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Update on a pilot project to collaborate on international GMP inspection activities

Background

The majority of international regulatory authorities are obliged by law to have systems in place to verify the GMP status of medicinal product manufacturers whose products are marketed on their territory. Most "developed" regulatory authorities ensure that these manufacturers in their territory are subject to routine GMP inspection. However, different approaches are taken to supervision of the manufacture of medicinal products outside a national territory, and to the supervision and inspection of active pharmaceutical ingredients. A number of countries have mutual recognition agreements (MRA) or memoranda of understandings (MoU) with other countries which allow them to rely on results from inspections performed by other countries. However these MRAs or MoUs are often limited in scope, and subject to certain restrictions. A large number of other international collaboration activities are also in place e.g. (V) ICH, WHO prequalification scheme, specific bilateral arrangements between countries, cooperation with EDQM etc.

Since the adoption of the ICH guideline on Quality Risk Management in 2005, the application of risk based approaches to the planning of inspections has increased in importance and there is increasing interest in additional international collaboration. Recent discussions between EU and US have focused on the possibility of administrative simplification between the regions, and discussions at the FDA international summit in November 2006 highlighted cooperation on inspections as a priority action area. This was further reinforced in the context of the Transatlantic administrative simplification workshop organised in Brussels November 2007 and the 2nd international summit in Dublin in December 2007.

In May 2007, EMEA launched the first phase of its EudraGMP database, which in further releases will allow certain GMP information on inspections performed by all EEA member states, as well as from its MRA partners (including the Australian TGA) and other international partners, to be accessible to the parties concerned,. A further release of this database includes a module for sharing inspection plans. U.S FDA also shares its GMP status on firms which are inspected by the US FDA through its Compliance status database (COMSTAT) with the EMEA and the TGA, along with other international regulatory partners.

The international industry associations have also raised the issue of international duplication of inspection and associated resource on a number of occasions. According to industry sources, EU, US, FDA and Brazil are the most active regulators inspecting in third countries.

Objective of this paper

The objective of this paper is to provide an update on a proposal for more coordinated international planning of inspections, with particular focus on a pilot project for Active Pharmaceutical Ingredients taking into account risk based approaches, building on equivalent GMP standards and mutual confidence between international regulators.

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Proposal

As an initial effort to improve international sharing of information and to facilitate more risk based approaches to inspection planning, it was proposed that a small group of interested regulators establish a pilot programme to coordinate inspection planning. This was based on the system currently operating in the EU where the EMEA outlines a yearly plan for centralised inspections and invites all Member States to contribute to this based on their own inspection plans.

Each regulator reserves the right to perform a dedicated "own" inspection, should they consider this necessary.

The basic idea is as follows:

Each regulator identifies a contact point specifically for inspection planning purposes. Regulators outline the inspections they have carried out during the last 24-36 months, and their preliminary inspection plans for the next 18 months. They provide this information to all other regulators involved in the pilot according to an agreed template. Following review of this information, they identify the following:

- If they have previously inspected the site
- If they plan to inspect the site within the same period
- If they have an interest in the site for some other reason (e.g. other products on the market or used in clinical trials in the territory concerned,)
- No interest

They communicate this information in a completed form to the other regulators involved.

Based on the information received and the common areas of interest identified, the regulatory contact points set up a teleconference to discuss further sites of interest.

The object of this teleconference is as follows:

1) to see if it is possible for one of the inspectorates to perform the planned inspection and provide outcomes (including where possible inspection reports) to the other interested inspectorates;

2) to investigate the possibility that one of the inspectorates would undertake to cover an area of inspection of interest to an other inspectorate(s); or alternatively

3) to see whether a joint (collaborative) inspection could be organised

The pilot phase is initially restricted to inspections of active pharmaceutical ingredients and to inspections carried out outside the participating regions. This is without prejudice to other ongoing collaborative work on inspections.

Opportunities for collaboration with the inspectorate of the country where the inspection will take place will also be explored.

Activities December 2007 to December 2008

Between December 2007 and April 2008, EMEA approached a number of European regulators active in the area of inspections of active pharmaceuticals, (UK MHRA, DE ZLG, FR AFSSaPS, IE IMB, EDQM), the US FDA and the Australian TGA. All authorities approached agreed to participate in the pilot project outlined and identified contact points for the project. PIC/S and WHO were also informed of the activity. A first teleconference was held on 1st July 2008 and a 2nd teleconference on 16th September 2008. These served to refine the proposed approach, agree on key performance indicators and to prepare templates for exchange of information as well as rules of engagement.

A provisional start date of November 2008 was decided upon and all parties agreed to share their inspection plans according to an agreed template.
Teleconferences to further discuss action and leadership on sites of interest to more than one party took place in late December 2008, marking the start of the operational phase.

Duration of pilot phase and reporting

The pilot phase will last for 18 months from the date it becomes operational. At the end of this period the outcomes will be analysed and a recommendation for future action made.

Expected deliverables and key performance indicators

The following have been identified as key performance indicators:

- Increased transparency and visibility of inspections performed by participating authorities
- Decrease in "duplicate inspections", (inspections of the same product or sites carried out by more than one participating authority within a similar time period)
- Overall increase in number of sites of API inspected by participating authorities for all inspections (pre-approval and surveillance/post-approval/GMP)
- Increase in number of inspections performed of value to more than one authority
- Positive assessment of the deliverables by the participant authorities

These performance indicators will be measured relative to baseline data collected from 2006 to 2008.

Relationship with Transatlantic Simplification Administrative process and Transatlantic Economic Council activities

Although this activity extends beyond the EU and US regions, also involving Australia, the deliverables and outcomes will also be considered within these frameworks.

Further developments

- Following the outcome of the pilot phase, if the program proves to be successful, the parties may consider expanding the scope of the initiative.

Abbreviations

AFSSAPS	French Health Products Safety Agency
API	Active Pharmaceutical Ingredient
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area
EMEA	European Medicines Agency
FDA	U.S. Food and Drug Administration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMB	Irish Medicines Board
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MoU	Memoranda of Understanding
MRA	Mutual Recognition Agreement
TGA	Therapeutic Goods Administration
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organisation
ZLG	Central Authority of the Länder for Health protection with regard to medicinal products for human and medical devices (DE)

Related Documents

Outline of a pilot project to rationalise international GMP inspection activities (published July 2008)
Rules of engagement and procedures for participating authorities (EMEA Doc. Ref. EMEA/INS/GMP/414323/2008)