s) from applicable

legislative requirements”..have “occurred with evidence that

- i. the safety, well-being or confidentiality of trial subjects either have been or have significant potential to be jeopardized, and/or
- ii. the clinical trial data are unreliable and/or
- iii. there are a number of Major non-compliances (ref. Major) across areas of responsibility, indicating

a systematic quality assurance failure...”

Additionally a critical inspection finding can be given “here inappropriate, insufficient or untimely corrective action has taken place regarding previously reported Major non-compliances...”

The FDA has at their disposal the following options to address regulatory violations. Table 1 illustrates some similarities and differences between the legal actions available to the FDA and EMA.

As shown from the wide list of enforcement actions listed above in Table 1, both the FDA and EMA have a large arsenal of enforcement options to use to bring about compliance. Although both regulatory authorities share regulatory information, it is unlikely that they will absolutely agree and collaborate on legal actions.

Summary

There have been significant changes in the political, economic, and regulatory landscape in both the US and EU over the last few years. These changes may not have always been for the better, but they have defined the future. Regulatory inspectorates have also been driven by these changes and are adapting. The EMA is working to increase its transparency and improving the way it assesses risk-benefit whereas the FDA is working on expanding its global role and strengthening its base in regulatory science. One of the most significant changes that has evolved is the way the FDA and EMA are working together through

both closer cooperation and in some cases bringing their practices together. This is particularly seen in their risk management programs, pediatric clinical trials and by sharing inspection practices. For those of us who work in the global arena, we have long craved for standardization, and these steps are hopefully the first of many.

Suggested Readings

Extension of Confidentiality Arrangement between United States FDA and the European Commission Enterprise and Industry Directorate-General, and the EMA 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

EMA-FDA GCP Initiative, 31 July 2009, EMA/INS/GCP/541006/2008.

Q&A on Initiative, published 2010 <http://www.ema.europa.eu/docs>, EMA/INS/GCP/172455/2010.

Annual Report of the Good Clinical Practice Inspectors Working Group 2009, 22 March 2010, EMA/INS/GCP/782679/2009.

EMA-FDA GCP Initiative – Terms of Engagement and procedures for Participating Authorities, 29 July

2009, EMA/INS/GCP/538414/2008, FDA Mod. 20 Aug 2009.

GCP Report Template 15 December 2006 and SOP C006/05 ‘Reporting of GCP Inspections’ effective 15 December 2006. MHRA website.

EuroPharma Today, 14 Jul 2010, FDA, EMA Confidentiality Agreement Expanding into “Clusters.”

<http://www.fda.gov/InternationalPrograms/Agreements/ConfidentialityCommitments/ucm100085.htm>. ■



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