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

Terms of reference for participating authorities

1. Introduction

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. The vast majority of regulatory authorities ensure that these manufacturers in their territory are subject to routine GMP inspections.

However, different approaches are taken to the supervision of the manufacture of medicinal products, and active substances/active pharmaceutical ingredient (API) outside a national territory. A number of countries are part of a political and economic union, 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 International GMP Inspectors Summit in November 2009 in Bethesda, 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 (TGA), Europe (EMA, EDQM, ANSM, AIFA, ZLG, MHRA, HPRA) and the United States (FDA). 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.

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.

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To further develop collaboration, all participants were supportive of continuing the API inspection collaboration, and extending the project to new contributors. As such, after the pilot phase the programme, as a full programme, was expanded to include the following additional members: the Danish Medicines Agency (DKMA) in 2011, the World Health Organization (WHO) in 2012, Health Canada (HC) in 2015 and Pharmaceuticals and Medical Devices Agency (PMDA) Japan in 2016. The current list of participating authorities is provided in Appendix 1.

The purpose of this document is to set out the objectives, scope and principles for the Programme to rationalise international GMP inspections of API manufacturers.

2. Objective

The objective of the programme is to foster greater international collaboration and information sharing to help better distribute inspection capacity, allowing more sites to be monitored, increasing inspectional oversight and reducing duplication.

Building on equivalent GMP standards and mutual confidence, the collaboration is a voluntary agreement between the participants:

- to coordinate inspection planning taking into account risk based approaches and conduct inspections described in 7.1.1 and 2;
- to share information on inspection outcomes.

3. Scope

This agreement applies to national and international regulatory authorities and regulatory organisations (thereafter referred to as 'participating authorities') that are participating in the programme and responsible for the coordination and conduct of GMP inspections of manufacturers of non-sterile and sterile APIs, of chemical and biological origin, for human and veterinary medicinal products, located outside the territories of the participating authorities. A complete list of the participating authorities to the programme is provided in Appendix I.

Whenever necessary, e.g. in case of suspected non-compliance, information on API manufacturing sites located within the territories of the participating authorities, in addition to those outside their territories, can be subjected to exchange of information and cooperation between participating authorities.

4. Requirements for participation to the programme

4.1 The requirements for regulatory authorities and regulatory organisations to join and maintain participation to the programme are:

4.1.1) to have a functioning API inspectorate;

4.1.2) to have a routine API inspection programme;

4.1.3) to use ICH Q7 guidance (or a system demonstrated to be equivalent to ICH Q7) with appropriate regulations, guidance and supervision for sterile APIs;

4.1.4) to have effective confidentiality arrangements among the participating authorities;

4.1.5) to provide information about inspections such as inspection plans, non-compliance findings and inspection reports/summary outcomes;

4.1.6) to participate in inspections as described in 7.1.1 and 2.

4.1.7) to have established confidence of GMP inspection capability with the participating authorities either through inspections as described in 7.1.1 and 2, observed inspections,PIC/S membership or other appropriate means;

4.1.8) to have a clear understanding of the objectives and expectations set out in the programme;

4.1.9) to be active contributors to the programme.

4.2 International organisations or regulatory organisations organising GMP inspections of API manufacturers, which may not fulfil all the above listed criteria, may be accepted as observers by the participating authorities and be given access to the information available within the programme for the benefit of public health globally.

4.3 Regulatory authorities and regulatory organisations who may not yet be in a position or do not wish to become participating authorities may request access to the information being shared.

4.4 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.

4.5 When a new regulatory authority or regulatory organisation submits a request for membership, the existing participating authorities will assess and decide whether to accept the applicant based on criteria noted above.

4.6 When relevant, a time period for probation can be fixed during which the applicant can join the programme as observer while the functional capacity of the applicant within the programme can be evaluated. A re-assessment of participating authorities may be conducted upon overall program review (see 6.9).

5. General principles

5.1 The reference GMP standard for inspections is ICH Q7: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. For sterile AS/API (not covered by ICH Q7), the participating authorities will follow additional regional guidelines as appropriate.

5.2 Participating authorities agree to share as soon as possible all planned inspection (and updates) and outcomes for scheduled inspections and inspections performed. If requested, the participating authorities agree to share inspection reports or summary outcomes (translated into English, if needed and possible) for third country sites as covered by the API programme.

5.3 A manufacturing site which is of interest to at least 2 participating authorities is defined for this programme as a ‘site of common interest’.

5.4 Where sites of common interest are identified, further bilateral/multilateral discussions on the scope (e.g. APIs covered/to be covered workshops/building etc.) will take place. Based on those, participating authorities agree to consider the following options with decreasing priority.

5.4.1) They will endeavour to take into account the results of an inspection (to be) carried out by a participating authority in managing their inspection activity covered within the scope of this project.

5.4.2) They may request one of the participating authorities to expand, if possible, the scope of their planned inspection to cover areas of interest to more than one participating authority.

5.4.3) Participating regulatory authorities may also regularly perform inspections of the concerned sites to gain and to maintain the confidence in each other, endeavouring to perform joint inspections rather than duplicated inspections.

5.5 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.

5.6 Inspections are carried out by participating authorities in accordance with their own national/internal rules for inspection, including any required inspection fees that will apply for each participating authority in any inspection.

5.7 Following mutually agreed close out of a joint inspection, each involved participating authority is responsible for administrative or enforcement actions if appropriate at national/regional level, e.g. database entry, issuance/update of certificates/licenses, as necessary.

5.8 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 participating authorities within the scope of their existing confidentiality arrangements, as necessary.

6. Principles for information sharing

6.1 Each participating authority delegates a single point of contact and a backup where necessary.

6.2 The secretariat for the programme is ensured by one participating authority in agreement with all members.

6.3 The contact points provide ongoing information and updates to the programme secretariat on inspection planning and outcomes.

6.4 Upon request from another participating authority, the contact points ensure that a copy of the inspection report/summary outcome is provided.

6.5 Information should be provided or input within agreed timelines and using a commonly agreed template or database for planning of inspections over an agreed timeframe.

6.6 The secretariat maintains and circulates information provided so that each party can identify sites of common interest.

6.7 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

6.8 A routine teleconference between contact points is set up to identify and progress information sharing, collaborative inspections as well as exchange of information on other topics that may arise and are of interest to the participating authorities.

6.9 To ensure that the objectives of the programme are met, the results of the programme shall be assessed at regular intervals using an agreed set of deliverables.

7. Principles for inspection planning and collaboration

7.1 To avoid duplication of inspections, participating authorities can collaborate on inspection planning using the following methods:

7.1.1) Reliance upon inspections. One participating authority conducts an inspection of site of common interest, potentially with requested expansion of scope for the non-participating authority, and other participating authorities take the outcome/inspection report into account when managing the inspection schedule of the same site.

7.1.2) Joint Inspections. Two or more participating authorities plan and conduct a joint inspection of the same site of common interest at the same time.

7.2 For inspections with extended scope on request of a participating authority, the following principles should be followed:

7.2.1) For planned inspections, the non-inspecting participating authority can request the inspecting participating authority to expand, if possible, the scope to ensure that it covers areas of interest to both or more participating authorities.

7.2.2) The inspecting participating 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.

7.2.3) Following an inspection of a site of common interest, in case the preliminary outcome indicates GMP non-compliance, the inspecting participating authorities will liaise with other concerned participating authorities before closing out the inspection process.

7.2.4) The inspecting participating authority shares with the other participating authorities the inspection outcome/report.

7.2.5) The participating 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.

7.3 For Joint Inspections, the following principles should be followed by the participating authorities taking part to the joint inspections:

7.3.1) The participating authorities should exchange available information on the site to inspect, including but not restricted to :

i. API name(s) and destination markets (if available)

ii. Site Master File and Validation Master Plan

iii. Product Quality Review

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

v. Building/lines to be inspected

7.3.2) The involved participating authorities agree on the final scope and timelines for the inspection.

7.3.3) The final inspection team will be composed of an appropriate team of inspectors from the participating authorities in order to rationalise the use of the inspectorates' resources.

7.3.4) If any other participating 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 inspection in accordance with the principles described under section 7.2.

7.3.5) The inspection planning contacts will together decide who the leading/facilitating inspection participating authority will be, taking into account the participating 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 APIs from the site concerned.

7.3.6) The lead inspector/s has/have the following duties:

i. Preparation of the inspection of the inspected site in liaison with the other inspectors of the team, e.g. via web conference. This preparation should take place sufficiently ahead of the inspection in order being able to cover the following:

- Defining the scope of the inspection considering number of APIs/buildings to be covered and expected timeframe for completion.
- Establishing a draft inspection schedule of the inspection in cooperation with the involved participating authorities.
- Setting a reporting deadline in agreement with all team members taking into account any specific national deadlines linked to re-inspection due dates or on-going submissions or procedures.

ii. If possible a single notification to the local regulatory agency of the planned inspection and inviting them to observe the inspection

iii. Conduct of the inspection:

- Leading the conduct of the inspection on site and ensuring the communication between the team members in terms of progress, arising issues, potential changes in the agenda, etc.
- Communicating between the inspected site and the inspection team, including opening and closing protocols and periodic update arrangements.
- Recording all the findings/observations jointly agreed by the inspection team.

7.3.7) It is expected that the inspection team's findings/observations in relation to GMP ICH Q7 (and other GMP guidelines where necessary) and the preliminary conclusions of the inspection will be jointly agreed on site. Where applicable by national procedures and mutually agreed, the inspection team may provide the inspected site with the list of observations.

7.3.8) Taking into account any applicable national/regional reviewing procedures, the lead inspector should send/provide the final list of deficiencies/initial inspection report to the inspected site. The issuance of a single inspection report, signed by all participating inspectors, is preferable. If possible, the manufacturer should be asked by the lead inspector to comment within a mutually agreed timeframe, if not done at the close of the inspection, in order to meet the reporting deadline.

7.3.9) The Corrective and Preventative Action Plan (CAPA) should be evaluated by the participating authorities.

7.3.10) In case the CAPA is considered satisfactory and a mutually agreed conclusion of the GMP compliance status of the inspected site has been reached by the participating authorities, a single report, if possible, or separate final inspection reports where necessary (in English, if possible and needed) will be prepared to close out the inspection process.

7.3.11) In the case of a negative inspection result, the inspecting participating authorities will liaise with each other to ensure a common understanding and if possible an agreed conclusion before finalizing the inspection process or taking regulatory action.

7.3.12) Each participating authority is responsible for any follow-up actions within their jurisdiction based on the commonly agreed outcome.

7.4 Any follow-up activities should be organised according to national/regional needs and as outlined in this section. Continued collaboration throughout the compliance life cycle of the firm is encouraged.

Appendix I – List of participating authorities

1. Australia - Therapeutic Goods Administration (TGA)
2. Canada – Health Canada (HC)
3. Denmark - Danish Medicines Agency (DKMA)
4. European Directorate for the Quality of Medicines & HealthCare/Council of Europe (EDQM)
5. France - Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)
6. Ireland – Health Products Regulatory Authority (HPRA)
7. Italy – Italian Medicines Agency / Agenzia Italiana del Farmaco (AIFA)
8. Japan - Pharmaceuticals and Medical Devices Agency (PMDA)
9. United Kingdom - Medicines and Healthcare products Regulatory Agency (MHRA)
10. The United States of America – The US Food and Drug Administration (FDA)
11. The European Medicines Agency (EMA)
12. The World Health Organization (WHO)