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Compliance and Inspection

Programme to rationalise international GMP inspections of active pharmaceutical ingredients/active substances manufacturers

Terms of reference and procedures for participating authorities

1. Background

The majority of national 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 programme, specific bilateral arrangements between countries, cooperation with EDQM etc.

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 pilot programme on international collaboration on GMP inspections of API manufacturers was conducted between December 2008 and December 2010 involving competent authorities from Australia, Europe and the United States. The purpose of the programme was to foster cooperation and mutual confidence between participating regulators through better communication and exchange of information on inspection planning.

New tools for work sharing and exchange of information were developed and used by the participants to share inspection reports and to organise joint inspections of API manufacturers located outside the participating regions.

Increased transparency and visibility of inspections performed by participating authorities allowed a successful collaboration between authorities on sites of common interest and increased the number of inspections performed of value to more than one authority. There was an unquestionable strong commitment of the participants in the pilot programme and there is an essential public health incentive to collaborate on the inspections of API manufacturers worldwide.

The project has contributed substantially to a better understanding of regional approaches to inspection and the building of mutual confidence. It has also highlighted the necessity not to exclude the API manufacturing sites located within the participating regions, whenever cooperation could be beneficial globally.

To further develop collaboration, all participants were supportive of continuing the API inspection collaboration, and extending the project to new contributors.

All participants agreed that clear criteria should be established for any potential new participant to be accepted or maintaining ongoing participation. In general, participants should have a clear understanding of the expectations and be active contributors to the program.

However, International Organisations or Non Governmental Organisations organising GMP inspections of API manufacturers, which may not fulfil all the below listed criteria, may be accepted as partners by the participating regulatory authorities and be given access to the information available within the programme for the benefit of public health globally.

In addition, authorities who may not yet be in a position or do not wish to become participating authorities may request access to the information being shared.

In both of the above cases, information sharing will be facilitated to the extent that confidential information is not compromised i.e. by the presence of appropriate confidentiality agreements between the exchanging parties and no local legislative impediments to the exchange.

Below are some of the requirements that must be met by all new and ongoing regulatory authority participants:

- have a functioning API inspectorate
- have a routine API inspection programme
- ICH Q7 guidance must be implemented, with appropriate regulations, guidance and supervision for sterile APIs
- confidentiality arrangements must be in place among the participating authorities/organisations
- ability and willingness to provide inspection reports
- ability and willingness to participate in joint inspections
- confidence has been established with existing participants either through joint inspections, participation in international technical fora (ICH) or other appropriate means.

Each new membership request will be examined and the existing participants will decide whether or not to accept the applicant. When relevant, a time period for probation can be fixed during which the functional capacity of the applicant within the program can be evaluated.

2. Objective

The overall objective is to foster greater international collaboration and information sharing to 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 terms of reference 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.

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. However when ever necessary, e.g. in case of suspected non conformity, an API manufacturing site located within the participating regions can be subjected to cooperation between participating authorities. A joint inspection will then include the national competent authority.

3.2 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.

3.4 Participating authorities agree to share inspection plans and inspection outcomes for such inspections carried out or proposed to be carried out.

3.5 Where sites of common interest are identified, participating authorities agree to consider the following options. .

- 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. Participating regulatory authorities may also regularly perform joint inspections of the concerned sites to gain and to maintain the confidence in each other.

3.6 Participating authorities are responsible for ensuring that appropriate confidentiality arrangements are in place between parties and local legislation permits their participation in the activities covered by this paper.

3.7 The national/regional rules for inspection fees should apply for each authority participating in any inspection.

3.8 Following close out of a joint inspection, each involved authority is responsible for administrative or enforcement actions if appropriate (see points 4.6.f / 4.7.I in the core procedure) at national/regional level, e.g. database entry, issuance/update of certificates/licences.

3.9 In the case that a regulatory action or license suspension is to be initiated by any of the participating authorities, such decision will be shared with the other authorities within the scope of their existing confidentiality agreements.

4. Procedure

4.1 Each participating regulatory authority involved in the project identifies a contact point specific to this programme.

4.2 The contact points complete and forward to the coordinating contact at the EMA inspection planning information elaborated according to a commonly agreed template to identify sites potentially to be inspected over an agreed timeframe.

4.3 EMA maintains and circulates information provided so that each party can identify sites of common interest.

4.4 When necessary a teleconference between contact points is set up to identify and progress information-sharing and collaborative inspections.

4.5 Compiled site information will be updated at agreed intervals and as often as necessary to ensure that new information and revised inspection plans are communicated.

4.6 Information-sharing inspections

a. A participating 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. The national/regional rules for inspection fees should apply for each authority participating in any inspection and may be adapted accordingly..

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 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 into English).

f. The authorities receiving the inspection report are responsible for any follow-up actions within their territory or jurisdiction based on the recommendations of the inspection report.

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, including but not restricted to :

i. AS/API name(s)

ii. Site Master File

iii. Product Quality Review

iv. Manufacturing process description (at least flow-chart)

vi. 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 inspected site in liaison with the other inspectors of the team
 - iii. informing the local regulatory agency of the planned inspection and inviting same to observe the inspection
 - vi. establishing a draft inspection itinerary of the inspection in cooperation with the involved authorities and with the inspected site,
 - v. fine tuning the scope of the inspection in terms of number of APIs/buildings covered and expected timeframe for completion
 - vi. leading the conduct of the inspection on site,
 - vii. communicating between the inspected site and the inspection team, including opening and closing protocols and periodic update arrangements.
 - viii. 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 3.2) and the preliminary conclusions of the inspection will be jointly agreed on site. Where applicable by national procedures, the inspection team may provide the inspected site 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 inspected site. 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 and timelines.
- 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. Provided that required timelines are met, the authorities involved in the inspection should exchange their Inspection Reports for final agreement on common areas covered by the whole inspection team. Furthermore, where the list of deficiencies and other key elements have been agreed by inspectors before issuing the preliminary inspection report, this exchange may not be applicable.
- 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.