EUROPEAN
COMMISSION

Brussels, 23.6.2026
C(2026) 4135 final

GUIDELINES

The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

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Annex 19

Reference and Retention Samples

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in as laid down in Commission Directive 2017/1572/EU for medicinal products for human use.

Status of the document: Revision of the 2006 version of Annex 19.

Reasons for changes: The GMP/GDP Inspectors Working Group and the PIC/S Committee jointly recommend that the current version of annex 19, on the Reference and Retention Samples, is revised with respect to reference and retention Samples for Parallel Imported/Parallel Distributed/Parallel Traded Products.

Deadline for coming into operation: 3 months from the date of publication by the European Commission.

1. Scope

1.1 This Annex to the Guide to Good Manufacturing Practice for Medicinal Products ("the GMP Guide") gives guidance on the taking and holding of reference samples of starting materials, packaging materials or finished products and retention samples of finished products.

1.2 Specific requirements for investigational medicinal products are given in Detailed Commission guideline on GMP for investigational medicinal products.

1.3 This annex also includes guidance on the taking of retention samples for parallel imported/ distributed medicinal products.

2. Principle

2.1 Samples are retained to fulfil two purposes, firstly to provide a sample for analytical testing and secondly to provide a specimen of the fully finished product. Samples may therefore fall into two categories:

Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed 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.

For finished products, in many instances the reference and retention samples will be presented identically, i.e. as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.

2.2 It is necessary for the manufacturer, importer or site of batch release, as specified under section 7 and 8, to keep reference and/or retention samples from each batch of finished product and, for the manufacturer to keep a reference sample from a batch of starting material (subject to certain exceptions – see 3.2 below) and/or intermediate product. Each packaging site should keep reference samples of each batch of primary and printed packaging materials. Availability of printed materials as part of the reference and/or retention sample of the finished product can be accepted.

2.3 The reference and/or retention samples serve as a record of the batch of finished product or starting material and can be assessed in the event of, for example, a dosage form quality complaint, a query relating to compliance with the marketing authorisation, a labelling/packaging query or a pharmacovigilance report.

2.4 Records of traceability of samples should be maintained and be available for review by competent authorities.

3. Duration of Storage

3.1 Reference and retention samples from each batch of finished product should be retained for at least one year after the expiry date. The reference 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.

3.2 Unless a longer period is required under the law of the Member State of manufacture, samples of starting materials (other than solvents, gases or water used in the manufacturing process) shall be retained for at least two years after the release of the finished product. That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter. Packaging materials should be retained for the duration of the shelf life of the finished product concerned.

4. Size of Reference and Retention Samples

4.1 The reference sample should be of sufficient size to permit the carrying out, on at least two occasions, of the full analytical controls on the batch in accordance with the Marketing Authorisation File which has been assessed and approved by the relevant Competent Authority / Authorities. Where it is necessary to do so, unopened packs should be used when carrying out each set of analytical controls. Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.

4.2 Where applicable, national requirements relating to the size of reference samples and, if necessary, retention samples, should be followed.

4.3 Reference samples should be representative of the batch of starting material, intermediate product or finished product from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). 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. Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.

4.4 It should be ensured that all necessary analytical materials and equipment are still available, or are readily obtainable, in order to carry out all tests given in the specification until one year after expiry of the last batch manufactured.

5. Storage Conditions

5.1 Storage of reference samples of finished products and active substances should be in accordance with the current version of the Note for Guidance on Declaration of Storage Conditions for Medicinal Products and Active Substances.

5.2 Storage conditions should be in accordance with the marketing authorisation (e.g. refrigerated storage where relevant).

6. Written Agreements

6.1 Where the marketing authorisation holder is not the same legal entity as the site(s) responsible for batch release within the EEA, the responsibility for taking and storage of reference/retention samples should be defined in a written agreement between the two parties in accordance with Chapter 7 of the EC Guide to Good Manufacturing Practice. This applies also where any manufacturing or batch release activity is carried out at a site other than that with overall responsibility for the batch on the EEA market and the arrangements between each different site for the taking and keeping of reference and retention samples should be defined in a written agreement.

6.2 The Qualified Person who certifies a batch for sale should ensure that all relevant reference and retention samples are accessible at all reasonable times. Where necessary, the arrangements for such access should be defined in a written agreement.

6.3 Where more than one site is involved in the manufacture of a finished product, the availability of written agreements is key to controlling the taking and location of reference and retention samples.

7. Reference Samples – General Points

7.1 Reference samples are for the purpose of analysis and, therefore, should be conveniently available to a laboratory with validated methodology. For starting materials used for medicinal products manufactured within the EEA, this is the original site of manufacture of the finished product. For finished products manufactured within the EEA, this is the original site of manufacture.

7.2 For finished products manufactured by a manufacturer in a country outside the EEA;

7.2.1 where an operational Mutual Recognition Agreement (MRA) is in place, the reference samples may be taken and stored at the site of manufacture. This should be covered in a written agreement (as referred to in section 6 above) between the importer/site of batch release and the manufacturer located outside the EEA.

7.2.2 where an operational MRA is not in place, reference samples of the finished medicinal product should be taken and stored at an authorised manufacturer located within the EEA. These samples should be taken in accordance with written agreement(s) between all of the parties concerned. The samples should, preferably, be stored at the location where testing on importation has been performed.

7.2.3 reference samples of starting materials and packaging materials should be kept at the original site at which they were used in the manufacture of the medicinal product.

8. Retention Samples – General Points

8.1 A retention sample should represent a batch of finished products as distributed in the EEA and may need to be examined in order to confirm non-technical attributes for compliance with the marketing authorisation or EU legislation. Therefore, retention samples should in all cases be located within the EEA. These should preferably be stored at the site where the Qualified Person (QP) certifying the finished product batch is located.

8.2 In accordance with 8.1 above, where an operational MRA is in place and reference samples are retained at a manufacturer located in a country outside the EEA (section 7.2.2 above), separate retention samples should be kept within the EEA.

8.3 Retention samples should be stored at the premises of an authorised manufacturer in order to permit ready access by the Competent Authority.

8.4 Where more than one manufacturing site within the EEA is involved in the manufacture importation/packaging/testing/batch release, as appropriate of a product, the responsibility for taking and storage of retention samples should be defined in a written agreement(s) between the parties concerned.

9. Reference and Retention Samples for Parallel Imported/Parallel Distributed/Parallel Traded Products

9.1 Physical samples of packaging materials used in the re-packaging process (e.g. labels, carton, patient information leaflet, other package inserts) should be retained for the duration of the shelf-life of the re-packaged finished product.

9.2 Reference samples of the re-packaged product are not required.

9.3 A retention sample of the re-packaged finished product should be taken for each re-packaging operation and retained for at least one year after expiry date.

9.4 The retention sample should represent the re-packaged finished product released for the market and should include the primary package as well as the secondary package. In cases where the secondary package is not opened, only the packaging material used needs to be retained.

9.5 Where it is duly justified that a physical retention sample of the re-packaged finished product cannot reasonably be retained, and this has been agreed in advance with the competent authority, a photographic/digital sample may be retained.

9.5.1 The photographic/digital sample should be a complete record, provide sufficient information allowing full visual examination and permit investigations of the re-packaged product equivalent to that possible with a physical retention sample. It should comprise high-quality photos of the re-packaged product and should allow traceability to the batch packaging record pertaining to that specific re-packaged finished product.

9.5.2 The photographic/digital sample should include all the data on both primary and secondary packaging, e.g. batch number, expiry date.

9.5.3 The photographic/digital sample should also show evidence that the safety features have been applied and allow the identification of information in braille.

9.5.4 Any photographic/digital sample stored electronically, should comply with the principles of Annex 11 to ensure integrity of the record over the retention period.

10. Reference and Retention Samples in the Case of Closedown of a Manufacturer

10.1 Where a manufacturer closes down and the manufacturing authorisation is surrendered, revoked, or ceases to exist, it is probable that many unexpired batches of medicinal products manufactured by that manufacturer remain on the market. In order for those batches to remain on the market, the manufacturer should make detailed arrangements for transfer of reference and retention samples (and relevant GMP documentation) to an authorised storage site. The manufacturer should satisfy the Competent Authority that the arrangements for storage are satisfactory and that the samples can, if necessary, be readily accessed and analysed.

10.2 If the manufacturer is not in a position to make the necessary arrangements this may be delegated to another manufacturer. The Marketing Authorisation holder (MAH) is responsible for such delegation and for the provision of all necessary information to the Competent Authority. In addition, the MAH should, in relation to the suitability of the proposed arrangements for storage of reference and retention samples, consult with the competent authority of each Member State in which any unexpired batch has been placed on the market.

10.3 These requirements apply also in the event of the closedown of a manufacturer located outside the EEA. In such instances, the importer has a particular responsibility to ensure that satisfactory arrangements are put in place and that the competent authority/authorities is/are consulted.