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Pilot programme for international cooperation in GMP inspection of manufacturers of sterile medicinal products for human use

Terms of reference for participating authorities

1. Introduction

The benefits of international collaboration in the inspection of manufacturers of active pharmaceutical ingredients have been demonstrated over a number of years¹. More efficient use of international inspectional resources facilitates broader inspectional coverage and allows risk-based inspection planning, thereby benefitting public health and patients by focusing on sites of highest identified risk.

The purpose of this document is to set out the terms of reference, including objectives, scope, requirements and general principles of an international inspection pilot programme covering manufacturers of sterile medicinal products. The purpose of the programme is to foster mutual cooperation and confidence between participating regulators through better communication and exchange of information on inspection planning.

The regulatory authorities² (hereafter referred to as 'participating authorities') taking part in this programme do so voluntarily. All participating authorities must be obliged by law to have systems in place to verify the Good Manufacturing Practice (GMP) status of medicinal product manufacturers whose products are marketed in their territory and imported from third countries. These regulatory authorities ensure that manufacturers located in their territory and in third countries are subject to routine GMP inspections to verify the GMP status. In committing to participate in the pilot each participating authority agrees to:

- coordinate inspection planning through risk-based approaches and share, in advance, their prospective inspection plans for the two years of the pilot with participating authorities;
- conduct inspections in the manner described herein;
- share information in English on inspection outcomes on a monthly basis;
- provide inspection reports to other participants if requested.

¹ [Final report on the International API inspection Pilot Programme.](#)

² This includes European Medicines Agency and World Health Organization.

2. Definitions

The below definitions are applicable in the context of this present document and are intended to ensure clarity among participating authorities.

- **Concurrent inspection:** two or more sole routine inspections performed independently but at the same time by two or more participating authorities. Generally, each inspection has a different scope but this can change on a case by case basis.
- **Duplicate inspection:** a routine inspection performed at the same time or within a very short timeframe (e.g. within 6 months) by two or more participating authorities in a completely independent manner focusing on the same scope, process or product.
- **Joint inspection:** a routine inspection planned, coordinated and conducted together by two or more participating authorities.
- **KPI:** key performance indicator is used to measure of pilot success.
- **Master list:** the consolidated list of sites of common interest provided and agreed to by each participating authority at the start of the pilot programme. The minimum set of information to be included regarding each site is set forth in Appendix III.
- **Participating authority:** regulatory authority taking part in the pilot phase of the international GMP sterile medicinal products inspection programme.
- **Site of common interest:** manufacturing site scheduled for inspection by at least two participating authorities.
- **Sole inspection:** a routine inspection planned, coordinated and conducted by one participating authority.
- **Third country:** a country which is not in the territory of supervision of any of the participating authority. EEA Member States are not considered third country.

3. Objectives

The objective of the pilot phase is to confirm the terms of reference and to foster international collaboration, and information sharing in GMP inspection planning.

4. Scope

- This agreement applies to national and international regulatory authorities and to regulatory components of international organisations that are responsible for the coordination and conduct of GMP inspections of manufacturers of sterile medicinal finished products for human use located in third countries. Participating authorities are listed in Appendix I.
- Products in scope are marketed sterile pharmaceutical medicinal products for human use of chemical origin and certain marketed therapeutic biotechnology-derived biological products (such as monoclonal antibodies and recombinant proteins). Products currently out of scope of this pilot are vaccines, cell and gene therapies and plasma derived pharmaceuticals.
- The pilot will cover routine surveillance inspections of previously GMP compliant sites. For-cause or pre-approval inspections can be included at the discretion of participants.

- The pilot will include only third country manufacturing sites of interest to at least two participating authorities (site of common interest) and reported in the Master List.
- Reliance on participating authorities' inspections should be preferred over sole inspections so that sole inspections are deferred or postponed based on another participating authorities' inspection.
- Joint inspections should be preferred over sole and concurrent inspections.
- For sole or concurrent inspections every effort should be made to equally distribute the work across all participating regulatory authorities. Inspectorates should agree to separate on-site inspection plans in advance to avoid unnecessary duplication. For sole or concurrent inspections, it is expected that resources will be allocated independently by the participating authorities and that separate reports will be drafted at the end of the inspection(s).
- Duplicate routine inspections should preferably be avoided.

5. Requirements for participation

- Each participating authority agrees to be an active and timely contributor to the pilot programme as established. Failure in this respect, such as non-participation in maintaining updated inspection information for tracking, as outlined in present document, may result in a participant being requested to withdraw from the pilot programme.
- Each participating authority has, and agrees, to maintain a functioning inspectorate and agrees to the following:
 - use of appropriate GMP guidance with accompanying regulations, guidance and supervision for sterile medicinal products under their own legal framework as outlined in Appendix II;
 - has and maintains current confidentiality arrangements with all other participating authorities;
 - regularly participates in teleconferences, joint inspections, and other communications proficiently in English, the working language for the pilot programme;
 - providing information to other participating authorities about inspections such as inspection plans, findings of non-compliance and inspection reports/summary outcomes, as outlined in the terms of reference;
 - participation in inspections as described in paragraph 6;
 - maintains a high standard for GMP inspection capability, utilizing a variety of mechanisms to do so, such as working with other participating authorities through inspections as described in paragraph 6, observed inspections, PIC/S³ membership or other appropriate means.
- Membership is limited during the pilot to those authorities listed in Appendix I. Requests for participation from other authorities during the pilot may be received and discussed by participants.

³ [Pharmaceutical Inspection Co-operation Scheme \(PIC/s\)](#)

6. General principles for the pilot

1.1. *Time and duration of the pilot*

- The pilot will last a minimum of two years after the approval of the present terms of reference (e.g. October 2019 to October 2021).
- After the conclusion of the pilot phase the participating authorities will perform an assessment of the programme taking into account the key performance indicators (KPIs) listed in Appendix IV. A report with conclusions and recommendations will be published accordingly.

1.2. *Operational aspects of the pilot*

- Each participating authority commits to share details on their prospective inspection plans for third country manufacturers through the master list via e-mail to the secretariat of the pilot programme.
- The template for the creation of the master list is in Appendix III. Sites will be identified for inclusion on the master list using risk-based approaches.
- Each participating authority commits to provide updates on the planned inspections and outcome of inspections performed during the pilot programme to the secretariat of the pilot programme on a monthly basis.
- The planning window for the prospective inspection plan will be for the period of the pilot programme, i.e., October 2019 – October 2021.
- Monthly updates to the master list should be provided to the secretariat 10 days before the scheduled teleconference.
- Once an inspection of a manufacturing site is scheduled, the [EudraGMDP](#) planning module should be updated with the details by the lead inspectorate.
- Any issues preventing the use of the planning module or any proposal for EudraGMDP improvement should be communicated to the EMA contact as listed in Appendix I.
- Where additional sites of common interest (not previously identified) are identified during the pilot, further discussions on their inclusion will take place amongst participating authorities on the monthly conference call or as appropriate.
- If requested, the participating authorities agree to share inspection reports or summary outcomes (translated into English, if needed) for third country sites covered by the programme.

1.3. *Modalities of managing the sharing of information*

- The secretariat for the pilot programme maintains operations and logistics and is designated by agreement of all participants on a 6-month rotational basis as outlined in appendix I.
- The secretariat will commit to perform the following tasks:
 - Organise the monthly teleconferences between contact points. In this regard the secretariat will:
 - send placeholders and dial in details to participating authorities;
 - draft and circulate agendas and meeting minutes;
 - send reminders to participating authorities.

- Note on the minutes: a participating authority will provide to the secretariat a short summary of a discussed agenda point. All participating authorities will review and provide input on the minutes within 1 week after each teleconference.
- Keep the master list as described in appendix III up-to-date with latest submitted information on inspections and share it with participating authorities. In this regard, participating authorities will commit to providing regular updates at least 10 days before the next teleconference.
- Each participating authority delegates a single primary point of contact and a backup as outlined in appendix I. These individuals will:
 - provide ongoing information and updates on inspection planning and outcomes to the secretariat in charge and participate in the monthly teleconferences. Participating authorities will commit to providing regular updates at least 10 days before the next teleconference.
 - Upon request from a participating authority, the contact points ensure that a copy of the inspection report/summary outcome/list of deficiencies/summary of findings is provided.

1.4. ***Monitoring and evaluating the pilot phase***

To ensure that the objectives of the pilot programme are met, KPIs agreed in appendix IV will be completed and discussed every 6 months.

7. Principles for inspection planning and collaboration

- To avoid duplication of inspections, participating authorities are expected to collaborate through this programme on inspection planning to facilitate reliance upon each other's inspections, or to conduct joint inspections to foster confidence building and collaboration between inspectorates.

1.1. ***Reliance upon inspection (with or without extended scope)***

- Should one participating authority be planning to inspect a site of common interest, another participating authority(ies) can ask for extension of the scope, in order to defer their own inspection. The following principles will be followed:
 - A participating authority(ies) can request the inspecting authority to expand, if possible, the scope of their inspection of a site of common interest to include products or processes of interest to the requesting authority. The secretariat will be informed accordingly for KPI purposes.
 - The inspecting authority will notify the requesting authority(ies) and the secretariat of their decision.
 - Following the inspection of the manufacturer (with or without extended scope), the inspecting authority) will alert or liaise with the concerned participating authorities if the preliminary outcome indicates GMP non-compliance before finalising the inspection outcome.
 - The inspecting authority will share with the concerned participating authority(ies) the outcome of the inspection or the inspection report as required.
 - The participating authority(ies) receiving the inspection report are responsible for any follow-up action within their territory or jurisdiction based on the recommendations of the inspection report.
 - The participating authority(ies) will inform the secretariat how they intend to use the outcome or report of the inspection in their decision making for KPI purposes.

1.2. **Joint inspections**

- Before performing the inspection, the two (or more) inspecting authorities will agree on the scope covered on whether there will be one or two separate inspection reports, and on who is going to lead the inspection.
- In case of two separate inspection reports, each inspection authority will issue an inspection report according to their own national procedures.
- The participating authorities should identify the opportunity for a joint inspection and exchange available information on the site to inspect, including but not restricted to:
 - Sterile medicinal product name(s), active pharmaceutical ingredient name and destination markets (if available);
 - Site Master File and Validation Master Plan;
 - Product Quality Review;
 - Manufacturing process description (at least flowchart);
 - Building/lines to be inspected;
 - Previous risk assessment or site compliance dossier/file;
 - Any other relevant information on the sites to be inspected.
- The final inspection team will be composed of an appropriate number of inspectors from the participating authorities in order to rationalise the use of the inspectorates' resources, as well as to ensure effective conduct of the inspection at the site.
- During the inspection planning the participants will decide who will be the leading authority in the inspection taking into account factors such as different legal requirements of each participating authority, the inspection history of the site and the number of medical products manufactured at the site of concern to each participant. The lead inspector has the following duties:
 - Preparation for the inspection of the concerned site in liaison with the other inspectors on the team (e.g. via web conference). This preparation should take place sufficiently ahead of the inspection and cover the following:
 - Planning of the inspection considering the inspection scope and the facilities to be covered and expected timeframe on-site.
 - Establishing a draft inspection schedule of the inspection in cooperation with the involved participating inspectors.
 - Setting a reporting deadline in agreement with all team members taking into account any specific national or procedural deadlines such as transparency initiatives for posting inspection results online etc.
 - Ensure all confidentiality arrangements are in place to fully conduct the joint inspection.
 - Provide a notification to the local regulatory agency of the planned inspection and inviting them to observe the inspection.
 - Lead the inspection on-site and ensure good communication between the team members in terms of progress, arising issues, potential changes in the agenda etc. Lead the

communication between the inspected site and the inspection team including opening and closing meeting, and the follow up responses from the inspected site.

- Oversee the finalisation of the inspection report according to national requirements or agree in the event of a joint report the appropriate requirements for finalisation of the report. Record all jointly agreed findings/observations by the inspection team.
- It is expected that the findings/observations identified by the inspection team and the preliminary conclusions of the inspection will be jointly agreed on-site by the inspecting authorities. Where applicable by national procedures and mutual agreement, the inspection team may provide the list of observations to the concerned site at the end of the inspection. In case of differences in observations or outcomes, the inspection team will clarify the reasons for the differences to all participant authorities (regulations, scope, etc.).
- In case of disagreements on compliance of the manufacturer following the inspection, each participating authority applies its own national procedure and the following steps may be undertaken:
 - The inspection lead will convene a teleconference between participating authorities in order to review the findings and discuss reasons for the disagreement. If still in disagreement, each participating authority will prepare individual inspection reports, related risk assessment, and will take the appropriate actions in their territory as needed.
 - The inspection lead will notify the secretariat of the remaining disagreement accordingly.
- 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 inspectors on the joint inspection team, is preferable. If possible, the manufacturer should be asked by the lead inspector to provide a response to the inspection findings within a mutually agreed time frame, if not done at the close of the inspection, in order to meet the reporting deadline.
- The Corrective and Preventative Action Plan (CAPA) should be evaluated by the authorities who took part in the joint inspection.
- Where the CAPA is considered satisfactory and a mutually agreed upon conclusion of the GMP compliance status of the inspected site has been reached by the joint inspection participating authorities. These authorities will then close out the inspection.
 - In the case of a negative inspection result not adequately addressed by the CAPA, the joint inspection participating authorities will liaise with each other in order to discuss the case and possibly agree on taking regulatory action, or another conclusion before finalising the inspection as needed.
 - Each participating authority is responsible for any follow-up actions within their jurisdiction based on the mutually agreed outcome.
 - 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.

1.3. ***Concurrent Inspections***

- Before performing the inspection, the two (or more) authorities should notify each other on the parts of the facility to be covered separately by each team.
- The lead inspector from each team should endeavour to exchange information between each team during the concurrent inspection, if such information would indicate an underlying non-compliance for the facility.
- It is expected that the findings/observations identified by each inspection team and the preliminary conclusions of the inspection would be shared between each team. In case the respective teams have established different compliance status, each participating authority should confer in advance if possible before finalising the decision.
- The secretariat should be notified of the results of the concurrent inspections collectively or by each team as mutually agreed to by the teams.

2. Appendixes

Appendix I – List of participating authorities

Participating Authority
Australia - Therapeutic Goods Administration (TGA)
Canada - Health Canada (HC)
EMA - European Medicine Agency
France - Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)
Japan - Pharmaceuticals and Medical Devices Agency (PMDA)
United Kingdom - Medicines and Healthcare products Regulatory Agency (MHRA)
United States – Food and Drug Administration (FDA)
World Health Organization (WHO)

Appendix II – List of GMP requirements

Inspectorate	GMP requirement
Australia - Therapeutic Goods Administration (TGA)	European Pharmacopoeia, or British Pharmacopoeia, or US Pharmacopoeia PIC/S Guide to Good Manufacturing Practice (GMP)
Canada – Health Canada (HC)	<ul style="list-style-type: none"> • Food and Drug Regulations • Food and Drugs Act
France - Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)	<ul style="list-style-type: none"> • European Pharmacopoeia • Eudralex volume 4
Japan - Pharmaceuticals and Medical Devices Agency (PMDA)	<ul style="list-style-type: none"> • PMD Act • GMP Ministerial Ordinance • Japanese Pharmacopoeia • PIC/S Guide
United Kingdom - Medicines and Healthcare products Regulatory Agency (MHRA)	<ul style="list-style-type: none"> • European Pharmacopoeia • Eudralex volume 4
European Medicines Agency (EMA)	<ul style="list-style-type: none"> • European Pharmacopoeia

Inspectorate	GMP requirement
	<ul style="list-style-type: none"> • Eudralex volume 4
World Health Organization (WHO)	<ul style="list-style-type: none"> • International Pharmacopoeia • WHO Technical Report Series (Main GMP text: TRS 986, Annex 2, 2014 + supporting guidelines)
United States – Food and Drug Administration (FDA)	<ul style="list-style-type: none"> • Food Drug and Cosmetic Act • Public Health Service Act • US Code of Federal Regulation • Compliance Programme 7356.002A/M • PIC/S Reliance Guidance

Appendix III Master list

The master list consists of an excel spreadsheet having as a minimum the following fields:

- Name and address of the site (including bloc/unit to be inspected).
- Inspecting participating authority(ies).
- Activities to be inspected.
- Date of planned inspection.
- Category of planned inspection (sole/joint/concurrent).
- Reason for planned inspection (routine surveillance, pre-approval or for cause).
- Previous inspection date of manufacturer.
- Inspection outcome (compliant/non-compliant).
- Lead inspector awareness of differences in opinion during on-site inspection (Yes/No). Was agreement reached before end of on-site? (Yes/No).
- Lead inspector awareness of differences in opinion during inspection completion (Yes/No). Did difference pertain to the inspection draft/final inspection report/preliminary inspection outcome/other (Yes/No)?
- Inspectorate aware of difference from lead inspector’s inspectorate in managing inspection outcome. (Yes/No). Did difference pertain to CAPA/follow-up activities/final inspection decision/other (Yes/No).

Appendix IV Key Performance Indicators (KPIs)

Key Performance Indicators (KPIs)
Total sites of common interest (to 2 or more RA)

Key Performance Indicators (KPIs)

Sole inspections performed during the pilot

Joint inspections performed during the pilot

Concurrent inspections performed during the pilot

Duplicate inspections performed during the pilot

Number of requests for scope expansion (reliance)

Number of deferred inspections (reliance)

Common opinions on inspection outcome

Divergent opinions on inspection outcome

Percentage of sites of common interest inspected

Number of inspection reports shared

Number of inspection reports shared that was specifically utilised by the receiving inspectorate (inspection relied upon or used to modify scope of inspection)