

International GCP Inspections

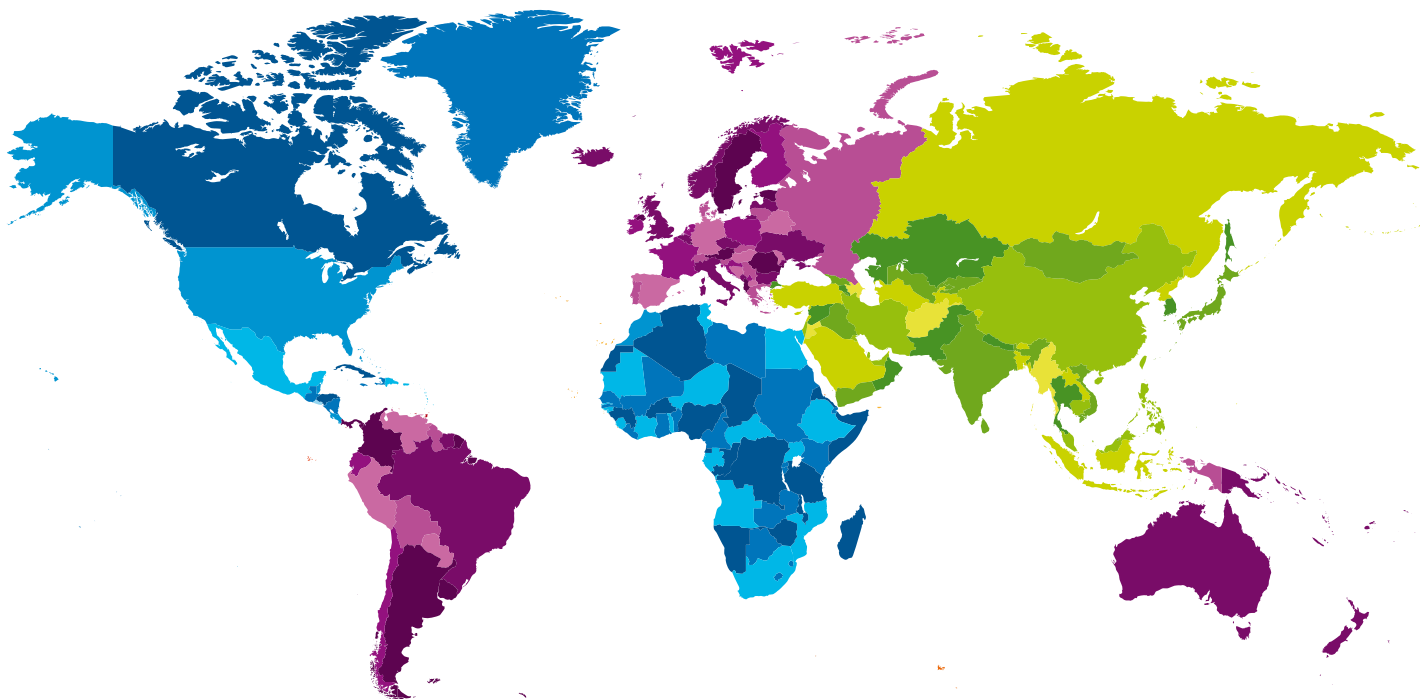
The EMA Perspective

Ana Rodriguez

Session chaired by Nicky Dodsworth MICR CSci

Reported by Nicky Dodsworth MICR CSci

Keywords: 3rd countries, European Medicines Agency (EMA), Food & Drug Agency (FDA), GCP inspections



The focus of the discussion at this session of the ICR Annual Conference was on international collaboration and the requirement to increase the number of inspections outside the European Union (“3rd countries”), rather than looking at the inspection process itself. The EMA are committed to ensuring the safety of patients in the European Union, and have considered how trials that are run outside Europe have been conducted both scientifically and ethically. If the data from these 3rd countries has been obtained unethically or the quality of the data is flawed, then this could put at risk patients in Europe who may be given the medicinal product following Marketing Authorisation.

The EMA acceptance of clinical trials data from emerging growth regions, coupled with increasing international collaboration between the EMA and FDA in the pilot phase GCP initiative made for an interesting update on how these processes are developing.

EU regulatory framework

The regulatory framework for clinical trials in Europe is based on the 2001/20/EC and 2005/28/EC Directives as well as supporting guidelines, EudraLex Volume 10 and ICH Guidelines (including GCP). We also need to consider 2003/94/EC, GMP Guidelines and GMP Annexes.

The Marketing Authorisation submission process is regulated under the 2001/83/EC Directive, Notice to Applicants, regulation 726/2004 establishing the EMEA and the Centralised Procedure, 2003/63/EU Annex I, and national legislation.

Guidance published by the European Commission and by the EMA must also be considered for all trials that are run in Europe. Regulation No. 726/2004, Recital 16 states “There is a need to provide for the ethical requirements of Directive 2001/20/EC... relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use to apply to medicinal products authorised by

the Community. In particular, with respect to clinical trials conducted outside the Community... it should be verified that these trials were conducted in accordance with the principles of GCP and ethical requirements equivalent to the provisions of the said Directive.”

Directive 2001/83/EC as amended, article 8 (ib) provides an ethical statement for clinical trials conducted outside the European Union. Article 13 states “... ethical requirements of Directive 2001/20/EC apply to all medicinal products authorised within the Community. For clinical trials conducted outside the Community ethical requirements equivalent to the provisions of that Directive.”

Directive 2003/63/EC Annex I is worded similarly, “They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.”

Increasing use of 3rd country data

There are an increasing number of trials and patients that come from 3rd countries. Between 2005 and 2009, approximately 60% of patients in trials submitted to support Marketing Authorisation Applications came from outside Europe. This number is also reflected in the number of trial sites.

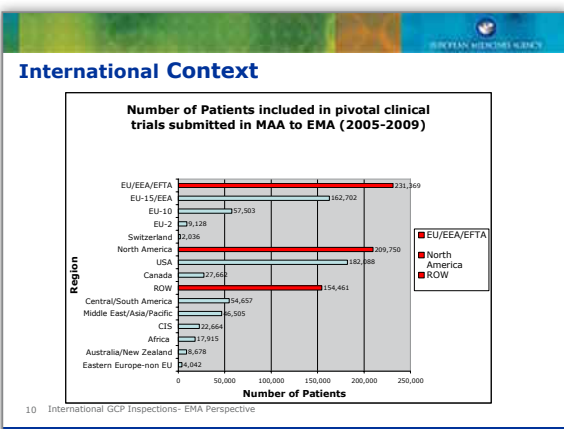


Fig. 1 Slide from presentation provided by Ana Rodriguez from data presented in EMA publication 5 November 2010: Clinical trials submitted in marketing authorisation applications to the EMA – Overview of patient recruitment and the geographical location of investigator sites, presented at ICR Annual Conference, Brighton, UK, 22nd March 2011

“Between 2005 and 2009, approximately 60% of patients in trials submitted to support Marketing Authorisation Applications came from outside Europe.”

The US/Canada still conduct clinical trials using the largest number of patients, but it can be seen that Brazil, Argentina and India are rapidly increasing the number of trials and numbers of patients being included in studies. Globalisation of clinical research is increasing and more trials are now being conducted outside Europe, in the emerging growth regions.

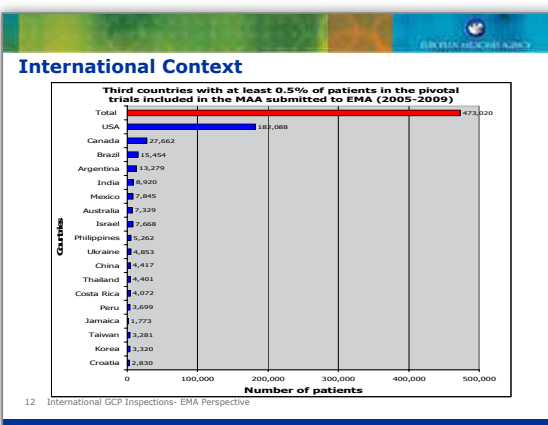


Fig. 2 Slide from presentation provided by Ana Rodriguez from data presented in EMA publication 5 November 2010: Clinical trials submitted in marketing authorisation applications to the EMA – Overview of patient recruitment and the geographical location of investigator sites, presented at ICR Annual Conference, Brighton, UK, 22nd March 2011

EMA consideration & strategy document

The EMA has considered how trials are being conducted in these 3rd Countries: are they being conducted as scientifically and ethically as they are in Europe? What is the regulatory framework for these countries to ensure adequate supervision of these trials?

In its 2008 Work Programme, the EMA defined their strategy to focus on international issues related to inspection and the requirement for consistency of ethical standards for trials conducted outside the EU. The action plan was

to provide greater review on the conduct of trials and the level of ethical standards outside Europe. This has led to an increased number of inspections in 3rd countries.

The EMA strategy document ‘Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications’,¹ defined two principles relating to acceptability and applicability:

- The data from trials run in 3rd countries can be included as part of the MAA, but can only be considered if it meets the required ethical principles and acceptable levels of data quality.
- The EMA also needed to consider how suitable the trials being run in 3rd

countries were to the European population and to their medical needs.

Based on these principles, two sets of processes were defined. Prospective guidance and scientific advice, including PIPs were put in place. Both assessment and inspection to confirm acceptability were also outlined in this paper. A strategy for a global approach was detailed by putting in place a network of regulators and international ethical and data quality standards. The

strategy paper was translated in to a detailed work plan for 2008-2010. This defined the practical application of ethical standards for clinical trials in the context of EMA activities. Also, practical steps were undertaken during the provision of guidance and advice in both the drug development phase and the Marketing Authorisation phase. The paper stated the requirement for international cooperation in the regulation of clinical trials and the need for review and inspection as well as for capacity building in this area.

Reflection paper

A working group was established in 2009, comprising representatives from throughout the EMA:

- Committee for Medicinal Products for Human Use (CHMP)
- Committee for Orphan Medical Products (COMP)
- Good Clinical Practice Inspectors’ Working Group (GCP-IWG)

- Health Care Professionals' Working Party (HCPWP)
- Paediatric Committee (PDCO)
- Patients' and Consumers' Working Party (PCWP), and
- The EMA secretariat

The group developed a reflection paper, which was published in May 2010: 'Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in Marketing Authorisation Applications to the EMA'.² Consultation on this paper ended on 30 September 2010. An international workshop was held on 6-7 September 2010 involving people from different regulatory authorities, various patient associations, industry and academia to provide their review and comments.

The key topics of the reflection paper are:

1. Clarification of the practical application of ethical standards for clinical trials on medicinal products for human use. This is intended to ensure that 3rd countries have the necessary regulatory framework, that local ethics committee and regulatory approvals are in place prior to a trial starting, that comprehensive information is provided to patients, patients are free to consent to a trial, fair compensation is provided, the ability of a patient to withdraw from a study if they wish and that patient confidentiality is being maintained. Vulnerable populations, the justification to use placebo versus an active comparator and access to treatment post-trial were also defined.

2. Definition of the practical steps to be undertaken during provision of guidance and advice during the drug development phase, including assessment of the therapeutic need in the EEA and documentation of this in the drug development plan. One important point that was highlighted was the considerations to be taken when designing clinical trials to be run in 3rd countries, with particular emphasis on validation of assessment scales and the definition of efficacy. These both need to be validated in the local country or be considered applicable to the local population. Issues related to feasibility were also detailed, as well as general measures to assure data

quality when conducting trials outside the European Union.

3. Determination of the practical steps to be undertaken during the Marketing Authorisation Phase. The report considered how issues are assessed, and how triggers for inspection were defined and identified. The assessors' review of actions taken for non-compliance was considered, along with the decision whether to re-inspect, issue warning letters (like the FDA) or re-educate sponsors, etc. The need for greater transparency in general, as documented in the 'European Public Assessment Report', was outlined.

4. Definition of how international collaboration in the regulation of clinical trials is going to be achieved. These considerations included the identification of priorities, opportunities and partners, and of other initiatives to avoid duplication of effort. This extended to how contacts would be established in various countries, the need for an action plan on how inspection in 3rd countries are going to be performed, and the use of joint inspections to assist in establishing regulatory and ethical frameworks in these countries. It was acknowledged that resource allocation would be key to this success. The focus on countries that have a limited regulatory framework and those where most patients are recruited into clinical trials was defined.

International collaboration

EMA International Relations Officers were established a few years ago. Additionally, confidentially arrangements have been developed with US, Canada and Japan. Bilateral discussions have been conducted between the European Commission and China, India and Russia. The EMA is also actively engaged with the World Health Organisation (WHO). The aim of these increased international interactions is for bodies to assist

each other, to build expertise and systems, to agree standards (ethical and scientific), to reduce duplication of effort and to fill the gaps in the global network.

“The aim of these increased international interactions is for bodies to assist each other, to agree standards, to reduce duplication of effort and to fill the gaps in the global network.”

EMA inspections prior to the joint initiative

Only about 220 GCP inspections were conducted by the EMA from 1997 to 2009 as part of the Centralised Procedure Inspection process. Ana stated that this was due to limited resources. Only a small number of sites are routinely inspected, usually based on areas of concern. Improving cooperation will increase the number of inspections that can be conducted and make more efficient use of resources.

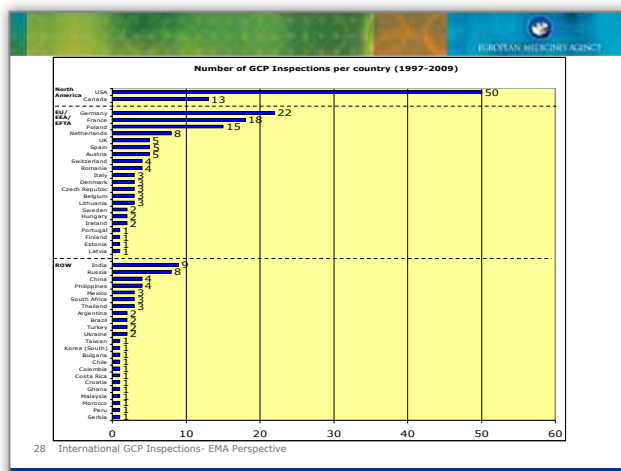


Fig. 3 Slide from presentation provided by Ana Rodriguez from data presented in EMA publication 5 November 2010: Clinical trials submitted in marketing authorisation applications to the EMA – Overview of patient recruitment and the geographical location of investigator sites, presented at ICR Annual Conference, Brighton, UK, 22nd March 2011

EMA-FDA initiative

The EMA-FDA joint inspection initiative was established in September 2009 within the framework of confidentiality agreements and national laws. The sharing of information was related to the authorisation and supervision of medicinal products and the review of

advanced drafts of legislation and/or regulatory guidance documents as well as information on inspections. This has been an important step as many clinical trials are submitted in support of both MAAs to the EMA and NDAs to the US FDA, frequently in parallel. The repetition of inspections on the same product and the same trials is not efficient. 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 and that the results are both credible and accurate. This improved collaboration and exchange of information has led to the focus of resources on areas of real need.

Prior to starting the initiative, FDA GCP staff spent several weeks at the EMA in December 2008 and they also participated in GCP-IWG training courses during 2008 and 2009. Following the creation of the EMA-FDA initiative in 2009, the terms of engagement and procedures for participating regulatory authorities were written. Following this, a Q&A document was published in 2010.


The pilot phase was conducted over 18 months and was designed to build experience and refine processes as well as identifying any difficulties. This phase had limited scope and was only targeted at medicinal products that were regulated by CDER in the US and the Centralised Procedure in the EU. Only new applications were targeted and inspection of sites were conducted in the US

and EU (although other sites were also inspected as part of the process). With the exchange of information, the EMA was aware of the sites the FDA were inspecting, the EMA could choose to go to these sites or others. Findings and best practice have been shared; this includes sharing information on interpretation of GCP. This has led to a much greater convergence and increased mutual understanding and confidence with the aim of creating a harmonised approach.

The report on the pilot phase³ has been published since this conference took place.

Joint inspections

The EMA does not have any inspectors; instead, it uses inspectors from Member States. In Europe, inspectors from the local Competent Authority took the lead in the country where the inspection is being conducted. When inspection was conducted in the USA, an inspector from the rapporteur country took the lead. Normally two EMA inspectors and two FDA inspectors were involved. Dates were mutually agreed, and pre-inspection preparations shared. Fees and travel arrangements were planned and conducted or charged as per EMA or FDA standards, which differ. During an inspection, there were joint open and closing meetings, joint overview meetings at the end of each day as well as joint interviews and sharing of study documents.



Each agency entered its own report into its own review process, but with mutually agreed findings and outcomes as far as was possible. EMA inspection reports were produced for each site, as well as an Integrated Inspection Report (IIR). The FDA issued inspectional observations (using Form 483) at sites when applicable and issued their Establishment Inspection Reports (EIRs) with findings and recommendations as usual. Reports were circulated to each agency for information at the end of the inspection process.

During each inspection the EMA and FDA inspected against their usual GCP reference standards, including ICH GCP and 2001/20/EC for the EMA; Title 21 CFR Part 11, 50, 54, 56, 58, 312 and 314 for the FDA. The EMA and FDA referred to the regulations of each of their respective countries, including local laws in the EU which are defined in the terms of engagement document. They inspected together, but this did not prevent separate inspections at other sites taking part in the same study. Alternatively, they could re-inspect if this was considered necessary or they could expand the scope of the inspection to cover areas of common interest. Enforcement actions can only be applied in the territory the inspectors cover, so the EMA can only enforce in Europe and the FDA only in the US.

As part of the joint inspection process, there were routine monthly teleconferences, product specific teleconferences, face-to-face meetings and other ad hoc exchanges.

“... seven joint inspections were conducted, involving three sponsors, four investigational sites and a CRO.”

ICR Training

Inspection worries? Be prepared!

This course will help you develop an effective strategy to plan efficiently for an audit/inspection, recognise and prioritise preparation methodologies and identify key stakeholders.

Presented in collaboration with Phlex
29 March, ICR office: £450*

* Other rates available for non-members and ICR members working in academia/healthcare provision.

Delegates can attend individual days of this course.

To find the training course that meets your needs, visit: www.icr-global.org/learning/training or download our full 2012 prospectus.





Several types of inspections have been performed under this pilot. Seven joint inspections (one triggered) were conducted, involving three sponsors, four investigational sites and a CRO. The countries involved included Denmark, France, Germany, Ireland, Spain, Sweden and UK. Six observational inspections were also conducted, involving two sponsors, two investigator sites and two CROs (in Ireland, US, Sweden and UK). Also, sequential and parallel inspections were conducted, mainly to share information and priorities.

Lessons learned & the future

It soon became apparent there was a lack of knowledge about each other's processes. There are differences in the way both agencies conduct inspections. The focus is different: the EMA approach is more systems based but the FDA is more data orientated. There are also many other process differences, including the way the EMA announce their inspections; this is usually formal and they request information to be provided in advance. The team of inspectors at the EMA is more specialised. The EMA prepare a formal inspection plan and request documents in advance, whereas the FDA approach is more informal. Sponsors are not notified of site inspections when the FDA inspects, but the EMA do provide this information. The EMA usually select fewer patients to review than the FDA. How findings are reported and the grading of these findings is also different. Some of the documents the agencies expect to see are different; for example, financial disclosure is not applicable to the EMA.

Several documents have been exchanged on the interpretation of GCP and training activities have been conducted for inspectors. Three

training sessions were organised by the EMA (October 2009, November 2010 and March 2011) and two were organised by the FDA (January 2011 and March 2011).

"A key similarity is that the findings from inspections are very similar in both regions."

A key similarity is that the findings from inspections are very similar in both regions. The FDA does publish this data and the EMA intends to publish something similar in the future.

It has been identified that a joint template does need to be developed to collect feedback from inspectees. The joint inspection process is very time consuming and it has been recognised that there needs to be one lead inspector at each site and that joint pre-inspection plans are important. Conversely, it was found that observational inspections consumed less time and resource.

Both joint and observational inspections will be continued to better identify the gaps with the aim of developing further confidence and mutual recognition. More parallel inspections will also be conducted to improve inspection coverage. Training will be strengthened in each agency's inspection procedures. Pre-defined metrics will be developed to assess GCP compliance and data reliability. Also there are


plans to widen the scope of inspections to cover other areas like generics and pharmacovigilance inspections.

Ana Rodriguez is Head of Clinical & Non-Clinical Compliance part of the Patient Health Protection Unit at the EMA. Nicky Dodsworth MICR CSci is Senior Director, Global Quality Assurance with Premier Research Group and Co-Chair of the ICR GCP Forum Steering Group.

References

1. European Medicines Agency (2008): Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications, available via www.emea.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016817.pdf
2. European Medicines Agency (2010): 'Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in Marketing Authorisation Applications to the EMA', available via www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/06/WC500091530.pdf
3. European Medicines Agency & US Food & Drug Agency (2011): Report on the Pilot EMA-FDA GCP Initiative, available via www.ema.europa.eu/docs/en_GB/document_library/Report/2011/08/WC500109777.pdf

To comment on this article, email comment@crfocus.org. Comments might be published on the Clinical Research focus web pages, with author's name/affiliation, unless notified otherwise.



**ICR
Team
Challenge**

Has your team got THE BEST BRAINS in clinical research?

Can you handle the pressure of our live
semi-final and Grand Final?

