



Medicines & Healthcare products
Regulatory Agency



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To whom it may concern,

GL on GMP for IMP: MHRA UK's response to EC consultation

In response to the public consultation seeking stakeholders' views on the content of the detailed Commission guideline on good manufacturing practice for investigation 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), MHRA wishes to express the following views and proposals to help the Commission develop its thinking and preparation of the required guideline.

Having represented the UK as Rapporteur on the Annex 13 drafting group, MHRA 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. MHRA does however consider reference to the Sponsor in a GMP document 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.*" – if the sponsor is responsible for the overall management of the trial, MHRA believes this covers all aspects, including specifications, instructions, product specification files, manufacture and release with certain aspects delegated according to written agreements. As a manufacturer will typically be contracted by the sponsor, MHRA 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...*"). MHRA 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.

Specifically, MHRA feel a strong need to retain reference to the two stage release process that is currently referenced in Annex 13 under the 'shipping' section, due to patient safety concerns. The lack of a two stage 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. MHRA 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.”* MHRA’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’)”*. MHRA 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.

MHRA therefore proposes that an additional section on distribution 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

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 authorisation 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. 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 distribution of the products minimises any risk to their quality and takes account of the applicable principles of Good Distribution Practice in accordance with the pharmaceutical quality system requirements listed in EU GMP Guide Part I: Chapter 1.
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.

Kind regards,

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