HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Question & Answers

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QP Forum

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Q & A

Q1. What is the HPRA's position in relation to how AI can be leveraged to perform GMP activities, e.g. writing deviations, customer complaints, audit and inspection responses etc.?

A1. New Annex 22 – 'Artificial Intelligence' is currently in draft status. This new annex establishes requirements for the use of AI and machine learning in the manufacturing of active substances and medicinal products. A stakeholder consultation was performed in 2025 and based on comments received, the draft annex is under revision and further focused stakeholder consultations are scheduled for 2026.

Where AI is utilised, testing / confirming the outputs is key, e.g. through verification of a 'Human in the loop' or using alternative guardrails. The company and the personnel responsible for the GMP activities in which an AI system is used are responsible for ensuring the correct application of the model and are responsible for the decisions made based on the outputs of those models. Therefore, to ensure accuracy of the AI outputs, the following are important:

- In-depth knowledge of the process the AI model is to be integrated in
- Review and verification of AI outputs to ensure accuracy
- Training and validation of the systems

In relation to the use of AI, inspectors may ask companies early in the inspection process i.e. at the opening meeting, if there are any GMP systems or processes where AI is being used. Inspection plans may be updated accordingly to allow time to inspect its use.

Q & A

Q2. What are HA requirements/expectations on AI for GMP use versus business use?

A2. The focus of GMP inspectors would be on the use of the AI on GMP processes/systems during inspection. When a company indicates that an AI tool is being used for 'business use only' and not for GMP purposes, then it needs to be sure the system in question does not fall under the remit of GMP.

Q & A

Q3a. How are companies meeting the requirement for 'The Order' specified in Annex 13.

A3a. As per the Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014 which replaced Annex 13, the expectation is that manufacturers receive a order from the sponsor or its representative for the IMP and it should:

- Request a certain number of units
- The order should be in writing, though it may be transmitted by electronic means
- It should be formally authorised by the sponsor or its representative
- Refer to the product specification file and the relevant clinical trial protocol, as appropriate.

Different companies have different systems in place to achieve this, i.e. paper based or electronic processes.

Provided the points above are fulfilled, it really comes down to what type of order format/process will work with your quality system and arrangements with the sponsor.

Q & A

Q3b: What is the starting point for companies to create their PSF, and how is this managed if it is not known whether a product will be supplied to the EU until much later?

A3b. As per section 2.1 of Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014:

- PSF should bring together essential reference documents to make sure the IMP is manufactured to GMP and the approved clinical trial application.
- Applicable sections of the product specification file should be available at the start of manufacturing of the first batch of IMP for a clinical trial.

However, there may be exceptional situations where IMP batches have been manufactured for one trial and then it has been decided that they could also be used for a different trial initiated in the period since the batches were manufactured.

In such a case, a QP would still need to perform certification to ensure the IMP meets the requirements of the new authorised CTA *(As per section 8 of Guidelines which refers to Article 12 of 2017/1569)*.

In terms of an order where a product was manufactured for a trial and it has been decided to use it in a different trial, then it would be expected that a new order from the sponsor (or representative) is available.

As per section 8 of the Guidelines, the products should not be released until the QP has certified compliance with GMP, the requirements of the approved CTA, and the PSF.

Q & A

Q4a. "What guidelines to follow when you are QP for MA holder who is responsible only for chemical and microbiological testing of veterinary medical products samples?

A4a. Refer to COMMISSION IMPLEMENTING REGULATION (EU) 2025/2091 of 17 October 2025:

- Several sections of the guideline refer to the QC laboratory areas (i.e. Article 14) and testing (Articles 35, 36, 37).

Q4b. What documentation is needed to be built up in existing QMS system? Any advice how to document the review process of sample receiving, analysing and final report issuing for veterinary medical product?

A4b. An existing QMS should be gap assessed against the requirements of COMMISSION IMPLEMENTING REGULATION (EU) 2025/2091 of 17 October 2025.

- Documentation practices can vary from paper-based checklists to electronic systems such as LIMS or other electronic laboratory management systems.

Q & A

Q5. What are the most important considerations, from a CA's perspective, when a company is qualifying a CMO from a third country?

A5. In terms of outsourcing manufacturing activities to a CMO, Chapter 7 and Annex 16 detail requirements:

- Audit of manufacturing site (Annex 16)
- Contract should be in place (Chapter 7)
- QRM processes utilised to monitor contract acceptor performance and to establish the timeline for next audit (Chapter 7)
  - Complexity and criticality of the activities performed at the site.
  - Findings of last audit.
  - Quality System review i.e. number and significance of deviations/suppler complaints raised/any quality defects identified relating to manufacturing activities performed at the CMO site/significant changes at the CMO site.
  - Warning letters/critical findings/compliance management by CAs
  - GMP status of the CMO and ongoing periodic due diligence (i.e. reverification of GMP validity status on a periodic basis)

Q & A

Q5. What are the most important considerations, from a CA's perspective, when a company is qualifying a CMO from a third country?

A5. cont'd:

- If it's a commercial supply chain, under 2001/83/EC then the expectation is that there is an EU GMP certificate available or the site is located in a region which has an MRA in place and the site has been approved by the mutually recognised CA.
- If it's an IMP supply chain, then the QP declaration may form the basis for GMP compliance status.
- The main difference between CMOs in third countries and the EEA:
  - CMOs in third countries may be operating to GMP guidance that is not equivalent to the EU GMP Guide, unless there is a MRA in place with the specific country or sites operating under a global PQS
  - There is no QP at the CMO in the third county with which EEA based QPs can share responsibilities.

Q & A

Q6. Releasing batches with deviations open where root cause is identified and corrective actions have been identified but the DE remains open but the batch is corrected / deemed no longer impacted.

A6. There may be situations where a deviation is still open when a batch is certified for release.

- However, the expectation is that for deviations with potential impact to product quality, that there has been adequate investigation and information available for a batch disposition decision to be made in line with QRM principles, in accordance with Section 3.1 of Annex 16.
- Such decisions should be clearly documented and demonstrate that the assessment and consideration of the deviation impact was made prior to certification of the batch.
- The expectation is that CAPAs are identified to prevent future occurrences of the issue. However, if the company is continuing to manufacture prior to the implementation of the CAPAs (i.e. in the case of longer term CAPAs), then mitigating actions (i.e. temporary shorter term CAPAs) should be implemented to ensure future batches will not be similarly impacted by the issue until the long term CAPA is implemented.

Q & A

Q7. Exemption from physical site of importation requirements for cell therapy product with <96 hrs shelf life.

A7. There is currently no exception/derogation regarding the requirement for a site of physical importation.

- The expectation is that all products from outside the EEA are received at a site which holds an MIA with 'site of physical importation' in its scope.
- However, in circumstances where a product has a very short shelf life and the requirement for a site of physical importation may negatively impact on the availability of a product, then this should be included in the MA application or as a variation for inclusion in the MA submitted to the EMA.
- This would allow for assessment by an EMA assessor, and if approved, then this would be accepted by GMP inspectors.
- A waiver of a requirement for a site of physical importation in exceptional circumstances is a discussion point at EU level with the view to adopting a harmonised approach.

Q & A

Q8a. Do we require a product specification file (PSF) for the manufacturing of a clinical working cell bank (WCB)?

A8a. The PSF should contain all of the essential reference documents to ensure that IMPs are manufactured according to good manufacturing practice for IMPs and the clinical trial authorisation.

- It is not expected that there is a dedicated PSF for WCBs, but rather, the GMP requirements for the WCB (i.e. manufacturing steps, characterisation testing, storage) which are detailed in the clinical trial application documents (e.g. in the IMPD), should form part of the PSF for the IMP.

Q8b. Do we need a QP to release a WCB or any QA member can do the release of the WCB?

A8b. There is no requirement for QP release of each WCB lot.

- The expectation is that the process for QP certification and release of the finished product, manufactured using the WCB, would include steps to ensure that the WCB was manufactured, stored and tested to GMP requirements.

Q & A

Q9. Annex 1 PUPSIT review, QP risk based decision making: Biologics

A9. Requirements for PUPSIT are detailed in para. 8.87 of Annex 1 of the EU GMP Guide, applicable for filter assemblies utilised to perform filter sterilisation of products and that is typically considered the requirement.

- Para. 8.87 of Annex 1 is not a requirement for bioburden reducing filters utilised as part of biological drug substance manufacture.

Q & A

Q10. In the context of sterile biopharmaceutical manufacturing under enhanced regulatory scrutiny, how does HPRA expect QPs to balance reliance on system-level controls versus batch-specific, first-hand manufacturing evidence when certifying batches under Annex 16—particularly where the site remains licensed but has unresolved critical observations or external enforcement actions?

A10. The expectation in these situations is that the principles of QRM are applied. Each case is likely to be different; the following considerations may apply:

- Are there alternative manufacturing sites?
- Is continued manufacture & release supported by risk assessment? Are mitigations in place for risks identified, for example, 'Person In Plant'?
- By what means does the QP ensure all information has been made available for each batch prior to release, to enable certification to GMP & the relevant MA(s)?
- Audit/meetings at regular intervals with set agendas to discuss for example, deviations, changes, CAPA implementation, CCS, self-inspection, update on regulatory status/enforcement actions etc.
- Increased level of oversight/review of batch related documentation
- Arrangements and oversight in complex supply chains

Q & A

Q11. EudraLex Volume 4, Part II – Basic Requirements for Active Substances Used as Starting Materials. Section 9.43 outlines the labelling requirements when an API is transferred outside of the manufacturer's materials management system. Clarification is sought as to whether the expiry date must be included on the label affixed directly to the Frozen API container, or whether it is acceptable for the expiry date to be provided on an accompanying label (e.g. a delivery contents label). COA also details the expiry date. API being shipped to CMO so use of barcode not suitable. Looking to avoid relabelling (Frozen API material), protect product etc., in cases where the expiry date is extended (as additional stability data becomes available).

A11: As per the question, it is a requirement of the EU GMP Guide, so it is expected that the requirements are followed.

- The expectation is that the label is applied to the physical containers of the material. Any deviation from this requirement would require justification and would need to be supported by a risk assessment. At a minimum, the label with expiry date would be required to be physically applied to the primary container; if not adhered, then affixed in such a manner that it may not become detached.

Q & A

Q12. Where an MAH is internal in an organisation, based in an EU member state, but the activities are delegated internally to other functions (e.g. manufacture, distribution, clinical activities, patient safety/PV, sales and marketing, etc), what oversight is expected of the MAH of the delegated activities and how (e.g. quality agreements, internal audits and quality management reviews) should this oversight be executed?

A12. The responsibilities, communication processes and arrangements for oversight should be detailed in quality agreements between the different functions.

- It would be expected that the MAH site/office is included in the global/corporate audit program similar to other sites with GMP responsibilities and relevant MAH activities reviewed as part of the management review process.
- The QP, the manufacturer and the MAH, all have specific responsibilities and these need to be teased out and documented under the company PQS.

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Thank you