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Report on the Pilot EMA-FDA GCP Initiative

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Glossary

Acronym	Region	Term
CBER	US	Center for Biologics Evaluation and Research
CDER	US	Center for Drug Evaluation and Research
CDRH	US	Center for Devices and Radiological Health
CFR	US	Code of Federal Regulations
CI	Global	Clinical Investigator
CHMP	EU	Committee for Medicinal Products for Human Use
CPGM	US	Compliance Program Guidance Manual
CRO	US /EU	Contract Research Organization
DIDP	US	Division of Information Disclosure Policy
DMC	Global	Data Monitoring Committee
DSI	US	Division of Scientific Investigations (<i>*Became Office of Scientific Investigations as of June 2011</i>)
DSMB	Global	Data and Safety Monitoring Board
EIR	US	Establishment Inspection Report
EMA	EU	European Medicines Agency
EU	EU	European Union
FDA	US	(United States) Food and Drug Administration
GCP	Global	Good Clinical Practice
GCP IWG	EU	GCP Inspectors Working Group
GMP	Global	Good Manufacturing Practice
ICF	Global	Informed Consent Form
ICH	Global	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILO	EU	International Liaison Officer
IMP	EU	Investigational Medicinal Product
IND	US	Investigational New Drug
IR	EU	Inspection Report
IIR	EU	Integrated Inspection Report
IWG	EU	Inspectors Working Group
MAA	EU	Marketing Authorisation Application
MS	EU	Member State

Acronym	Region	Term
MD	US /EU	Medical Device
NAI	US	No Action Indicated
NDA	US	New Drug Application
OAI	US	Official Action Indicated
OC	US	Office of Compliance
OIP	US	Office of International Programs
OND	US	Office of New Drugs
ORA	US	Office of Regulatory Affairs
OSI	US	Office of Scientific Investigations (*previously known as Division of Scientific Investigations)
PI	Global	Principal Investigator
QA	Global	Quality Assurance
SAE	Global	Serious Averse Event
SOP	Global	Standard Operating Procedure
SPC	EU	Summary of Product Characteristics
US	US	United States
VAI	US	Voluntary Action Indicated

1. Executive Summary

This report outlines the results of the pilot European Medicines Agency (EMA)-Food and Drug Administration (FDA) Good Clinical Practice (GCP) Initiative which was launched in September 2009 under the framework of the confidentiality arrangements established between the European Commission, the EMA and the US FDA. The main objectives of the initiative were to share information on inspections and GCP-related documents of common interest and to conduct collaborative inspections.

The pilot initiative has been very productive. A considerable amount of information has been exchanged, and this communication has facilitated improvements in the agencies' inspection coverage and decision-making processes. The thirteen collaborative inspections conducted under the initiative have contributed greatly to each agency's understanding of the other's inspection procedures; they have also led to the identification of potential improvements to these procedures. Both agencies have learned several general lessons during the process, while acknowledging that every inspection is unique and that there will always be some individual differences between inspectors (e.g., background differences that may lead to a focus on different aspects during the inspection).

The EMA and the US FDA now intend to continue with the initiative, incorporating lessons learned during the pilot. The agencies will also consider opportunities for expanding the scope of the initiative.

2. Background

The clinical development of pharmaceutical products has become a global undertaking. In most cases sponsors submit the same clinical trials in support of Marketing Authorisation Applications (MAAs) to the EMA and New Drug Applications (NDAs) to the US FDA. Subjects participating in the pivotal clinical trials in these MAAs/NDAs are often recruited in both Europe and the US (1, 2). Regulators in the US and European Union (EU) must verify 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 investigational plan, and have data that have been correctly reported. The increasing globalisation of large scale and complex clinical trials, coupled with limited inspection resources, dramatically limits the range of trials and clinical investigators who can be inspected for GCP compliance. If regulators can work in a collaborative and synergistic manner in carrying out GCP inspections and implement information exchanges, then inspectional resources can be used more efficiently, and inspection coverage can be improved.

Although the US FDA and EMA each have systems and programs in place to verify compliance with applicable regulatory requirements and provisions of GCP, these programs have not historically included bilateral, systematic coordination and conduct of GCP inspections on marketing applications of common interest, nor have they developed a systematic and timely mechanism for sharing relevant GCP-related information. Communication and cooperation between US FDA and EMA on GCP harmonisation and inspection has long been a strategic objective, with formal information-sharing confidentiality arrangements. However, there has been limited strategic and structured use of these arrangements for GCP compliance efforts.

For this reason, and based on previous experience in the good manufacturing practices (GMP) field (3), the EMA and US FDA agreed to launch a pilot EMA-FDA GCP Initiative (4). This initiative has involved EU inspectors, the EU GCP Inspectors Working Group (GCP IWG), FDA inspectors, the EMA Clinical and Non-clinical Compliance Section, the EMA International Liaison Officer (ILO), the FDA Center for Drug

Evaluation and Research (CDER), the FDA CDER Office of Scientific Investigations (OSI), the FDA CDER Office of Compliance (OC), the FDA CDER Division of Information Disclosure Policy (DIDP), the FDA Office of Regulatory Affairs (ORA), the FDA Office of International Programs (OIP), the FDA Office of New Drugs (OND) and, most recently, the FDA Center for Biologics Evaluation and Research (CBER).

This initiative is being carried out under the framework of the confidentiality arrangements established between the European Commission, the EMA and the US FDA (5). It commenced in September 2009 with an 18-month pilot phase which focused on a subset of regulated products, specifically, those regulated by CDER at the US FDA and by the EMA through the centralised procedure in the EU.

The pilot generally focused on applications pertaining to new drugs and on joint inspections for sites located in the US and EU (with one exception). The initiative did not include joint inspections for generic drug applications, although limited information exchanges related to such applications did occur.

3. Objectives of the Report

The objectives of this report are to provide a summary of the activities performed during the pilot phase of the EMA-FDA GCP Initiative, along with an objective assessment of the experience, and to propose a way forward in the future cooperation between EMA and US FDA in the area of GCP and inspections. The results are reported in line with the key objectives of the EMA-FDA GCP Initiative:

1. To conduct periodic information exchanges on GCP-related information
2. To conduct collaborative GCP inspections
3. To share information on interpretation of GCP

4. Methods

Both agencies agreed on a procedure to move forward with the objectives for this initiative, which is well described in the "Terms of engagement and procedures for participating authorities" (6). Both agencies also developed the document "FDA EMA Good Clinical Practice Initiative Frequently Asked Questions and Answers" (7) for staff and the public.

An action plan for the pilot phase was developed with responsible persons from each agency appointed to undertake the following:

- Ensure the implementation of the initiative
- Streamline the sharing of information and timely communication of inspection outcomes
- Facilitate communication between the EU and US FDA inspectors and assessors regarding the exchanges of information and the collaborative inspections
- Evaluate the progress of the initiative and implement changes as needed
- Report on the initiative at the end of the pilot

5. Results of the Pilot GCP Initiative

The pilot GCP initiative has met its intended objectives and has been judged by both agencies to be extremely successful, and it has further strengthened the confidence in inspections between the partner organisations. The results presented are reported according to the key objectives of the EMA-FDA GCP Initiative, and a summary can be found in **Table 1**.

5.1. Exchange of Information

The GCP initiative is one of several activities carried out within the framework of the confidentiality arrangements established between the US FDA, the EMA and the EU Commission. EMA and FDA have made public a statement of authority and confidentiality commitment not to publicly disclose non-public information shared by both agencies (8, 9).

Information shared flowed through the respective international offices to track the information requested/provided and to guarantee the necessary clearances for the sharing of information. 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 EMA is the International Liaison Officer (ILO). Any redaction of FDA documents needed was done through CDER's Division of Information Disclosure Policy (DIDP).

More than 250 documents were exchanged during the pilot phase. Of these, more than 50% were product-specific documents concerning 54 different products. The documents exchanged include the following:

- Information on inspections planned/conducted
- EMA inspection requests/FDA assignments
- Inspection reports or summaries of critical or relevant findings
- Inspection outcomes (preliminary and/or final)
- Assessment outcomes in relation to the inspected application discussed
- Lists of applications submitted to both agencies
- US FDA Refuse to File letters
- US FDA Complete Response letters
- US FDA Advisory Committee briefing documents
- Policies
- Guidances (draft versions as well as final documents)
- Procedures
- Templates

These exchanges occurred through several channels:

a) Exchanges via e-mail (Eudralink): These were primarily ad hoc exchanges to address requests for information from both sides. A form was agreed upon by both parties to standardise and formalise the requests and to help track the information exchanged. For all exchanges, the secure "Eudralink" system was used. In most cases, these requests led to further discussion and follow-up during routine, monthly teleconferences.

b) Teleconferences: The pilot phase included 23 teleconferences, including 6 product-specific teleconferences concerning 4 different products. These calls included staffs from the EMA Clinical and Non-clinical Compliance Section, the EMA ILO, the EMA and FDA Liaison Officials, EU inspectors (as relevant), the FDA CDER OSI, the FDA ORA, the FDA OIP and, most recently, the FDA CBER. In general during these teleconferences the following agenda topics were covered:

- Product-specific inspections for which information on planned inspections or the availability of inspection reports/outcome was requested.
- List of inspections planned and conducted. This information has been very useful in identifying potential inspection reports available for exchange and also in identifying candidates for observed inspections and/or sequential inspections.
- Exchanges of information on applications submitted to each agency per month. These exchanges greatly facilitated identification of applications submitted to both agencies in parallel, with the aim of identifying candidates for joint inspections, sequential inspections, or parallel inspections. For those applications identified as submitted sequentially, feedback and/or the inspection report from the agency that inspected first was requested to facilitate inspection planning by the other authority and to improve the inspection coverage.
- Discussions and follow-up on joint and observed inspections.
- Topics of interest: training opportunities, conferences, GCP-related documents of interest under preparation or discussion, etc.

In the case of joint inspections, ad hoc product-specific teleconferences were held, during which the involved EU and FDA inspectors discussed:

- Selection of trials and sites to be inspected
- Potential dates for joint inspections
- Scope of the inspection
- Inspection team (per site)
- Communication of the joint inspection to the sponsor/applicant
- Pre-inspection meeting plans
- Organisational matters

c) Face-to-face meetings: Four meetings have taken place during the pilot, in October 2009, March 2010, June 2010, and November 2010. These meetings generally focused on evaluating the progress of the pilot, identifying lessons learned, and process improvements.

5.2. Collaborative inspections

This section describes only those collaborative inspections for which EU and US inspectors were together at the inspection site, i.e., joint and observed inspections. Parallel and sequential inspections, as defined in the “Terms of engagement and procedures for participating authorities” (6), were coordinated via the information exchange methods explained above in **Section 5.1** in order to facilitate inspection coverage and the decision-making process.

5.2.1. Joint Inspections

A total of 7 joint inspections, concerning 3 different applications, have been carried out as part of this initiative. The sponsor site was selected for inspection for 3 applications (2 sponsor sites in the US and 1 sponsor site in France); for one application a CRO located in Canada was subject to inspection; and the rest were 3 clinical investigator sites (2 sites in the US and 1 site in Germany). Inspectors from Germany, the United Kingdom, Spain, Denmark, France and the US FDA have been involved in these inspections.

Although the intention was to limit joint inspections to sites in the US and EU during the pilot phase, an exception was made in the case of a site in Canada (the CRO mentioned above). As inspectors from EU and US were going to inspect this site during the same timeframe (EU inspectors for a triggered inspection for an approved product on behalf of EMA and FDA for a pre-approval inspection), it was determined to be a good opportunity for a joint inspection.

The Joint Inspection Process

Before the joint inspection programme began, an EMA-FDA Joint Inspection Plan was developed to outline the steps to be taken before, during and after an inspection.

Before each inspection, teleconferences took place in advance to agree on the dates of the inspections, sites to be inspected, etc. (**see 5.1.b**). In addition, announcement letters, EMA inspection requests, FDA assignments, inspection plans and other relevant information (EMA/FDA guidance on clinical investigation, list of subjects of interest, etc.) were shared within the joint team (**see 5.1**) to facilitate the preparation of a joint inspectional plan.

Each inspection was to have a lead inspector from the host country (i.e., US FDA leading for the inspection in the US and EU inspectors leading for the inspections in Europe) with work in pairs, one US FDA inspector with one EU inspector, for the document review and interview sessions. However, in practice, this approach was not always feasible for the inspectors or transparent to the inspected party as foreseen in the joint inspectional plan.

During the close-out meeting, each agency followed its own procedures. The EU inspectors provided verbal feedback on the findings of the inspection, while the FDA inspectors provided the inspectee with verbal feedback and a document, called Form FDA 483 "Inspectional Observations", which lists the observations made by the inspector during the inspection.

Similarly, after the inspection, each agency followed its own procedures for reporting the inspection and further follow-up. Both agencies continued to exchange information and shared final inspectional reports as well as inspectees' responses to the inspection findings.

Feedback on the Joint Inspection Process

During the pilot, a "Feedback Form for Inspections" was implemented with the intention to collect written feedback in a standardised way from the inspectors on the joint inspection experience and the observed similarities and differences between the US FDA and EU inspection processes.

Feedback from inspected parties was obtained informally from a number of sponsor personnel. They were asked to provide comments on the joint inspection process following the close-out meeting. There was one sponsor who specifically requested the opportunity to give feedback. The agencies are presently exploring appropriate mechanisms for obtaining written feedback from inspectees subject to upcoming joint inspections and a more formal process will be implemented in the future.

5.2.2. Observational Inspections

The pilot included 6 observed inspections related to 3 different applications. US FDA observed 3 EU inspections in the US, and EU inspectors from UK, Ireland and Sweden observed US FDA inspections in their respective countries. Three of the sites inspected were CRO sites, 2 located in the US and 1 in Ireland; another 2 were sponsor sites located in the US and UK; and the last one was a clinical investigator site in Sweden.

Contrary to the joint inspections, for the observed inspections the “Terms of engagement and procedures for participating authorities” (6) foresaw the importance of preparing a summary of similarities and differences between the conduct of the inspections observed by the GCP inspector of the inspecting authority and the process used by the observer’s regulatory agency. For this purpose a template for observation of an investigator site inspection was prepared before the start of the first observational inspection, and the feedback was collected. Later, a separate template for observation of a sponsor/CRO inspection was developed.

The observed inspections were much easier to arrange and very well received by the inspected entities and the inspectors. These inspections also allowed the opportunity for much questioning by the observer. Some differences in inspectional styles were noted from the feedback received but not in the overall assessments.

5.3. Shared Information on Interpretation of GCP

During the pilot initiative, the EMA and US FDA have shared different pieces of GCP-related guidance documents, position papers and policies in order to harmonise the agencies’ understanding of GCP and to standardise the requirements for industry wherever convergence would be beneficial for the clinical research process.

There has also been an extraordinary opportunity for FDA staff and the EU inspectors to discuss their own inspection experiences when they have been involved with the collaborative inspections and through participation in meetings and training programmes. Many questions have been asked, and there have been many in-depth discussions on best practices.

The documents shared, some of which are still in draft form or in the consultation phase, have been:

- **From US FDA**

- Guidance for Industry- Providing Regulatory Submissions in Electronic Format- General Considerations (10)
- Guidance for Industry- Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (11)
- Draft Guidance for Industry: Electronic Source Documentation in Clinical Investigations (12)
- FDA Compliance Program Guidance Manual for Sponsors/CROs/Monitors (7348.810) (13)
- FDA Compliance Program Guidance Manual for Clinical Investigators (7348.811) (13)
- Draft Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (14)
- Draft Guidance for Industry Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination (15)

- **From EMA**

- Reflection paper on expectations for electronic source documents used in clinical trials (16)
- Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples (17)
- Italian legislative decree on definition of the minimum requirements which Contract Research Organisations (CRO) shall satisfy in order to work within clinical trials on medicinal products (18)
- Guideline on validation of bioanalytical methods (19)

EMA also engaged US FDA experts to participate via teleconference in the discussions on some of the above documents held at the quarterly EU GCP IWG meetings, with the aim of ensuring consistency in the way both agencies approach these topics.

In addition, the EMA and US FDA have invited each other to regular and ad-hoc training meetings to increase each agency's knowledge of the other's procedures and to share best practices. The following trainings have been attended by EU or US inspectors and staff:

- **Organized by US FDA**

- FDA Advanced Clinical Bioresearch Monitoring on 14-18 March 2011 (attended by 4 EU inspectors from Germany, France, Spain and Denmark)

- **Organized by EMA**

- EU GCP Inspectors' Working Group (IWG) training course held in Rome on 11-14 October 2009 (attended by 4 FDA representatives from OSI, ORA and OIP)
- EU GCP IWG training course held in London on 3-5 November 2010 (attended by 4 FDA representatives from OSI and OIP. One FDA staff person from the Center for Devices and Radiological Health gave a presentation via teleconference, and 1 OSI staff joined this teleconference).
- EU GCP IWG Basic course on 2-4 March 2011 (attended by 1 FDA representative from ORA, and 14 staff from OSI joined via teleconference).

Table 1: Overview of the Results of the EMA FDA GCP initiative

Objective	Total number of documents exchanged	T-cons	Face-to-face meetings	Number of products concerned	Number of types of documents (see section 5.1)	Participants in the t-cons
1. To Conduct Periodic Information Exchanges on GCP-Related Information	> 250	23 (6 specific products)	4	54	26	<ul style="list-style-type: none"> • EMA Clinical and Non-clinical Compliance Section • EMA ILO • EMA and FDA Liaison Officials • EU inspectors • FDA OSI/CDER • FDA OC/CDER • FDA ORA • FDA OIP • FDA CBER

Objective	Type of Inspection	Number	Number of Products Concerned	Type of site per product under inspection	Location of inspected sites	Country of inspectors involved
2. To Conduct Collaborative GCP Inspections	Joint inspections	7	3	1 Sponsor 1 CI 1 CI	US US Germany	Germany, UK and US FDA inspectors
				1 Sponsor 1 CI	France US	France, Spain and US FDA inspectors
				1 Sponsor 1 CRO	US Canada	UK, Denmark and FDA inspectors
	Observa-	6	3	1 Sponsor	UK	US FDA/UK

Objective	Type of Inspection	Number	Number of Products Concerned	Type of site per product under inspection	Location of inspected sites	Country of inspectors involved
	tional inspections			1 CRO 1 CI	Ireland Sweden	US FDA/Ireland US FDA/Sweden
				1 Sponsor 1 CRO	US US	US FDA/Denmark US FDA/Spain/ Germany
				1 CRO	US	US/Sweden/ Germany

Objective	Documents exchanged	Training Activities	Training Presentations			
3. To Share Information on Interpretation of GCP	11	4	> 50			

6. Discussion and Lessons Learned

Every organisation has its own culture, internal processes and habits of functioning that are not readily observable to those outside the organisation. In the case of the FDA and EMA, this has limited the agencies' abilities and willingness to coordinate and synergise their GCP inspectional efforts. The pilot GCP initiative, under the EMA-FDA confidentiality arrangements, has created a structured environment for communication, information exchange and collaboration, and EMA and FDA staff have rapidly developed a greater understanding of their counterpart's policies and procedures. Several general lessons have been learned in the process, while acknowledging that there always will be some individual differences with all inspections and between inspectors (e.g., background differences which may lead to a focus on different aspects during the inspection).

6.1. Exchange of Information

The considerable volume of information exchanged reflects the effective and fluid communication maintained during the pilot phase, which has supported the following:

- Improving inspection coverage, avoiding inspection of sites already inspected by the other authority, and therefore avoiding the duplication of inspections, reducing the burden to the inspectee, and using the inspection resources in a more efficient way
- Influencing the inspection decision-making process, since information exchanged has been the basis for triggering inspections in some cases and for cancelling inspections in others
- Gaining a better understanding of each other's inspection procedures and processes

Sustaining this pace of exchange in the long-term will require more resources dedicated to the collaboration, as well as a common tracking system and procedures for handling the information exchanged in order to ensure adequate follow up, effective and timely communication, and rational use of the information in decision-making.

6.2. Collaborative Inspections

The experience with these inspections has been very useful to better understand each other's procedures and share best practices, and to identify the gaps in each other's inspection processes. The experience has been very positive and has shown that each agency's inspection procedures are more similar than different and that the main differences are linked to the level of detail in each aspect of the process, the approach to inspect, the inspectors involved and their qualification, and some differences in the reporting process.

In general, the following aspects in relation to the preparation, conduct and reporting inspections are the same:

- a) Type of inspection: routine versus "for cause" or "triggered"
- b) Inspection request (EMA)/assignment (FDA): in both cases this document indicates to the inspectors the clinical trial protocol(s) and sites to be inspected and the scope of the inspection.
- c) Preparation of the inspection:
 - Identification of contact points at each inspected site
 - Scheduling of the inspection
 - Review of documentation/information related to the inspection of concern

- Preparation of an inspection plan

d) Conduct of the inspection:

- Opening meeting to explain the basis and purpose of the inspection, to present the inspection plan and confirm the resources, documents and facilities needed
- Review of trial related documents (subjects' case report forms, lab reports, trial file at the site, etc.) with direct access, interviews and observation of activities, equipment and conditions in the inspected areas
- Documentation of the deficiencies observed and copies of records to substantiate the deficiencies or inconsistencies identified
- Closing meeting to present inspection findings to the inspectee(s) and to ensure that the results of the inspection are understood

d) Reporting of the inspection: although there are some differences in the reporting process, at the conclusion of the inspection each agency is required to prepare an inspection report per site inspected and make available that report to the concerned site regardless if comments from the inspectee are requested (EMA) or not (FDA only requires comments to the Form FDA 483, when issued).

By contrast, the following aspects in relation to the preparation, conduct and reporting inspections are different:

- The approach to inspect: system versus data oriented and, therefore, in the sample size of documents to be inspected
- Inspectors involved/qualifications:
 - Specialisation/background of the inspectors [clinical trials (EU) versus broader range of inspections (FDA)].
 - Experience in working as a team: the EU inspectors are used to working in teams whereas FDA inspectors often work alone.
 - Continuity of inspections for an application: For EMA requested inspections, at least one member of the team is usually involved in the inspections at all sites, which facilitates the follow-up of issues identified in the other sites. FDA inspectors work out of their districts and rarely do several inspections for one application. The FDA Center contact is responsible for the communication and coordination of issues identified.
- Number of findings: FDA can only cite non-compliances against US regulations (i.e., for CDER Title 21 CFR 11/50/54/56/58/312 and 314) but not ICH GCP as EU inspectors. Therefore, fewer findings are expected to be reported by FDA inspectors than EU inspectors in the same circumstances.
- Reporting of findings at the close-out meeting: FDA determines findings and has a written document (Form FDA 483) that is given to the inspectee at the final close-out meeting. EU inspectors give oral feedback on the most relevant findings at the close-out meeting but the written report is provided to the inspectee for comments later in the process.
- Differences in the grading of the findings versus overall grading of the outcome of the inspection: FDA has a final classification determination for the totality of a site inspection but does not grade every finding. The EU inspectors have a grading system and grade every finding.

From a practical point of view, the joint inspections have been more difficult than initially expected in contrast to the observational ones. The observational inspections have been much easier to plan and lend themselves to better viewing of the other agency's inspectional procedures. The experience with

the joint inspections has demonstrated that the planning and conduct can be difficult for the following reasons:

- The agreement of the inspection dates and number of days at each site (scheduling a common time in the calendars of 4 - 5 busy people is not easy)
- Availability at the inspected site of adequate rooms to allocate a joint team (often with 5 - 6 members) for reviewing documents and performing interviews
- Coordination of the distribution of tasks within the team
- Coordination of the requests for documents and keeping track of copies being made
- Ability to look at the files "together"
- Concentration during the inspection (as it can get very noisy with so many people involved)

Contrary to the observed inspections, during a joint inspection it can be unclear how much of one agency's inspectional activities affect the other's activities. Also, staff must spend most of their time on their own inspection and are unable to focus on their counterpart's inspectional techniques. Therefore, more emphasis on observed inspections is suggested for the future of the initiative when trying to increase the knowledge among inspectors of their counterpart's inspection procedures.

The feedback received from the inspectors involved was generally very positive. Much was learned watching the others ask questions and interact with the site. Negative comments dealt more with the process itself as indicated above.

Overall suggestions for improvement of the collaborative inspections are the following:

- Ensure someone always takes the lead during the inspections. Although this has been stressed in various documents, it still is worth remembering.
- Have an agreed upon pre-inspection plan with the same inspectional approach that the group follows as much as possible.
- Do not break off into too many smaller groups during the conduct of the inspection. Agree that 2 teams are feasible.
- Ensure prior to the inspection that the scope of inspection is the same for both FDA and EMA (in one case the EMA scope covered 2 trials whereas the FDA covered 3).
- Increase the knowledge among inspectors of their counterpart's inspection procedures, including inspection preparation, conduct, and reporting.
- Consider the fact that these are more resource-consuming than other inspections.
- Gather feedback from the inspectors on their experience with the joint inspections in order to improve the process.
- Gather feedback from the inspectees on their experience with the joint inspections in order to improve the process.
- Make sure staffs participating in joint inspections are enthusiastic about working with a group and also willing to develop a joint inspectional plan.

There is the need for more collaborative inspections before making any definitive statements regarding acceptance of inspection findings. However, both sides are learning best practices from each other and identifying ways in which they can improve their inspections.

Some of the main differences and similarities between EMA and FDA learned from the experience with the collaborative inspections are summarised in **Attachment 1**.

6.3. Shared Information on Interpretation of GCP

As noted in **Section 5**, several guidance documents have been shared between the agencies. Discussion of the documents during the teleconferences and agencies' staff who gave presentations on the documents, with time for questions and answers, has been very helpful. It was hoped that earlier drafts of such documents could be shared for comments before drafts were made public, but with the volume of work and the limited resources, this has not always been possible.

The shared training experiences have been extremely helpful in understanding not only each other's inspection techniques, but also each other's interpretation of GCP. It is hoped that these exchanges will continue and that there will be more formal documentation of potential disagreements.

7. Conclusions and the Way Forward

The pilot EMA-FDA GCP Initiative launched in September 2009 has received a tremendous amount of positive publicity from many different sources (20). It has improved communications between the agencies and strengthened each agency's trust in the other's inspectional efforts. The main objectives have been achieved, and the results obtained have exceeded expectations, as outlined in this report. Thus, to this point the initiative should be judged as a success.

Based on the experience with the pilot, it is the wish of both parties to continue with the initiative, taking into account the following considerations learned from this experience:

- To carry out more inspections together in order to identify the gaps in each agency's inspection processes and to fill in those gaps—with the broader aim of moving from “confidence building” to “confidence in,” with mutual acceptance of inspectional findings in the near future.
 - As part of this exercise, there is a need to develop a more user-friendly template to gather feedback from the inspectors and also develop a formal process to gather feedback from the inspectees on their experience of the noted differences during the joint inspection.
- To perform more observed inspections as they have proven to be less time- and resource-consuming than joint inspections, making the identification of advantages and gaps in each other's inspection process more efficient
 - As part of this exercise, gather feedback from the observational inspections in a more analysis-friendly mechanism.
- To continue performing joint inspections, but expanding the initiative to sites outside the US and EU
- To focus the joint inspections on sponsors and CROs instead of investigator sites in order to work towards developing a truly harmonised quality-systems approach to sponsor/CRO inspections
- To begin to focus on triggered inspections if opportunities arise
- To perform more parallel inspections for those applications submitted in parallel to both agencies and then to exchange the inspection reports/outcomes as part of the information exchange process with the goal of improving inspection coverage, avoid duplication of inspections, and provide a better picture of sites' GCP compliance status to improve the decision-making process

- To harmonise pre-defined metrics to assess GCP compliance and data reliability
- To strengthen training/understanding of each region's inspection procedures, in terms of preparation, conduct, and reporting of inspections, and to identify opportunities for joint training activities
- To develop a common system for tracking of information and to establish procedures for handling the large amount of information exchanged
- To assign more human resources to this initiative at both agencies
- To explore the possibility of expanding the initiative to other areas like bioequivalence (BE) trials in generic applications
- To explore the possibility of expanding the initiative to the FDA's Center for Biologics Evaluation and Research (CBER)

The "Terms of engagement and procedures for participating authorities" will be revised with the above considerations in mind.

8. References

1. Office of Inspector General Report "Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials"
<http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf>
2. Clinical trials submitted in marketing authorisation applications to the EMA. Overview of patient recruitment and the geographical location of investigator sites
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf
3. EMA FDA GMP Pilot Initiative
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4. EMA-FDA GCP initiative announcement
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm174983.htm>
5. Confidentiality arrangements concluded between the EU (EC and EMEA) and the US FDA/DHHS
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6. Terms of engagement and procedures for participating authorities
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8. Statement of authority and confidentiality commitment from the European Medicines Agency not to publicly disclose non-public information shared by the United States Food and Drug Administration
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/09/WC500096630.pdf
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14. Draft Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf>
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21. Office of Scientific Investigations web page

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090085.htm>

22. FDA ORA web page

<http://www.fda.gov/AboutFDA/CentersOffices/ORA/default.htm>

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000072.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800268ad

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http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004446.pdf

25. EU inspection procedures and guidance for GCP inspections

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000140.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800296c6&jsenabled=true

26. FDA Good Clinical Practice Regulations

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm#FDARegulations>

27. ICH E6 Guidelines on good clinical practice (ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95)

http://ec.europa.eu/health/files/eudralex/vol-10/3cc1aen_en.pdf

28. Directive 2005/28/EC

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29. Clinical Trial Directive 2001/20/EC

<http://www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf>

30. Form FDA 482
<http://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM127428.pdf>
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32. Procedure for reporting of GCP inspections requested by the EMEA
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http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000327.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580024596#section1

9. Attachment 1 – Inspection Similarities and Differences: FDA versus EMA

Topic	FDA	EMA
<p>1-General background information on each agency and their inspection programmes</p>	<p>The Office of Scientific Investigations (OSI), located in the Office of Compliance, Center for Drug Evaluation and Research (CDER) at the US FDA, is known as “Center headquarters.” It partnered with field personnel in 1977 to form the Bioresearch Monitoring Program. The division oversees inspections of clinical investigators, sponsors, and contract research organizations, pre-clinical laboratory studies, institutional review boards, and handles complaints and possible criminal cases developing from the work of these entities (21). In the US, CDER inspects almost all New Drug Applications (NDAs) and many supplements that involve vulnerable subjects, mainly a small sample of all sites involved in the pivotal trials. The initial consult for a routine (pre-approval) inspection request comes from the Office of New Drugs in CDER (after the application has been accepted for review) to OSI. Staff in OSI coordinate the inspections, sending the assignment and background materials to field personnel. The FDA’s Office of Regulatory Affairs (ORA) is the lead office for all FDA field activities and the bulk of the inspections are done by their staff independently (22). Inspections during the NDA phase are generally “routine”, but can be “for cause” or “directed”. Inspections can also be conducted at any point in the drug development process.</p>	<p>The European Medicines Agency (EMA) was established in 1995 as a decentralised agency of the European Union (EU). GCP inspections have been requested since 1997 (23). EU GCP inspections are carried out by the GCP inspectors of the Member States National Competent Authorities. During the validation phase, prior to the start of the assessment phase of a centralised Marketing Authorisation Application (MAA), the EMA Compliance and Inspection Sector performs a GCP validation of all new application/line extensions received and some variations when new clinical trial information is provided. The request for an inspection is made by the Committee for Medicinal Products for Human Use (CHMP) in a document stating the grounds for the inspection, the scope and suggested sites as well as any other information relevant to the inspectors. The Compliance and Inspection Sector coordinates inspections (24) through the Member State Inspectorates. There are two types of inspections:</p> <ul style="list-style-type: none"> a) Triggered inspections based on the concerns from the clinical assessors during the review of the dossier, focusing the inspection on issues or information of concern. b) Routine inspections. The Compliance and Inspection

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	Inspections during the investigational new drug (IND) phase are generally “for cause.”	Sector may also propose a routine inspection based on a set of predefined criteria. Not all MAAs are subject to a GCP inspection. The numbers of inspections are, ultimately, limited by the available resources from the Member State Inspectorates who also need to inspect the ongoing trials in their territories. Each inspection involves usually at least 2 inspectors from separate Member States.
2-History of Inspections	Inspections performed since 1977.	Inspections for EMA applications performed since 1997.
3- Inspection Manuals, Guides and Procedures		
a) Inspection Manuals, Guides and Procedures	FDA uses Compliance Program Guidance Manuals (CPGMs) to direct its field personnel on the conduct of inspectional and investigational activities (13)	The GCP Inspectors Working Group has developed procedures for the coordination, preparation, conduct and report of GCP inspections carried out in the context of the Centralised Procedure (25).
b) GCP Standards	For FDA CDER, Title 21 CFR Parts 11/50/54/56/58/312 and 314 (26). These regulations contain aspects reflected in the ICH GCP Guideline but with less level of detail.	ICH Topic E6: Good Clinical Practice (27) Directive 2005/28/EC (28) Clinical Trial Directive 2001/20/EC (29) Local requirements
4- Inspection requests		
a) Requestor of the inspection	Inspection requests (consults) are issued by the Office of New Drugs in CDER to OSI.	EMA inspection requests are adopted by the CHMP.
b) Types of sites inspected	Clinical investigators, sponsors, monitors, CROs, and IRBs.	The same type of sites can be inspected as part of the EMA programme (i.e. GCP inspections carried out by the EU inspectors in the context of the centralised marketing authorisation procedure) or national programmes (i.e. GCP

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		inspections carried out by the EU inspectors in the context of the national, decentralised or mutual recognition marketing authorisation procedures or as part of the oversight of the conduct of clinical trials in Europe)
5- Inspection team	FDA inspectors are field personnel from FDA's Office of Regulatory Affairs (ORA) and from various Districts across the country, rarely forming any team and rarely inspecting more than one site in the inspectional assignment. OSI reviewers or other subject matter experts from CDER may accompany ORA investigators, as needed.	Each inspection normally involves at least 2 inspectors from different EU MSs. The same team or at least one inspector in the team (normally the Reporting Inspector) is involved in the inspections at all/most of the sites, facilitating the follow-up of findings observed in previous sites inspected.
6- Inspection Announcement	For routine inspections, FDA will often call the site shortly before an inspection is scheduled. FDA conducts both announced and unannounced inspections. For foreign inspections, an announcement letter is sent by the ORA staff.	EMA sends a formal announcement letter to the applicant. In the announcement letter the applicant is requested to confirm in writing that the sites accept to be inspected and that they will make all required documents available for direct access by the inspectors. The applicant is also requested in this letter to prepare copies of an initial set of documents for provision to the inspectors (clinical study report, data listing, protocol, etc.) for the preparation of the inspection. The inspectors can then supplement this list with additional requests to the applicant (24).
7- Inspection Preparation		
a) Inspection Plan Preparation	The ORA field investigator prepares his/her inspectional plan per guidance, training, and experience based on the assignment from OSI.	A central inspection plan is prepared by the EU Reporting Inspector (RI) and finalised in agreement with the EU Lead Inspectors (LIs). Based on the

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		central inspection plan, the LIs will prepare local inspection plans for each selected site (24).
b) Request of information to the applicant prior to inspection	Rarely. Background documents (protocol, informed consent, data line listings, etc.) for review are usually pulled from the submitted application.	In the inspection announcement letter, EMA requests that the applicant provides the inspectors with a set of documents for the preparation of the inspection (see Section 6 in this table).
8- Inspection Conduct		
a) Notice on Arrival	FDA field personnel must present credentials along with Form FDA 482, "Notice of Inspection", to the most responsible person at the site for domestic inspections (30). Credentials are shown for all foreign inspections.	EU inspectors from Member States have national credentials that are available upon request. As noted in Section 5, there is an announcement letter.
b) Inspection of System v Data	FDA inspections focus on the reliability of the data and human subject protection.	EMA inspections review the data but focus on the systems and processes in place to reliably obtain that data and to ensure the protection of the human subjects.
c) Collection of Evidence	The FDA has enforcement action ability and the field investigator collects copies of documents, paying very strict attention to the handling of the copies as they could be used as evidence in a potential case.	The EMA can take the actions indicated in section 9d. Other enforcement actions are the responsibility of the Member States and subject to local regulations. EU Inspectors may collect copies of documents to help them with writing their reports but they do not necessarily consider these copies of documents evidence and are not collecting document copies with that intent.
d) Continuity of follow up of issues from previous sites inspected	Headquarters is expected to coordinate as usually there are different ORA field investigators at each site to be inspected.	At least one member of the team inspects all sites (normally the reporting inspector). This facilitates follow-up observations from one site to another.
9- Reporting		

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a) Closing meeting	Upon completing the inspection, a discussion of the inspectional findings takes place. If objectionable conditions are observed, FDA provides the most responsible person with the document Form FDA 483, "Inspectional Observations", which lists the observations made by the ORA field investigator during the inspection (31).	During the final closing session with the key organization and department representatives from the inspected entity, the lead inspector highlights provisional inspection findings but there is no written summary of the same left with the inspected entity at the conclusion of the inspection.
b) Grading of individual findings	No. There is an overall classification of the inspection (No Action Indicated, Voluntary Action Indicated, Official Action Indicated) but not of each individual or group of findings.	EU inspectors categorize all the findings or a group of findings as critical, major or minor (32).
c) Comments from the inspectees	Not needed unless a Form FDA 483 is presented. Otherwise, the inspectee may respond to the 483 observations orally during the exit interview and/or respond in writing after the inspection. If the inspectee chooses to respond in writing to the deficiencies listed on the 483, the response should be a written response within 15 days of the inspection for consideration regarding a potential Warning Letter. If no enforcement action is contemplated, or after enforcement action is concluded, the FDA provides inspected establishments with a final inspection report, called an Establishment Inspection Report (EIR).	Yes. The IR is sent to the inspectee and/or the sponsor responsible with a request for comments on major factual errors, points of disagreement or remedial actions to be provided, to be sent to the Lead Inspector, within 15 days of receipt of the report. If a response is not received within the stipulated time frame, the absence of a reply is recorded in the IR. On receipt of comments, these are included in the final version of the IR as an appendix. The inspectors will consider the responses of the inspectee and will indicate, as an additional appendix, whether or not these are acceptable and what impact, if any, they have on the original inspection findings (32).
d) Overall outcome/classification of the inspection	The ORA field investigator finalizes the inspection and recommends a classification. The EIR, Form FDA 483 (if issued), copies of any materials collected during the inspection, and any	The Reporting Inspector compiles an Integrated Inspection Report (IIR) in English based on the individual IRs. The IIR will summarise the major and critical findings and contain an

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	<p>inspectee response that has been received by the District Office are forwarded to Center headquarters for further evaluation and final classification of the inspection outcome. A final classification (No Action Indicate, Voluntary Action Indicated, Official Action Indicated) of the inspection is made by OSI (33).</p> <p>OSI generates a Clinical Inspection Summary (CIS) of all inspection results for an application and makes a final recommendation to the Office of New Drugs review division regarding reliability of the data inspected per site and as a whole. Recommendations may also include additional inspections needed before any final conclusion can be made.</p>	<p>evaluation of the quality of the data submitted and compliance with the principles of GCP based on the findings at all inspected sites. Any finding that is process related and not site specific will also be highlighted in the IIR. The IIR will also contain a conclusion on whether the quality of the data inspected as a whole or in parts may be used for the evaluation by the assessors regarding acceptance/non acceptance of the trial data. The IIR conclusions recommend any follow-up to be requested from the applicant or a further inspection if considered necessary (32).</p>
<p>e) Action to be taken after a negative inspection</p>	<p>Data from a specific site can be rejected as part of the application. If the CIS recommends rejection of all data inspected, the Office of New Drugs will consider as part of the overall evaluation of the application and issue a Complete Response Letter (34) to the sponsor that its new drug application (NDA) to market a new drug will not be approved in its present form. The letter will describe specific deficiencies and, when possible, will outline recommended actions the applicant might take to get the application ready for approval. There are a number of steps that the FDA can take in addition to rejecting the data when an inspected entity is classified as OAI.</p> <ul style="list-style-type: none"> • Warning Letter: A Warning Letter identifies serious 	<p>The actions that EMA can take as a consequence of a negative inspection are:</p> <ul style="list-style-type: none"> • Negative opinion • Loss of certain data or trials • Restriction on claims in Summary of Product Characteristics (SPC) • Refusal, suspension or revocation of the marketing authorisation application <p>In case of fraud, the responsibility falls in the MS where the clinical trial was conducted.</p>

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	<p>deviations from applicable statutes and regulations and is issued for violations of regulatory significance. Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected. Warning Letters are issued to achieve voluntary compliance, and include a request for correction and a written response to the agency. It is an informal advisory to a firm communicating the Agency's position on a matter, but does not commit FDA to taking enforcement action. Redacted copies are publically posted (35).</p> <ul style="list-style-type: none"> • Other Actions: FDA may disqualify a clinical investigator from receiving investigational products pursuant to FDA's regulations if he/she has repeatedly or deliberately failed to comply with all applicable regulatory requirements or the clinical investigator has repeatedly or deliberately submitted false information to the sponsor. The FDA may also offer a restricted agreement with an investigator with respect to their conduct of clinical investigations. If convicted of criminal misconduct, FDA may ban, or debar, such individuals from participating in the drug industry and a firm can be fined heavily for employing such a person (36). FDA may defer substantive scientific review of one or more of a firm's applications and/or withdraw the approved 	

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	applications (37).	
9- Other		
a) Financial Disclosure	Yes (38).	No
b) Inspections Fees	No	Yes. EMA charges a fee to the applicant for each site inspected (39).