

To: Fabio D'Atri and Caroline Attard, SANTE, European Commission

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In response to the public consultation seeking stakeholders views on the content of the **detailed Commission guideline on good manufacturing practice for investigational products for human use, pursuant to the second paragraph of Article 63(1) of regulation (EU) No. 536/2014** (herein referred to as the guideline on GMP for IMP), MPA wishes to express the following views and proposals to help the Commission develop its thinking and preparation of the required guideline.

MPA is aware of the Commission's view that GMP applies to manufacturers only and that limited reference to sponsor responsibilities has been included in the guideline on GMP for IMP consultation document. MPA does however share the view already presented by MHRA, that reference to the Sponsor in a GMP document for IMPs is appropriate and should be retained, as there is no other obvious guideline for the relevant tasks of the sponsor to be described in relation to IMP responsibilities. The definition of 'Sponsor' in Article 2(14) of Regulation 536/2014 says "*Sponsor* means an individual, company, institution or organisation which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial." As a manufacturer will typically be contracted by the sponsor, MPA believes there are GMP oversight responsibilities in that regard as it is a fundamental requirement of GMP to define responsibilities of both parties in a written agreement. The current GMP Directive 2003/94/EC does make several references to the sponsor's responsibilities, for example in particular with respect to systems for complaints and recall (Article 13(2) "*...the manufacturer shall, in cooperation with the sponsor, implement a system...*") and for ensuring contract laboratories are in line with that submitted with the CTA (Article 11(2) "*...the sponsor shall ensure that the contract laboratory complies with the content of the request...*"). MPA therefore believe that the Clinical Trial regulation 536/2014 already places obligations on the sponsor which relate to manufacturing and the guideline on GMP for IMP should be seen as seeking to help explain those obligations rather than expand on them.

Other specific comments from MPA are presented below:

Two-step release process for MP

MPA feel a strong need to retain reference to the two step release process that is currently referenced in Annex 13 under the 'shipping' section, due to patient safety concerns. The lack of a two step release process can endanger patients by introducing the possibility of (uncontrolled) dosing at the site before approvals are in place. This could invalidate insurance which has its own risks to the rights of patients. MPA therefore believes there needs to be clear understanding of when an IMP can be released for use at the clinical site and a feedback mechanism to ensure that the IMP is certified by the QP against the correct information in the CTA. That same section in the current Annex 13 also includes that "*The Sponsor should ensure that the details set out in the clinical trial application and considered by the Qualified Person are consistent with what is finally accepted by the Competent Authorities. Suitable arrangements to meet this requirement should be established.*" MPA's understanding and interpretation of this is that there needs to be provision in place to ensure that the QP is made aware of the Regulatory approval and any conditions specified to ensure that the certification is in line with the CTA. Without commitment from the sponsor to provide the relevant information this is impossible to achieve. Often this part of the process is managed at Contract Manufacturing Organisations by defining that when the sponsor requests distribution of the supplies, this is taken as confirmation that step 2 has been performed. Article 63 (1) of the CT Regulation 536/2014 says "*Investigational medicinal products shall be manufactured by applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ('good manufacturing practice')*". MPA believes that control of when the products can be released is fundamental to GCP and GMP so the Qualified Person should have provision to understand (or at least be able to define in a written agreement) who is responsible for what part of this process.

Distribution of IMP

MPA suggests adding guidance regarding quality and control of distribution, by e.g. referring to Good Distribution Practice. Furthermore, MPA consider it important to retain the text from Annex 13, paragraph 47 regarding exceptional transfers of IMP from one trial site to another. These types of transfers are never optimal, but could serve a purpose as a last resort to avoid having to interrupt patients' treatment in a way that could affect patient safety. It would be of great value to specify conditions for such transfers described in the guideline.

MPA therefore proposes that an additional section on distribution, covering the above two aspects, should be included in the guideline on GMP for IMP, to retain the GMP expectations for Sponsors that already expressed in the current published version of Annex 13 under the shipping section.

The suggested wording for inclusion is as follows:

Distribution (*new section*):

1. Investigational medicinal products should remain under the control of the sponsor until after completion of a two-step procedure: certification by the Qualified Person; and release by the sponsor for use in a clinical trial following fulfilment of the requirements of Article 4 of Regulation 536/2014. Both steps should be recorded and retained in the relevant trial files held by or on behalf of the sponsor. The sponsor should ensure that the details set out in the clinical trial application and considered by the Qualified Person are consistent with what is finally authorised by the Member States. Suitable arrangements to meet this requirement should be established. In practical terms, this can best be achieved through a change control process for the Product Specification File and defined in a Technical Agreement between the Qualified Person and the sponsor.
2. The manufacturer/importer is responsible for ensuring that the quality of the investigational products is maintained during distribution and that the applicable principles of Good Distribution Practice in accordance with the pharmaceutical quality system requirements listed in Eudralex Volume 4 Part I: Chapter 1 is accounted for.
3. Transportation and distribution of investigational products should be conducted according to instructions given by or on behalf of the sponsor in the distribution order. Records to support the chain of custody and, where appropriate, temperature control of the product must be maintained. Responsibility for the control of the investigational medicinal product remains with the sponsor (or representative) until it has been accepted by the investigator site.
4. De-coding arrangements should be available to the appropriate responsible investigator site personnel before investigational medicinal products are received at the investigator site.
5. A detailed inventory of the shipments made by the manufacturer/importer should be maintained. It should particularly mention the addressees' identification.
6. Transfers of investigational medicinal products from one trial site to another should remain the exception. Such transfers should be covered by standard operating procedures. The product history while outside of the control of the manufacturer, through for example, trial monitoring reports and records of storage conditions at the original trial site should be reviewed as part of the assessment of the product's suitability for transfer and the advice of the Qualified person should be sought. The product should be returned to the manufacturer, or another authorised manufacturer, for re-labelling, if necessary, and certification by a Qualified Person. Records should be retained and full traceability ensured.

Recalls and returns

MPA proposes to retain the wording from Annex 13, paragraph 50 relating to recall of comparator products. It is recognised that comparator products fall within the definition of IMP, and that retrieval of IMP is already described in 2.12.1 in the proposed guideline on GMP for IMP document. However, MPA strongly feels that it is worth emphasising the requirement to recall comparator products when needed, as this requires a completely different procedure to be in place, sometimes connecting back to the purchase of comparator. This procedure should be under the responsibility of the Sponsor, with possible assistance from the involved manufacturer.

2.12.1 Recalls (*text to be added*)

The Sponsor should ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the Sponsor the need to recall any product supplied.

Destruction

MPA proposes to retain the responsibility for destruction of IMP with the Sponsor, as described in Annex 13, paragraph 53. With the current suggested wording in the guideline on GMP for IMP document, all returned or unused IMP at the clinics would need to be transported back to the manufacturer for destruction. This could cause expensive international transport only for the purpose of destruction. Many clinics and hospitals have routines for destruction of IMP, which meets the same standards as those used by manufacturing sites, and allows traceability. By keeping the responsibility with the sponsor, local destruction would be allowed for as long as reconciliation is performed and the destruction is properly documented.

2.12.3 Destruction (*revised first sentence*):

The Sponsor is responsible for the destruction of unused and/or returned investigational medicinal products. Investigational medicinal products should therefore not be destroyed without the prior written authorisation by the Sponsor.

On behalf of MPA, Sweden

Helena Lindberg
GCP inspector

Ann Marie Janson Lang
Ad-hoc CT delegate