

# ***OMCL Network of the Council of Europe***

## **GENERAL DOCUMENT**

PA/PH/CAP (12) 32 R14

Sampling and Testing of Centrally Authorised Products –  
Procedure for Generics Programme

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<b>Concerned Network</b>	EU/EEA OMCLs – EU/EEA Sampling Organisations

# **SAMPLING AND TESTING OF CENTRALLY AUTHORISED PRODUCTS**

## **PROCEDURE FOR GENERICS PROGRAMME**

### **Introduction**

A generic medicinal product for human use is defined by Article 10 of Directive 2001/83/EC, as amended, as "a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, isomers, mixture of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form." The same definition applies to generic veterinary medicinal products (Article 13.2b of Directive 2001/82/EC, as amended). Human and veterinary reference medicinal products are defined as medicinal products authorised under Article 6 of Directive 2001/83/EC or Article 5 of Directive 2001/82/EC, respectively. A reference medicinal product can either be a centrally authorised medicinal product or be authorised through a Mutual Recognition/Decentralised or National procedure. Alternatively, a generic medicinal product of a centrally authorised reference medicinal product can be authorised through one of the four available procedures and thus might not necessarily be a CAP.

When a generic medicinal product as defined above has been authorised through the Centralised procedure, it might be included as such in the CAP Annual Programme. Under these circumstances, the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version, applies.

Generic medicinal products authorised through the Centralised procedure can also be included in a specific CAP Generics Programme. The Generics Programme is an individual testing programme, which is part of the CAP Sampling and Testing programme, where Centrally Authorised Generic Products with the same or similar dosage form and containing the same Generic INNs, and ideally for which there is a developed common test method from previous testing experience in the OMCL network available, are sampled and tested over a period of 5 years. It should be read in conjunction with the General procedure PA/PH/CAP (05) 49 in its current version.

This paper describes the operational procedure for post-authorisation sampling and testing of Generics CAPs, when they are included in the Generics Programme. This only applies to chemical products. It contains a step-by-step description starting from the planning of the forthcoming test programme (year n-1) to the presentation of the Annual Report to the EMA (year n+1).

In the eventuality of Out-Of-Specifications results, appropriate verifications will take place according to the established procedures and using the registered methods for the sample in question, if different; any subsequent action is the responsibility of the EMA.

The establishments in this procedure do not prevent the OMCLs from liaising with their National Competent Authority within the framework of their regulatory activity.

*Statements made in italics in this procedure are comments related to the steps described.*

## Planning of the Forthcoming Programme

### Step 1: Proposed Programme

The list of Generics INNs to be tested during 5 years is selected by the EMA secretariat, in collaboration with the EMA Scientific Committees and agreed with the EDQM and the CAP Advisory Group. This list becomes part of the 5 year co-operation agreement signed between EMA and EDQM and can only be modified by written agreement between EMA and EDQM.

When the list is available, the EDQM Secretariat helps to identify volunteers (Scientific Advisor) for each Generic INN (e.g. survey sent to the OMCL Network), so that the workload can be equally split over 5 years and ideally between as many OMCLs as possible.

A draft timetable indicating the year of testing and the OMCL selected per each Generic INN is prepared by the EDQM and provided to the EMA Secretariat. This timetable is maintained and updates are presented during the CAP annual meeting.

For the purpose of programme planning and budgeting, the sampling and testing of each Generic INN Group will be organised as "yearly" programme, as set out in the following steps.

### Step 2: Final Adoption of the Programme for Year n

In **January** (year n-1) the EDQM informs EMA which Generic INNs will be tested in the following year in accordance with the 5 year draft timetable.

Based on this information, the EMA will prepare the list of products associated to the proposed Generic INNs which is normally adopted during the **February** (year n-1) meetings of the CHMP and CVMP.

The EMA Secretariat informs the EDQM, Department for Biological Standardisation, OMCL Network & HealthCare (DBO) of the decision in a timely manner (registered sources of a Generic CAP product and list of the trade name products with a given International Non-proprietary Name - INN, to be considered). The receipt of this list is confirmed by the EDQM in writing.

### Step 3: Preparatory phase

#### Gathering of the Documentation and Information Package necessary to carry out the Yearly Programme

In **March** (year n-1), after confirmation of the annual list of products, the EMA contacts the MAHs of the listed Generic CAP products asking them to provide the EDQM within 5 weeks with the relevant information from the original application, as amended during the assessment of the application and by relevant variations including health and safety information about the active substance, the finished product and special precautions to be taken during analysis and information on potential classification as a controlled substance.

In addition, a written statement that "the methods and specifications provided directly to the EDQM for the control of the active ingredient and the finished product are those included and approved in the original application as amended by any subsequent relevant variations"

must be included. The MAH is asked to automatically supply any Part II/Module 3-related documentation that may have been amended by a variation and approved after the date of submission of the initial information package to the EDQM.

For detailed information, please refer to the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

To help plan the future sampling phase, the companies are also asked to forward directly to the EDQM the present and prospective market situation of the product up to the end of year n-1 (EEA Member States where the product is or will be marketed plus estimate of stocks available for low-volume products), together with additional information on special distribution patterns (other than the usual channels) of the product in the various member states. Obtaining updates regarding the market situation for a product included in an ongoing programme lies within the responsibility of the EDQM, which will request the necessary information directly from the MAH.

Each Generic CAP is identified by an internal EDQM code (CAP 20xx/Y) and its EU number. The EDQM coding system makes it possible to distinguish between different trade name products, thus ensuring easy traceability of the test samples.

Documentation is stored at the EDQM, DBO, in an archive system with restricted access.

For each Generics CAP programme, all registered CAP products ("registered sources") for a given INN, plus the reference medicinal product are included in the list of products. For reasons of efficiency, products will be grouped by MAH and not dealt with individually.

#### - **Preparation of the "INN test Protocol"**

As the necessary documentation and information are received, the EDQM compiles all the quality documents and transfers them to the Scientific Advisor (**second quarter of the year n-1**). The Scientific Advisor is asked to fill in an acknowledgment of receipt of confidential documents.

On the basis of the documentation available, the Scientific Advisor will prepare an "INN Test protocol" including the parameters and methods selected for the testing of the active substance – when applicable, and the finished products. The Scientific Advisor shall give a rationale/justification regarding the choice of the test parameters for the active substance and/or for the finished products.

The methods to be used for the testing of generics products and related APIs are proposed by the testing OMCL according to past experience with the molecule and can be Ph. Eur., MAH and/or in-house methods specifically developed. It is the OMCL responsibility to ensure that the testing methods are accurate for the purpose of the testing campaign of the INN generic products.

By the end of **September of the year n-1** at latest, the Scientific Advisor should provide the pharmaceutical forms and strengths selected for the testing as well as an estimation of the amount of pharmaceutical dosage units required for the testing.

The final "INN test Protocol" should be ready by **December of the year n-1**. The Scientific Advisor should also define and identify the Common Test Sample and the relevant non-commercially available reference materials.

- **Sampling preparation**

On the basis of the market availabilities received from the MAHs, a Sampling questionnaire is set up.

The Sampling Questionnaire consists of a table indicating the Member States where the products are marketed, a proposal for sampling country(ies) and the estimated number of units to be sampled. General information regarding the products (such as EU numbers and special storage conditions) is also provided in the questionnaire. In **October of the year n-1** at latest, the EDQM distributes this Questionnaire to the nominated contact persons of each National Authority, and requests confirmation within 1 month regarding the availability on their respective market of the products tentatively allocated to each of them. A first estimation of the sample size may be given for information. In case of problems of availability of a given product in one country, sampling will be allocated to another Member State.

Samples are to be collected along the distribution chain by the competent national services of, as a general rule, three EEA Member States<sup>1</sup>: the choice of the countries is made by the EDQM taking climatic conditions of the different Member States into account and with the aim of sharing the sampling workload equally among the countries. Sales volumes are also taken into consideration. As far as possible, samples should be taken from all areas of the distribution chain (wholesaler, pharmacy, hospital or veterinarian as applicable).

In general, 3 market samples are withdrawn from the EEA market per group of generics. Within each sampling country, samples should originate from a single batch to ensure comparability and adequacy of the results of the different tests performed (1 batch per sampling country).

As some groups of generics contain more than two trade name products (e.g. co-marketed products), the following criteria for targeting and attributing sampling are applied:

<b>Number of trade name products</b>	<b>Sampling rule</b>
<b>1</b>	three samples of the concerned brand product are drawn.
<b>2</b>	two samples per each trade name are drawn.
<b>≥ 3</b>	one sample per each trade name is drawn.

The sample size is a case-by-case decision depending on the number of pharmaceutical dosage units needed per test procedure, the number of presentations of the dosage forms to be tested, the availability of the product, the size of the market, the clinical use of the

<sup>1</sup> Because of the reduced size of its market, Liechtenstein is not included among the sampling locations.

product etc. The general rules may be adapted on a case-by-case basis to take into account the specific market situation (e.g. product available in a single member state only).

After receipt of the responses and by **November of year n-1** at the latest, the EDQM establishes the final Sampling Plan. The 5-years Generics programme is tabled every year at the CAP Annual Meeting where the Generic Sampling Plan for the following year is presented for adoption.

The actual sampling phase should be initiated by the **end of year n-1** in order to start the active testing phase in the **1<sup>st</sup> semester of year n**.

## Year n

### Step 4: **The Sampling and Testing Programme**

The two procedures for sampling and testing are run in parallel during the first semester of the year.

#### Step 4A1: **The Vouchers**

Handling of vouchers is similar to the General CAP programme.

For each trade name product, Vouchers for rapid sample replacement are sent to the legal contact person of the MAH or to its agent for signature with a deadline of 2 to 4 weeks for returning them to the EDQM. The EDQM indicates in Section 1 of the Voucher the maximum number of pharmaceutical dosage units required for the testing programme based on the parameters selected by the Scientific Advisor. Section 1 of the Voucher is signed by the MAH or its agent and the originals are returned to the EDQM. By signing the Vouchers the MAH commits to rapidly replacing the indicated number of pharmaceutical units or fewer (whichever was sampled in practice). The EDQM issues the Vouchers for all products and sends them to the relevant MAHs in late **November**/beginning **December of year n-1**. Once the duly filled-in documents have been returned, they are kept at the EDQM until initiation of the sampling operations.

Sequentially during the programme, a Sampling Information Notice containing essential information, such as the anticipated sample size, is sent to the Sampling Contact Person who is normally part of the national Inspectorate Services, but for some National Competent Authorities belongs to other services. This is done in order to identify as early as possible any issue that might be linked to the availability of the required amount of pharmaceutical units and give National Authorities enough time to organise sample collection. A calculation of the required number of pharmaceutical dosage units is attached to the letter in order to make the request more transparent.

**Step 4A2: Sampling****Market samples**

Once the signed Vouchers are returned and after the completion of Section 2 of these documents by the EDQM, indicating the EDQM project number and the exact amount of pharmaceutical units needed, Official Sampling Requests, containing a Cover Letter, one Voucher, a Sampling Form, a Shipment Cost Form, where applicable, and conditions of delivery are sent by the EDQM to the nominated contact persons in the sampling Member States. Vouchers are designed to enable replacement of the collected units by the MAHs. A calculation of the required amount of pharmaceutical dosage units (Summary of Test Parameters) is attached to the letter in order to make the request transparent. These documents are sent in **January of year n** to allow management of the sampling phase until the end of the first quarter of the year of the on-going programme (year n).

For detailed information regarding sampling of market samples, please refer to Step 6A2 of the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

**Drug substance**

A request for samples from the MAH is done on the basis of a list of the last 5 active substance batches used in the manufacture of recent finished product batches. This list will be provided by the MAH. The EDQM Secretariat and the Scientific Advisor will select one batch from the pool and request the adequate quantity of substance from the MAH.

Other sampling strategies for active substances might be envisaged, such as the sampling of the active substance at the relevant active substance or finished product manufacturing sites by EEA GMP inspectors. Another alternative approach could be to request material from active substance batches matching with the finished product batches drawn for testing. This requires a longer preparatory phase which would then need to be considered during the planning of the programme.

**Common test sample and reference materials**

In parallel to the shipment of the Official Sampling Request sent to the sampling contact persons, a Cover Letter and a Sampling Form are sent to the MAH(s) to request a Common Test Sample (CTS), in the case of the CAP generic programme, the originator, all necessary non-commercially available reagents and standards and all additional relevant documents (Certificates of Analysis, Material Safety Data Sheets etc). The EDQM states in this cover letter to the MAH that testing will be performed according to a Test Protocol developed for this specific purpose within the OMCL network.

**Step 4A3: Receipt of all Samples, Reference Materials and Reagents**

For detailed information, please refer to the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

**Step 4A4: Sample Preparation and Labelling**

The samples are labelled by DRS (Division of Reference Standards and Samples) /EDQM and prepared for dispatching to the testing OMCL following the established timetable. Storage conditions for the samples, reference materials and special reagents are clearly indicated on the label and in an attached leaflet which includes further important information on all sent materials such as batch numbers, expiry dates, etc.

**Step 4B1: Preparation of Individual CAP Testing template**

Individual CAP Testing templates defining the terms of collaboration between the testing OMCLs and the EDQM are issued by EDQM and sent to the relevant OMCL for each INN Generic programme. These contracts have to be signed by an authorised representative of each party. The Individual CAP Testing template defines the agreed practical conditions for testing and reporting (duration of the testing phase and funding) and cross refers to the INN Test protocol and Results Data Sheet (see step below). A signed original is kept at EDQM, DBO. At the same time persons responsible for testing are informed about the expected time schedule of the testing phase.

**Step 4B2: Elaboration of Results Data Sheets**

Once the final set of the test methods and the protocol for a product are settled, the EDQM designs the Results Data Sheets (RDS) specific to each INN Generic programme. They actually consist in a template for the OMCLs to report their testing results. The RDS indicate clearly how many independent tests/assays are to be carried out as well as the number of replicates within each independent test/assay. For each test to perform, the RDS contain tables to be filled in by the testing OMCLs with their system suitability and analytical results.

**Step 5: Dispatching Samples / Results Data Sheets**

For detailed information, please refer to the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

**Step 6: Testing Phase**

Testing is the responsibility of the participating OMCL. A Cooperation Agreement (framework contract) is signed between the EDQM and the testing OMCL(s). This contract establishes the general terms governing the testing and includes the amount of the financial contribution provided to the OMCL(s) to support the costs incurred in the testing. Testing cannot be further subcontracted, if not agreed in advance in writing by the two contracting partners, i.e. the EDQM and the OMCL/Competent Authority. In exceptional cases when two OMCLs are involved and in the event of problems during the testing phase the OMCLs will first contact each other for mutual assistance (cc. EDQM) and contact the EDQM if assistance from the MAH is necessary. Any information concerning observations or changes in the test procedures which may affect all participants will be communicated via the EDQM.

**Step 7: Results Data Sheets Completed**

The participants complete and send back the Results Data Sheets together with type chromatograms and any comments in due time. Each trade name product should comply with their respective approved specifications.

The report is due 40 working days after receipt of the test samples by the latest, the date of receipt being documented on the acknowledgement of receipt for the samples. An extension of the testing period may be granted on a case-by-case basis when numerous tests are requested for a given product and/or when testing of the active substance is included in the testing protocol.

Where clarifications are required, the EDQM directly contacts the person responsible for testing at the OMCL.

The analyses performed using the Common INN Test Protocol should be seen as quality screening. In the event of out-of-specification (OOS) situations, further action is needed in accordance with the procedure in place for handling OOS results and in particular retesting using the MAH-approved method.

**Step 8: Testing Reports**

For each Generic INN Group tested, within one month after the receipt of all the results the EDQM will issue:

1. An INN Group Testing Report summarising the tests and results.
2. A confirmation that testing was completed and there is no reason to question the compliance of the samples/batches shall be provided for products where no out-of-specification results were obtained.
3. Individual Testing Reports for products with out of specifications results or in exceptional cases provided there is a justified request from the EMA.

Testing Reports are issued on an ongoing basis and are distributed to the relevant samplers, EMA and all OMCLs.

The EMA distributes confirmation of testing or Individual Testing Reports, as applicable, to MAHs for information or comments.

The EMA will then distribute all INN Group Testing Reports and Individual Testing Reports to the (Co-)Rapporteurs for information, comments and follow actions, where applicable.

**Step 9: Follow-up actions**

As per the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version, enforcement or any other follow-up measures are coordinated by the EMA in connection with the Rapporteur/Co-Rapporteur and where appropriate the testing OMCL(s). The EMA has responsibility for the actions initiated as an outcome of the testing. A report on the outcome of the annual programme including follow-up measures initiated further to the testing is published by the EMA.

**Step 10: Annual status report at Annual Meeting**

The EDQM reports about the status of the programmes during each yearly CAP Annual Meeting (focus on Year n+1).

**Last year of the co-operation agreement****Step 11: Final report to EMA/OMCLs**

An overall CAP testing report covering the 5 year sampling and testing programmes performed on Centrally Authorised Generic Products is set up by EDQM and is distributed to the EMA and the OMCLs. The Rapporteur and Co-Rapporteur receive the document for information on the overall outcome of the testing exercise.

**General Remarks****• Discussion and Optimisation**

The improvement of the general scheme is the responsibility of both the EMA and the EDQM based on experience gained during current application of the present procedure. To this end, the CAP Advisory Group is consulted.

## ***History Sheet of Technical Post-Approval Changes***

### **Title of document: PA/PH/CAP (12) 32 R14 - General Procedure for Sampling and Testing of Generic Centrally Authorised Products**

**4<sup>th</sup> Edition:** (2018):

- Restructuring of the whole procedure according to the new strategy adopted for the sampling and testing of Generics products.

♥ **Date of becoming effective** (*month and year*): **December 2018**

### **Title of document: PA/PH/CAP (12) 32 11R - General Procedure for Sampling and Testing of Generic Centrally Authorised Products**

**3<sup>rd</sup> Edition:** (2014):

- Overall editorial revision of the document.
- Introduction: Inclusion of details about the selection of products included in the programme.
- Step 1: Inclusion of details on programme establishment.
- Step 3A1: Inclusion of details about documents to be provided by the MAHs.
- Step 3A2: Inclusion of details about the number of OMCLs participating in the programme.
- Step 3B1: Inclusion of details about the nomination of the Scientific Advisor in the event of there being no candidates.
- Step 3B2: Requirements for the used reference materials.

♥ **Date of becoming effective** (*month and year*): **December 2014**

### **Title of document: PA/PH/CAP (12) 32 9R - General Procedure for Sampling and Testing of Generic Centrally Authorised Products**

**2<sup>nd</sup> Edition:** (2013):

- Introduction: Inclusion of details related to the EDQM/OMCLs testing contract: eventual need of national regulatory action.
- Step 3A2: Inclusion of details on group establishment.
- Step 3B1: Inclusion of details about the nomination of the Scientific Advisor.
- Step 3B2: Inclusion of details about the duties of the Scientific Advisor: selection and procurement of the materials necessary for the feasibility check; assistance of the EDQM and checking of relevant quality parameters of non-commercially available reference materials prior testing.
- Step 5C1: Amendment of the timeline to send out the Testing Questionnaire.
- Step 9: Information that a financial contribution is provided to the testing OMCL(s) and inclusion of the Cooperation agreement.

♥ **Date of becoming effective** (*month and year*): **December 2013**

### **Title of document: PA/PH/CAP (12) 32 6R - General Procedure for Sampling and Testing of Generic Centrally Authorised Products**

**1<sup>st</sup> Edition:** (2012): new programme.

♥ **Date of becoming effective** (*month and year*): **November 2012**