

6 September 2005

EMEA
7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom

Sampling of Investigational Medicinal Products

As a result of the EMEA GMP Inspection Services meeting with Interested Parties on 12 May 2005, ISPE is delighted to provide a document that could serve as the basis for future guidance on the sampling of IMP's. This document has been jointly developed with EFPIA.

Yours Sincerely,

A handwritten signature in black ink, appearing to read "Robert P. Best". The signature is written in a cursive, flowing style.

Robert P. Best
President/CEO



Sampling of Investigational Medicinal Products

Introduction

During the 2nd EMEA GMP Inspection Services meeting with Interested Parties on 12th May 2005 the issue of sampling of IMPs was discussed and it was stated that input from industry would be welcome. EFPIA and ISPE have jointly set up a document that could serve as basis for future guidance on the sampling of IMPs and we are pleased to share this document with the GMP inspectors group.

Recommendations for additional guidance on sampling of IMPs

The draft Annex 19 concentrates on EU marketed products and is ambiguous with regard to IMPs, as the GMP principles for marketed products cannot be directly transferred to IMPs (please refer to the “Current Industry Practices section” below for illustration).

Therefore, it would be very impractical for IMP manufacturers to have requirements for IMPs outlined in documents, which are written with a focus on marketed products.

Therefore it is suggested that:

- Sampling of IMPs is addressed in Annex 13 only, as Annex 13 already contains provisions for sampling in paragraphs 36 and 37.
- The new Annex 19 should not include IMPs in the scope and be limited to authorised medicinal products in order to avoid any conflicting requirements with the current Annex 13.

Should a change to Annex 13 be considered necessary, we would propose having additional clarifications about sampling, quantities and the role of the QP in this activity to supplement the current paragraphs 36 and 37 in the Quality Control section. The text in blue below shows the proposed changes to Annex 13, paragraphs 36 and 37.

The proposed text for Annex 13 would read as follows:

36. Samples of each batch of investigational medicinal product, including blinded product should be retained for the periods specified in Directive 2003/94/EC. Such samples should be of sufficient size to permit the carrying out, on two occasions, of the full analytical controls, on the batch in accordance with the information provided by the sponsor pursuant to Article 9(2) of Directive 2001/20/EC unless justified by the manufacturer (e.g. availability of material for early phase clinical trials, type of product).

37. Consideration should be given to retaining samples from each packaging run/trial period until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results.

The QP certifying the IMPs for a clinical trial should ensure that such samples, including those manufactured and packed at different sites, are accessible to the Competent Authorities. Where necessary, the arrangements for such access should be defined in a written agreement.

Current Industry Practices for sampling of IMPs:

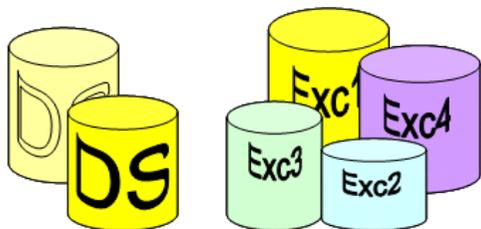
The diagrams on the following pages give an illustration of current practice of sampling of IMPs. They are included here for information purposes only.

Note:

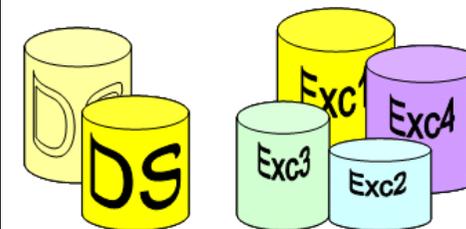
- Sampling plan A reflects the approach taken by some IMP manufacturers to retain IMP samples directly after the bulk manufacturing step, whereas the sampling plan B reflects the alternative approach to retain the IMP samples in the primary packaging material used in the clinical trial.
- The sampling for Blinded Trials illustrates that the sampling as outlined in the draft Annex 19 cannot be transferred to IMPs, as
 - companies may have different approaches to address Annex 13 No. 37 depending on the system they have implemented, and, in addition,
 - no samples can be taken for the “IMP finished product”.

Sampling for IMPs – Current Industry Practice

Drug Substances, Excipients, Key Packaging Components



Samples are stored at the site of analysis / release at an amount to allow for 2 analyses. * (1)



Pharmaceutical Manufacturing

Bulk Drug Products

Pharmaceutical Manufacturing

Dry Products

Injectables & Drug in the bottle



Sampling Plan A:

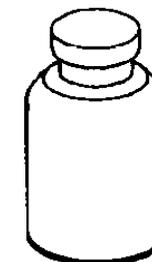
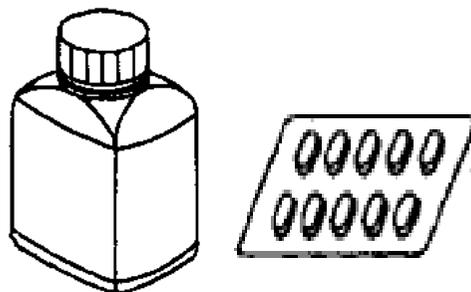
Samples are stored at the site of analysis / release at an amount to allow for 2 analyses. * (1) (2)

Sampling Plan B:

No samples (will be kept on primary packed material)

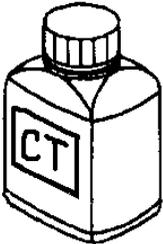
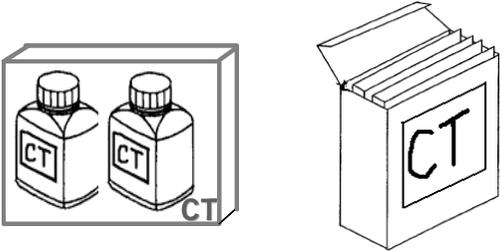
Samples are stored at the site of analysis / release at an amount to allow for 2 analyses. * (1) (2)

Primary Packaging

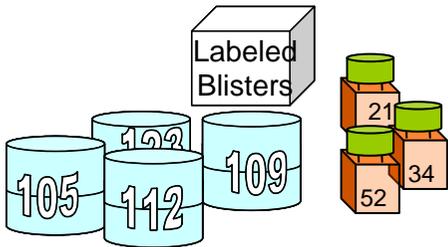
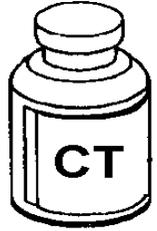
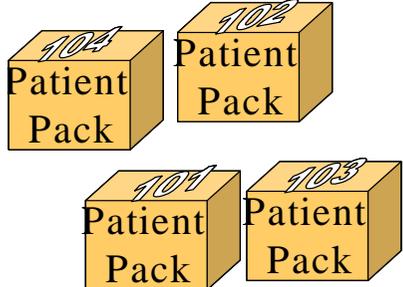
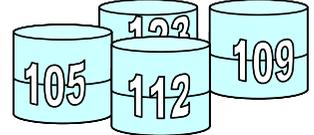
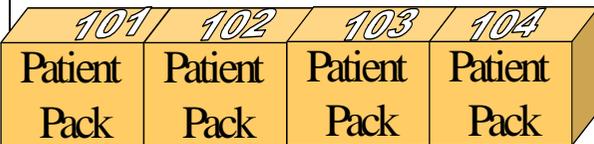
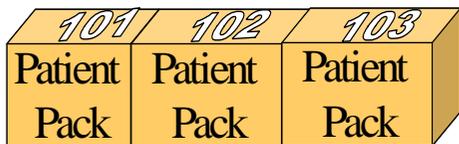


Continue with Sampling of Final Packs for Open Trials or with Sampling of Packs for Blinded Trials

Specific Sampling Plan for Open Trials

Labelling	Labelling	Labelling and Secondary packaging
	<p>Samples may be taken during the labelling procedure (3).</p>	
<p style="text-align: center;">Secondary packaging</p> <div style="text-align: center;">  </div>	<p style="text-align: center;">Final Packs for the clinical trial</p> <p>Samples may be taken during the packaging procedure (3).</p>	
		

Specific Sampling Plan for Blinded Trials

Labelling	Creation of Treatment Groups as per trial design requirements at labelling stage	Labelling
	<p>Samples may be taken during the labelling procedure (3).</p>	
<p style="text-align: center;">↓</p> <p style="text-align: center;">Secondary Packaging</p>	<p style="text-align: center;">Creation of Treatment Groups as per trial design requirements at secondary packaging stage</p>	<p style="text-align: center;">↓</p> <p style="text-align: center;">Secondary Packaging</p>
	<p>Samples may be taken during the packaging procedure (3).</p>	
<p style="text-align: center;">↓</p> <p style="text-align: center;">Finishing</p>	<p style="text-align: center;">Assembly of Treatment Groups – Finished Patient packs</p>	<p style="text-align: center;">↓</p> <p style="text-align: center;">Finishing</p>
	<p>No samples are kept of the finished patient packs, as each pack is an individual pack with respect to labelling and each study arm may have a different content.</p>	

Comparators:

- Secondary Repackaging: 1 unit is retained after repackaging.
- Primary Repackaging or Modified Comparator: See above as for Bulk Drug products.

*		Reduced sampling may be performed depending on phase of development (Phase I products) and type of product.
(1)	Directive 2003/94/EC Article 11, 4	“For an investigational medicinal product, sufficient samples of each batch of <u>bulk formulated product and of key packaging components used for each finished product batch</u> shall be retained for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer. Unless a longer period is required under the law of the Member State of manufacture, <u>samples of starting materials, other than solvents, gases or water, used in the manufacturing process shall be retained</u> for at least two years after the release of product. That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter. All those samples shall be maintained at the disposal of the competent authorities”
(2)	EU GMP Annex 13, 36	“Samples of each batch of investigational medicinal product, including blinded product should be retained for the periods specified in Directive 91/356 as amended for investigational medicinal products (2003/94/EC)”
(3)	EU GMP Annex 13, 37	“Consideration should be given to retaining samples from each packaging run/trial period until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results”