From:
Sent: 24 November 2015 12:43
To: SANTE-D6-GL-GMP-IMP; SANTE PHARMACEUTICALS D6
Cc:

Subject: Public consultations on Good Manufacturing Practice for Investigational Medicinal Products for human use and inspection procedures - B

Dear European Commission Members,

Following the discussion with other member states about 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), in response to the public consultation on the guideline on GMP for IMP, fully supports the views of UK and Sweden and wishes to express the following proposals described below.

consider that sponsor responsibilities should be retained in the guideline on GMP for IMP consultation document as there is no other guideline for the relevant tasks of the sponsor to be described in relation to IMP responsibilities.
Sponsor, in the Article 2(14) of Regulation 536/2014, is defined as responsible for the overall management of the trial. believes this definition covers all aspects, including specifications, instructions, product specification files, manufacture and release with certain aspects delegated according to written agreements. Sponsor must have GMP oversight responsibilities because he will often contract a manufacturer, and should be a fundamental requirement of GMP to define responsibilities of both parties in a written agreement.
The current GMP Directive 2003/94/EC make several references to the sponsor's responsibilities, in particular with respect to systems for complaints and recallls (Article 13(2)) and for ensuring contract laboratories are in line with that submitted with the CTA (Article 11(2)). therefore believes 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.

proposes to add/retain the following wording on the section 2.12.1 Recalls:
" 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." The wording of paragraph 50 (Annex 13) related to the recall of comparator products should be retained, because this requires a completely different procedure to be in place, sometimes connecting back to the purchase of comparator. This procedure should to be under the responsibility of the Sponsor, with possible assistance from the involved manufacturer.

proposes to review the wording of the first sentence on the section 2.12.3 Destruction:
" 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 authorization by the Sponsor." The responsibility for destruction of IMP with the Sponsor, as described in paragraph 53 of Annex 13, should be retained. With the 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 increase the cost of international transport, only for the purpose of destruction. Many clinics and hospitals have routines for destruction of IMP, which meet 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.

believes that it should be retained 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.

therefore believes that 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.
- 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')*".

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.

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 are 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,