Guidance for Industry: Sample Retention for Advanced Therapy Products

Version 1.0

(Draft for Information)

Drug Office

Department of Health

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A. Introduction

This document is intended to provide guidance on the interpretation of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* published by the Pharmaceutical Inspection Co-operation Scheme ("the GMP Guide) with respect to requirements on retention of samples at manufacturers of advanced therapy products ("ATPs").

This guidance represents the Drug Office's current thinking on this topic and should be viewed only as recommendations. It does not establish legally enforceable responsibilities, create additional requirements, form the basis for GMP inspections, place any restraint on the development of new concepts or technologies, or operate to bind the Drug Office or the public. There may be other acceptable approaches that provide an equivalent level of quality assurance.

B. Purpose

To provide guidance to the industry on sample retention strategies for advanced therapy products

C. Scope

This guidance relates to requirements for reference and retention of samples of materials and products at ATP manufacturers.

D. Definition

Reference sample:	A sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analyzed should the need arise during the shelf life of the batch concerned. Where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates that are transported outside of the manufacturer's control should be kept.
Retention sample:	A sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, patient information leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned. There may be exceptional circumstances where this requirement can be met without retention of duplicate samples e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products.

E. Background

It is a requirement of GMP that the quality control department oversees the control of the reference and retention samples of materials and products. General requirements on sampling and storage are given in *Annex 19 Reference and Retention Samples of* the GMP Guide.

The ATP manufacture of commonly involves the processing of starting materials (e.g. cells or tissues incorporated as an integral part of the finished product) and raw materials (e.g. reagents, culture media, buffers, sera, enzymes, cytokines, growth factors, feeder cells) to give the active substances, intermediate and finished products. The afore-mentioned general requirements associated with reference and retention samples are applicable to these materials and products.

Due to the intrinsic limitations of certain types of materials, products (e.g. limited quantities and short shelf-lives) and manufacturing processes (e.g. a continuum that the point of obtaining the active substance cannot be defined) involved in the manufacture of ATPs, modified sampling and retention strategies may be adapted. It is the responsibility of ATP manufacturers to assess the impact of and justify the modified strategies, taking into consideration any mitigation measures. These actions taken should be formally documented.

While this guidance does not intend to address all applicable requirements in the GMP Guide, adaptations specific to ATPs are described.

F. Guidance

1. Sampling Strategies

1.1. Reference samples should be representative of the batch of starting material, raw material, active substance, intermediate product or finished product from which they are taken.

1.2. As a general principle, a reference sample of sufficient size to permit the carrying out, on, at least, two occasions of the full analytical controls on the batch. It is acknowledged that this may not always be feasible due to scarcity of the materials or limited size of the batches (*e.g.* autologous products, allogeneic products in a matched donor scenario, products for ultra-rare diseases, products for use in first-in-man clinical trial with a very small scale production).

1.3. The sampling plan should be documented. The sampling plan should be adapted to the specific characteristics of the product. In designing the sampling strategy, the manufacturer should take into account the risks, the practical limitations that may exist, and possible mitigation measures (*e.g.* increased reliance on in-process testing).

2. Storage Conditions

2.1. Samples should normally be stored under the conditions foreseen in the product information. However, for materials/products with a short shelf-life, it should be carefully considered if other storage conditions that maximise stability can be used.

3. Special Considerations of Materials and Products

3.1. Starting Materials

3.1.1. Due to the scarcity of materials, it is justified not to keep reference samples of the cells/tissues used as starting materials in the case of autologous ATPs and certain allogeneic ATPs (matched donor scenario). In other cases where the scarcity of the materials is also a concern, the sampling strategy may be adapted provided that this is justified and appropriate mitigation measures are implemented.

3.1.2. Samples of starting materials should generally be kept for two years after the release of the finished product batch. The retention period should be adapted to the stability and shelf-life of the product and, therefore, shorter periods may be justified. In cases of short shelf-life, the manufacturer should consider if the retention of the sample under conditions that prolong the

shelf-life (such as cryopreservation) is representative for the intended purpose. For instance, cryopreservation of fresh cells may render the sample inadequate for characterization purposes but the sample may be adequate for sterility or viral safety controls (the volume of the samples can be reduced according to the intended purpose). When the cryostorage of a sample is considered inadequate for the intended purpose, the manufacturer should consider alternative approaches (*e.g.* sample of intermediate product such as differentiated cells).

3.2. Raw Materials

3.2.1. Reference samples of critical raw materials (*e.g.* cytokines, growth factors, enzymes, sera) are important for the investigation of possible quality problems of the product. The assessment whether a specific raw material is critical should be done by the manufacturer having regard to the specific risks and possible mitigation measures (*e.g.* increased QC controls). The decisions taken should be documented. Samples of critical raw materials should be retained during the shelf-life of the relevant raw materials.

3.3. Active Substances and Intermediate Products

3.3.1. It is acknowledged that for ATPs it is not always possible to separate the sampling of the starting materials, active substances, intermediate and finished products. The considerations regarding scarcity of starting materials apply - adapted as necessary - to the expectations on the retention of samples of active substances and intermediate products.

3.3.2. The adaptation regarding retention period of starting materials may be applied for active substances and intermediate products.

3.4. Packaging Materials

3.4.1. Samples of packaging materials should be retained for the duration of the shelf life of the finished product concerned.

3.4.2. The retention of samples of primary packaging material may not be necessary in certain cases, having regard to the risks of the materials and/or other relevant consideration (*e.g.* increased QC controls, primary packaging material certified as a medical device). A decision not to keep samples of primary packaging materials should be duly justified and documented.

3.4.3. Availability of printed materials as part of the reference and/or retention sample of the finished product can be accepted.

3.5. Finished Products

3.5.1. Retention sample of finished product should generally be kept per batch for at least one year after the expiry date. A retention sample is, however, not expected in the case of autologous products or allogeneic products in a matched donor scenario as the unit produced with the patient's tissues/cells constitutes should be administered to the patient. When it is not possible to keep a retention sample, photographs or copies of the label are acceptable for inclusion in the batch records.

3.5.2. The retention sample should be contained in its finished primary packaging or in packaging composed of the same material as the primary container in which the product is marketed.

3.5.3. Where a batch is packaged in two, or more, distinct packaging operations, at least one

retention sample should be taken from each individual packaging operation.

3.6. Investigational ATPs

3.6.1. Reference and retention samples of investigational ATPs, including blinded products should be kept 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.

3.6.2. Consideration should be given to keeping retention samples 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.

3.6.3. Reference sample of the product contained in its primary packaging or finished product is accepted.

G. Useful Reference Materials

1. European Commission. (2017). Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products.
2. Pharmaceutical Inspection Co-operation Scheme. (2018). Guide to Good Manufacturing Practice for Medicinal Products Annexes (PI 009-14 [Annexes]).

Document Information

Version	Date	Description of Change
1.0	02 Jul 2019	First version (draft for information)

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