SUMMARY OF THE RESPONSES TO THE PUBLIC CONSULTATION ON THE COMMISSION DELEGATED ACT ON PRINCIPLES AND GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR INVESTIGATIONAL MEDICINAL PRODUCTS FOR HUMAN USE AND INSPECTION PROCEDURE, PURSUANT TO THE FIRST SUBPARAGRAPH OF ARTICLE 63(1) OF REGULATION (EU) NO 536/2014

1. GENERAL REMARKS

Currently, Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use[1] also sets out principles and guidelines for good manufacturing practice (GMP) for investigational medicinal products for human use.

However, once Regulation (EU) No 536/2014[2] becomes applicable, manufacture and import of investigational medicinal products used in clinical trials carried out under that Regulation cannot follow Directive 2003/94/EC.

Instead such products will have to be manufactured and imported under good manufacturing practice for investigational medicinal products for human use laid down by the Delegated Act provided for in Article 63(1) of Regulation (EU) No 536/2014.

The Commission should prepare a delegated act to specify the principles and guidelines of GMP for investigational medicinal products for human use and the detailed arrangements for inspection, pursuant to the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014.

With a view to prepare the Delegated Act, the Commission services launched a public consultation in 2015. Stakeholders were invited to provide their views on the requirements for the principles and guidelines of GMP and the detailed arrangements for inspection for ensuring the quality of investigational medicinal products and answer some questions by 24 November, 2015.

The consultation document carried over the majority of the principles and guidance set out in Directive 2003/94/EC relating to investigational medicinal products for human use.

This document presents a factual summary of the responses to the public consultation. It does not present the views of the European Commission.

2. CONTRIBUTORS TO THE PUBLIC CONSULTATION

The number of contributions received was 26. Nine contributors claimed confidentiality or anonymity over their submissions. Their contributions will therefore not be published or published only in anonymous form.

[1] OJ L 262, 14.10.2003, p. 22.

[2] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1.

Contributors can be classified as:

Sector	**Contributors included**
Public authorities	8
Industry stakeholders	11
Professional organisations	6
Academia	1

3. OUTCOME OF THE PUBLIC CONSULTATION

3.1 Topics of the responses

The main comments and remarks of the responses were made on the following topics:

- Request for clear definition and interface of manufacturer and sponsor responsibilities, inclusion of the "importer";
- Concerns of potential duplication of already existing GMP requirements;
- Aspects around the conformity of third country manufacturer and products (GMP standards equivalent to EU, QP declaration of equivalence);
- Documentation of any kind of GMP relevant activities and handling of electronic data storage;
- The need for validation of manufacturing processes;
- Request for definitions of retention and reference samples, testing of samples after end of shelf life;
- Harmonised retention period for starting materials;
- Possibility of transitional Qualified Person (QP) and further elaboration on responsibilities of QP;
- Complaint handling process: communication obligations of manufacturer when product defects occur, e.g. defined responsibilities for rapid unblinding;
- Elaborating on specific aspects for advanced therapy investigational medicinal products (self-inspection, reconstitution);
- Supervision by inspections (also on the approach for investigational medicinal products manufactured in third countries), sharing of inspection reports, inspectors' empowerment/ competences/obligations.

3.2 Response to Commission questions

As part of the consultation several questions were asked to inform the development of the delegated act.

<u>Question 1a:</u> Would a requirement for a product specification file (a reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release, shipping of an investigational medicinal product) be useful to be introduced?

13 contributors responded positively to this question, while 4 did not see the need to introduce the requirement for a product specification file. This would be sufficiently covered in the actual guidelines on good manufacturing practice for investigational medicinal products for human use and inspection procedure. Other contributors argued that the investigational medicinal product dossier as well as the batch record information, usually contain sufficient information already.

Question 1b: Do product specification files exist for manufacture of all investigational medicinal products in the EU?

16 contributors responded positively to this question, 1 contributor reported that such information is already documented, even though the term "product specification file" is not always used. There were no negative responses.

Question 2: Different options exist for the retention period of batch documentation:
a) Retention of at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used, whichever is the longer period.
b) Retention for at least 25 years after the end of the clinical trial in line with the retention period of the clinical trial master file.

Option a) was preferred by 6 contributors, while option b) was preferred by 10 contributors. Other contributors could not decide or opted for other retention periods (such as 15 years).

Question 3: Would it be feasible to require that Certificates of Analysis should accompany each shipment of imported investigational medicinal products as a means to ensure that analytical control had been carried out in the third country? Please elaborate your answer to this question.

Feasibility was confirmed by 11 contributors. The main trends being that:

- This is currently already considered best practice
- A full Certificate of Analysis (CoA) is needed to be able to estimate GMP and patient (and courier) safety.
- The CoA is normally included in the package of documents which the QP should have for certification.
- The CoA helps to rely on proper documentation in order to evaluate the quality of the batch, ensure that the product has been analysed as agreed, may supplement the existing information for investigational medicinal product available at the importer's site and make sure that defined acceptance criteria when applying test methods to the batch in question are met.
- The CoA ensures that any imported investigational medicinal product, which was ordered according to specifications laid down in a quality agreement, fulfils the defined specifications.

However, 10 contributors were against introducing this requirement. The following main issues were raised:

- The QP is responsible for ensuring that an imported investigational product has been fully tested before it is certified for supply; how they obtain documentation for this should remain flexible.
- While it is important to receive the CoA at a certain point in time prior to final certification of the investigational medicinal product, it does not necessarily need to accompany each shipment during importation.
- For imported active comparators, especially when already licensed, there is often no CoA provided
- Investigational medicinal products from a single batch may be split into several shipments by a manufacturer outside the EU for delivery into the EU. Each shipment,

since it comprises the same batch, would be then have to be covered by the same certificate of analysis.
- For outsourced batch manufacturing it is also possible that the testing of the batch in question is still ongoing in another country or even in the EU while shipping the product to the sponsor.

Question 4a: Should retention samples also be required to be retained by the manufacturer?

This question was answered positively by 17 contributors, while 3 parties opposed to it. The latter argued that

- Retention samples are primarily used in cases where the authenticity of a product needs to be confirmed, e.g. counterfeit identification. Where reference samples and retention samples are inter-changeable, are sufficient in quantity and presented identically, there should be no requirement for retention samples. Availability of printed materials, literally or in the form of an electronic file or photograph, should be accepted without the need for retention samples.
- There is no benefit for the retention samples to be kept by the manufacturer while they are already in possession of the sponsor. Having duplicate samples with the manufacturer as well as with the sponsor may simply be unfeasible for small amounts of investigational medicinal products, especially for early phase studies.

Question 4b: If only reference samples are required, would a requirement for photos of the investigational medicinal product, the packaging and the labelling to supplement the reference sample be useful? Please justify.

Answers to this question were given bearing in mind the answers on question 4a.

Some contributors that did not agree to the necessity of retention samples and in principal supported the requirements for reference samples. They felt that photographs provide good means to demonstrate the real manufacturing steps without incurring a major cost burden and a reliable source in case of randomisation and blinding rather than keeping only one sample. Electronic systems used to retain this information would need to comply with Annex 11. Some contributors opted for issuing a recommendation rather than a requirement to have photos of reference samples available.

In contrast, other parties noted that photos should not be acceptable, as they might be digitally altered.

Question 5a: In how many clinical trials authorised under the Clinical Trials Directive has Article 13(3)(c) of that Directive been used? Please provide figures both as actual number of trials and as percentage of the trials authorized, if available.

The majority of contributors did not have any data available. Exact figures were not provided. Data on percentages provided was very diverse and ranged between 1 and 100%. The use as investigational medicinal product of comparators authorised in a third country was estimated at 5-15%.

Question 5b: In how many clinical trials authorised under the Clinical Trials Directive, is the comparator product not authorized in an ICH country (EU, US, Japan, Canada and

Switzerland)? Please provide figures both as actual numbers of trials and as percentage of the trials authorized, if available.

Again very little data was available. Single contributors stated small numbers of trials (2-5), other large percentages 30-50%. Non-ICH countries, from which comparators were sourced, included Brazil and Australia.