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Pilot project to rationalise international GMP inspection activities

Rules of engagement and procedures for participating authorities (active pharmaceutical ingredients/active substances)

1. 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 in their territory. Most “developed” regulatory authorities ensure that these manufacturers in their territory are subject to routine GMP inspections. 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. Recently discussions with 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.

A number of international collaborative activities have since been initiated which are addressed elsewhere. This document outlines a pilot project which is initially focussed on inspections of active pharmaceutical ingredients/active substances.

2. Objective

The overall objective is to see whether greater international collaboration and information sharing can help to better distribute inspection capacity, allowing more sites to be monitored and reducing unnecessary duplication.

The purpose of this paper is to outline common principles and rules of engagement for agreement between participating authorities for more coordinated international planning of inspections, taking into account risk based approaches, building on equivalent GMP standards and mutual confidence between international regulators.

This pilot project is restricted to inspections of active pharmaceutical ingredients.

3. Principles

- 3.1 The scope of these activities is the sharing of information and collaboration on GMP inspections on active substances(AS)/active pharmaceutical ingredients (API) in countries outside the participating regions, including sterile AS/API.
- 3.2 Participating authorities agree to share inspection plans and inspection outcomes for such inspections carried out or proposed to be carried out during an 18 months period, which will begin once a working methodology has been agreed.
- 3.3 Where sites of common interest are identified, participating authorities agree to consider the following options (preferably the first two ones) :
 - a. They will endeavour to take into account the results of an inspection (to be) carried out by a participating authority in planning their inspection activity covered within the scope of this project.
 - b. They may request one of the participating authorities to expand the scope of their planned inspection to cover areas of interest to more than one participating authority.
 - c. If options 3.3.a and 3.3.b are not possible for any reason, participating authorities may perform a collaborative inspection of the concerned site.
- 3.4 The reference GMP standard for the inspections will be ICH Q7: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. For sterile AS/API (not covered by ICH Q7), the involved authorities will follow additional regional guidelines as appropriate.
- 3.5 Initial exchange of information on inspection planning will be done using an agreed template (attached in section 6).
- 3.6 Exchange of inspection reports and/or more detailed planning information shall be subject to specific confidentiality agreements with the authorities and companies, as necessary, concerned.
- 3.7 Participating authorities are responsible for ensuring that appropriate confidential arrangements are in place to allow them to participate in the activities covered by this paper.
- 3.8 The normal rules for national/regional coordination of inspections will apply, e.g. in EU for coordination of EMEA or EDQM inspections.
- 3.9 The national/regional rules for inspection fees should apply for each authority participating in any inspection.
- 3.10 Following close out of the any inspection, each involved authority is responsible for administrative or enforcement actions (see points 4.6.f / 4.7.1 in the core procedure) at national/regional level, e.g. database entry, issuance/update of certificates/licences.
- 3.11 Each authority reserves the right to perform their “own” inspection. However, if deficiencies are found regulatory authorities performing their “own” inspections of sites of common interest will liaise with other concerned authorities to ensure a common understanding and if possible an agreed conclusion. See points 4.6.d and 4.7.k in the core procedure for the handling of a negative inspection result

4. Procedure

- 4.1 Each regulatory authority involved in the pilot project identifies a contact point specifically for inspection planning purposes.
- 4.2 The contact points circulate between them a spreadsheet elaborated according to a commonly agreed template (see section 6) to outline the sites potentially to be inspected over an agreed timeframe.
- 4.3 Once all authorities involved in the project have filled in the spreadsheet, it is re-circulated so that each party can identify sites of common interest.
- 4.4 A teleconference between contact points is set up to agree on the sites to be finally included in the scope of the project. There are two possible scenarios:
 - a. Information-sharing inspections (go to section 4.6 only): one authority involved is willing to rely on the outcome of an inspection performed/planned by another authority willing/able to perform the inspection.
 - b. Collaborative inspections (go to section 4.7 only): two or more authorities sharing a common interest for a site agree to jointly perform an inspection. Typical examples may include:
 - i. Common interest in inspecting a large multi-product manufacturing site, producing a range of AS/API, which are not necessarily all of common interest
 - ii. Legal requirements obligate a participating authority to perform at least part of the inspection
- 4.5 The filled in spreadsheet with site information will be updated at agreed intervals to ensure that new information and revised inspection plans are communicated.
- 4.6 Information-sharing inspections (when possible, this is the preferred option)
 - a. An authority is willing to share the outcome/report of an inspection performed or planned with another authority expressing the same or similar interest. There are the following options:
 - i. The non-inspecting authority accepts the scope (for planned inspections) and/or outcome/report (for performed inspections) of the inspecting authority without any modification.
 - ii. The non-inspecting authority requests the inspecting authority to expand the scope to ensure that it covers areas of interest to both or more participating authorities.
 - b. The inspecting authority accepts, if possible, the extension of the scope of the inspection taking into account any need to amend the time schedule and dates for the inspection
 - c. The inspection is carried out in accordance with the national rules of the inspecting authority.
 - d. In case the inspection team anticipates a negative inspection result, the inspecting authorities will liaise with other concerned authorities to ensure a common understanding and if possible an agreed conclusion before closing out the inspection process.
 - e. The inspecting authority shares with the other parties the inspection outcome/report in national format (if needed translated in English).

- f. The authorities receiving the inspection report are responsible for any follow-up actions within their territory based on the recommendations from the inspectors.
- g. Any follow-up inspection should be organised as outlined in this procedure.

4.7 Collaborative inspections

- a. The concerned regulatory authorities exchange complete available information on the site to inspect, covering:
 - i. AS/API name(s)
 - ii. (if available) Site Master File
 - iii. Manufacturing process description (at least flow-chart)
 - iv. Building/lines to be inspected
- b. The involved authorities agree on the final scope and timelines for the inspection.
- c. The final inspection team will be composed of inspectors from two (maximum three) national regulatory authorities in order to rationalise the use of the inspectorates' resources.
- d. If other authorities cannot participate due to the limitations in the composition of the inspection team as described above, they may use the outcome/report of the collaborative inspection in accordance with the procedure described under section 4.6
- e. The inspection planning contacts will together decide who the leading inspection authority will be, taking into account the authorities having legal requirements for the inspection, the inspection history of the site and the number of concerned medicinal products authorised by or submitted for authorisation using active substances from the site concerned.
- f. The lead inspector has the following duties:
 - i. setting a reporting deadline in agreement with all team members taking into account any specific deadlines linked to re-inspection due dates or on-going submissions or procedures,
 - ii. technical preparation of the inspection with the inspectee in liaison with the other inspectors of the team
 - iii. establishing a draft inspection itinerary of the inspection in cooperation with the involved authorities and with the inspectee,
 - iv. fine tuning the scope of the inspection in terms of number of APIs/buildings covered and expected timeframe for completion
 - v. leading the conduct of the inspection on site,
 - vi. communicating between the inspectee and the inspection team, including opening and closing protocols and periodic update arrangements.
 - vii. recording all the findings/observations jointly agreed by the inspection team
- g. It is expected that the inspection team's findings/observations in relation to GMP ICH Q7 (and other GMP guidelines where necessary, see 3.4) and the preliminary conclusions of the inspection will be jointly agreed on site. Where applicable, the inspection team may provide the inspectee with the list of observations.

- h. Taking into account any applicable national/regional reviewing procedures, the lead inspector should send/provide the final list of deficiencies to the manufacturer. The manufacturer should be asked by the lead inspector to comment within a reasonable timeframe, if not done at the close of the inspection, in order to meet the reporting deadline.
- i. On receipt of comments on the list of deficiencies, the participating authorities should agree with the action plan proposed by the company taking into account any applicable national/regional reviewing procedures.
- j. Unless otherwise agreed, separate final inspection reports (in English) will be prepared to close out the inspection process, one by each of the authorities involved in the inspection team.
 - i. The authorities involved in the inspection should exchange their Inspection Reports for final agreement on common areas covered by the whole inspection team.
 - ii. When one single report is possible, each participating inspector will sign it.
- k. In the case of a negative inspection result, the inspecting authorities will liaise with each other to ensure a common understanding and if possible an agreed conclusion before closing out the inspection process.
- l. Each participating authority is responsible for any follow-up actions within their territory based on the commonly agreed outcome.
- m. Any follow-up inspection should be organised as outlined in this procedure.

6. Template for exchange of site information

No	Local/ regional identifier	Firm	Address	Zip Code	City	State/province	Country
		Name of the manufacturing site		Zip code of the manufacturing site: avoid dashed or blank fields, if possible		State or province of the manufacturing site	
Consecutive number		Address of the manufacturing site		City of the manufacturing site		Country of the manufacturing site. Use ISO country names (see tab "ISO country codes")	
	Key number allocated by local or regional system/database						

