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Sampling and Testing of Centrally Authorised Products – Procedure for the Biosimilars Programme

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SAMPLING AND TESTING OF CENTRALLY AUTHORISED PRODUCTS

PROCEDURE FOR THE BIOSIMILARS PROGRAMME

Introduction

A biosimilar is a biological medicine highly similar to another biological medicine already approved in the EU (called 'reference medicine') in terms of structure, biological activity and efficacy, safety and immunogenicity profile.

A biosimilar is not regarded as a generic of a biological medicine. This is mostly because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication of the molecular micro-heterogeneity.

Biosimilar medicinal products authorised through the Centralised procedure can be included 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.

Biosimilar medicinal products authorised through the Centralised procedure can also be included in a specific CAP Biosimilars programme, in which, one project is launched every year focusing on one defined product group of Biosimilars using in-house validated methods or common test methods established during a feasibility study. The launch of one product per year depends on the capacity of the Network, gaps might be necessary when projects are not finished at their due dates in order to avoid too many Biosimilar projects running in parallel. Each project will run over a period of 3 years starting with a feasibility study in year N followed by a testing phase of market samples based on the outcome of the feasibility phase. A feasibility study might not be necessary for all parameters.

This paper describes the operational procedure for the CAP Biosimilars programme. It contains a step-by-step description starting from the planning of the forthcoming test programme (year n-1) to the overall CAP testing report and the individual testing reports on the products included in the programme. It should be read in conjunction with the General procedure PA/PH/CAP (05) 49 in its current version.

In the eventuality of Out-Of-Specifications results, appropriate verifications will take place according to the established common test procedures (e.g. [Procedure for Handling Out of Specification Results for CAP](#), PA/PH/CAP (16) 103 in its current version) and using the authorised methods for the sample in question, if different from the common test method; 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.

Year n-1: Planning of the Biosimilars Programme

Step 1: Proposed Programme

The Centrally Authorised Biosimilar Products associated to a list of Biosimilar Products Groups to be tested ideally one per year is selected by the EMA Secretariat, in collaboration with the EMA Scientific Committees and agreed with the EDQM and the CAP Advisory Group. The list of molecules is rediscussed and reprioritised at the Advisory Group Meetings.

For each Biosimilar Products Group the activities can include activities related to development of common tests methods and product sampling and testing which can take place over the course of several years. For the purpose of programme planning and budgeting, the method development, sampling and testing activities for each Biosimilar Products Group will be organised as “yearly” programme, as set out in the following steps.

The EDQM Secretariat helps to identify volunteers (Scientific Advisor) for each Biosimilar Products Group (e.g. survey sent to the OMCL Network), so that the workload can be equally and ideally shared between as many OMCLs as possible.

A draft timetable indicating the year of testing and the OMCL(s) selected per each Biosimilar Products Group is prepared by the EDQM and provided to the EMA Secretariat. This timetable is maintained, and updates are presented during the CAP annual meeting.

Step 2: Final Adoption of the Programme for Year n

The list of products associated to the proposed Biosimilar Products Groups to be tested is normally adopted during **Q1** (year n-1) meetings of the CHMP. The EMA Secretariat informs the EDQM Secretariat of the decision in a timely manner (including registered sources of a Biosimilars 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 to the EMA by the EDQM by return email.

Step 3: Preparatory phase

Step 3A1: Gathering of the Documentation and Information Package necessary to start a project within the Biosimilars Programme

Shortly after the adoption of the list of products, the EMA contacts the MAHs of the listed Biosimilars CAP products, asking them to provide the EDQM within 5 weeks (**Q1/Q2, year n-1**) with the relevant information from the original applications, as amended during the assessment of the application and by relevant variations including health and safety information about the active substance, the finished products 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 planning the future sampling phase, the companies are also asked to forward directly to the EDQM the present and prospective market situation of the products (EEA Member States where the products are 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 products in the various member states. Obtaining updates regarding the market situation for products included in an ongoing programme lies within the responsibility of the EDQM, which will request the necessary information directly from the MAH.

Each Biosimilar CAP within a project 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, in an electronic archive system with restricted access.

Testing recommendations may be provided by the EMA if assessors raise concerns on specific issues (e.g. as a result of a quality defect or during the initial evaluation). The Scientific Advisor(s) and the EDQM will consider these recommendations, if provided, for the establishment of the test protocol. If needed, discussions can be organised between the rapporteurs, the EMA, the EDQM and the OMCLs to better understand the concern and request for a specific method.

Step 3A2: Establishment of the Biosimilar product list

Whenever a Biosimilars CAP project is established, all authorised CAP products for a given INN, plus the reference medicinal product are included in the list of products. As a rule, products are grouped and tested together, and not dealt with individually, for reasons of efficiency.

Step 3B1: Designation of the Scientific Advisor

Scientific Advisor(s) will be selected among the OMCLs that volunteered following a questionnaire sent to all OMCLs by the EDQM. More than one OMCL can be appointed as Scientific Advisor in a Biosimilar CAP Programme if test parameters are divided between several OMCLs. The feasibility, if applicable and the testing of the market samples will be performed in the Scientific Advisor's OMCL, and each test parameter will be tested by one OMCL, if possible. The following cumulative criteria should be considered to select the most suitable OMCL(s) and Scientific Advisor(s):

- More than one OMCL can be Scientific Advisor, the test parameters can be divided between more OMCLs to economise resources and/or per experience;
- Availability of the OMCL to participate in the project;

- Non-biological OMCLs can also apply for the programme for the testing of physico-chemical parameters;
- Participation in the development of a *Ph. Eur.* monograph and/or in BRP collaborative studies on the same molecule;
- Previous CAP testing of the product(s);
- Assessment of the respective CAP dossier(s) as (Co)Rapporteur;
- Assignment on a rotating basis, where possible, to aim at a fair distribution between OMCLs considering their involvements in Regular and Biosimilar programmes.

The Scientific Advisor(s) should be confirmed at the latest at the CAP annual meeting in November of year n-1. The EDQM prepares the corresponding Testing Agreement.

Step 3B2: Parameters to be tested, Compilation of the MAHs' Test Methods and establishment of a draft INN Test Protocol
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Upon reception of the necessary documentation and information, the EDQM compiles all the quality documents from the registration files, SOPs from the MAHs; and transfers them to the Scientific Advisor(s) (**at the latest Q4 of year n -1**). The Scientific Advisor(s) is/are asked to fill in an acknowledgment of receipt of confidential documents.

If recommendations of the Rapporteurs/Co-Rapporteurs for the different trade name products are provided by EMA, they will be forwarded by EDQM to the Scientific Advisor(s) for consideration.

Based on the documentation available and taking into account the recommendations from the Rapporteurs/Co-Rapporteurs, if any, the Scientific Advisor(s) select(s) the parameters to be tested on the active substance, if needed, and on the finished products. The strength(s) and pharmaceutical form(s) of the finished products to be tested are also selected.

The Scientific Advisor(s) prepare(s) a draft INN Test Protocol (i.e. the group of methods – *Ph. Eur.*, MAH and/or specifically developed in-house methods – used for the testing of all the Biosimilars and active ingredients, if needed) together with the common specifications based on the documents received. The following aspects will have to be considered: variety of the MA dossiers concerned including specifications, types of APIs, possible variations in the dosage form etc. Pharmacopeial methods – when available - will also be considered in the establishment of the common procedures. As far as possible, the establishment of common procedures that are suitable for all finished products as well as all active ingredients should be sought.

The **draft INN Test Protocol** should be available by Q1 **of year n**. If the Scientific Advisor(s) has/have deviated from the testing recommendations of the Rapporteurs/Co-Rapporteurs, a rationale/justification should be given regarding the choice of the test parameters. The EDQM will send the document to the EMA that will inform the Rapporteurs/Co-Rapporteurs. In case of a strong testing recommendation based on potential concerns, the EDQM will inform EMA as soon as possible when the given parameter is not considered in the Test Protocol. Discussions might be organised between the rapporteurs, the EMA, the EDQM and the OMCLs.

Year n: Feasibility study

Step 4: Feasibility study

The need to perform feasibility checks of the preselected methods is the decision of the Scientific Advisor(s) before the finalisation of the INN Test Protocol. It is dependent on the parameters to be tested, and on the experience of the OMCL with the given products:

- The selected methods are based on compendial methods, in-house methods or lead SOPs from manufacturers.
- If feasibility testing performed, it should be performed according to the principles of the OMCL guideline on Validation of Analytical methods, PA/PH/OMCL (13) 82 in its current version.
- Not all Biosimilars (i.e. Reference medicinal product and Biosimilars from each identified group) included in the project need to be tested (e.g. not all strengths or co-marketed products need to be considered). The Scientific Advisor will define the samples to be tested and material needed. These samples will be obtained from the market or the MAHs with the assistance of the EDQM.
- Normally more testing OMCLs can be involved in the feasibility study for all or part of the parameters. The testing of the market samples for the test parameters will be performed by the Scientific Advisors involved in the feasibility study, in some cases one or more parameters can be tested in a second OMCL. The fee paid for the feasibility study is shared depending on the number of Scientific Advisors and on the number of parameters tested.

The Scientific Advisor(s) should also define and identify the Common Test Sample (CTS) and any necessary relevant non-commercially available reference materials. The same batch of reference standard should be used in the feasibility study and in the testing phase, whenever possible.

The feasibility study should be finalised by **Q1 of year n+1** at the latest. A report including a description of the experimental work performed (i.e. details of the method development work and of the method verification) and a conclusion is prepared by the Scientific Advisor and provided to the EDQM. Upon receipt, the EDQM informs the EMA of the results of the feasibility study, so that the corresponding Biosimilars project can be included in the programme of year n+2.

Year n+1: Preparation of the Sampling plan and Testing protocol

Step 5: Preparation of the Test Protocols & Preparation of the Sampling Plan

Step 5A: Adoption of the programme for n+2

Any newly registered Biosimilar Products from the same Biosimilar Products Group which were not already adopted by the CHMP in year n-1, might be adopted during the **February** (year n+1) meetings of the CHMP depending on the status of the project.

Step 5B1: Finalisation of the INN Test Protocol

The final INN Test Protocol must be ready by Q2-Q3 of year n+1 after endorsement/feedback for the Common Test Procedures by the Rapporteur/Co-Rapporteur or the relevant EMA body. Where possible, a CombiStats template is provided to support the statistical evaluation of the data that will be obtained during the testing phase.

Step 5B2: Dispatching Protocol, Final Confirmation of OMCL Participation

The final INN Test Protocol and Result Data Sheet are sent to the OMCLs to provide all details related to the testing. This is done approximately at the same time as the sampling phase starts or the latest at the time of the dispatch of the samples from the EDQM to the testing OMCL(s).

Step 5B3: Preparation of Product Testing Agreements

Product Testing Agreements defining the terms of collaboration between the testing OMCLs and the EDQM are issued by the EDQM and sent to the relevant OMCLs once confirmation of participation has been received by the EDQM.

For details, see the general procedure PA/PH/CAP (05) 49 in its current version.

Step 5C1: Preparation of the Sampling Plan: Pre-selection of Sampling Countries

A preliminary Sampling Plan is set up on the basis of the marketing situations received from the MAHs. Samples are to be collected along the distribution chain by the competent national services of, as a general rule, three EEA Member States¹: 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 among the countries. Sales volumes are also taken into consideration.

In general, 3 market samples are withdrawn from the EEA market per group of identical Biosimilars. 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). The following criteria for targeting and attributing sampling are applied:

¹ Because of the reduced size of its market Liechtenstein is not included among the sampling locations

Number of trade name products	Sampling rule
1	Three samples of the concerned brand product are drawn.
2	The products are sampled in 2+2 fashion (2 samples / tradename).
3	One sample per each trade name is drawn.
≥ 3	Maximum three market samples are selected; preference is given to the trade name products that are commercially available in a larger number of member states (MS).

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) and the number of products included in the project. The number of samples to be tested should also be economised depending on the workload of the sampling network.

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 product etc.

Step 5C2: **The Sampling Questionnaire**

A Sampling Questionnaire for the Biosimilar project is established following the same principle as laid down in document General procedure for sampling and testing of CAPs, PA/PH/CAP (05) 49 in its current version.

Step 5C3: **The Final Sampling Plan**

After receipt of the responses and by **November of year n+1** at the latest, the EDQM establishes the final Sampling Plan.

The actual sampling phase should be initiated by the **end of year n+1** to start the active testing phase in the **1st semester of year n+2**.

Step 5C4: **The e-vouchers**

The EDQM issues the e-vouchers for all Biosimilar products following the same principle as laid down in document General procedure for sampling and testing of CAPs, PA/PH/CAP (05) 49 in its current version and sends them to the relevant MAHs in **November or beginning of December of year n+1 at the latest**. Once the duly filled-in documents have been returned, they are kept at the EDQM until initiation of the sampling operations.

Step 5C5: Sampling Information Notice
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A Sampling Information Notice containing essential information, such as the anticipated sample size, can be sent in **Q4 of year n+1** 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 to identify as early as possible any issue that might be linked to the availability of the required number of pharmaceutical units and give National Authorities enough time to organise sample collection.

Step 5C6: Request of the CTS, drug substance and reference materials

In parallel to sending the Sampling Information Notice to the sampling contact persons and based on the detailed information provided by the Scientific Advisor, the EDQM prepares (a) request(s) (cover letter by email and sampling form) to the MAH(s) concerned to require the CTS and other non-commercially available standard and material. The EDQM states in this cover letter to the MAH(s) that testing will be performed according to an INN Test Protocol developed for this specific purpose within the OMCL Network. Direct shipments from the MAHs to the testing OMCLs are organised for all material in connection with CAPs requiring the use of cells.

Drug substance

A request for samples from the MAH is done based on 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 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.

Step 6: Presentation of the Biosimilars Programme at the Annual Meeting
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A status report on the Biosimilars projects is given at the CAP Annual Meeting in November Year n+1.

Year n+2

Step 7: The Sampling and Testing Programme

Sampling and testing are run in parallel during the first semester of the year.

Step 7A1: Sampling of the market samples

Once the signed e-vouchers are received with the completion of Section 2 by the EDQM, indicating the EDQM project number and the exact amount of pharmaceutical units needed,

Official Sampling Requests, containing a Cover Letter, links to the ACT Platform containing the e-voucher, the Sampling Form, the Shipment Cost Form, where applicable, and conditions of delivery are sent via email to the nominated contact persons in the sampling Member States. E-vouchers are designed to enable replacement of the collected units by the MAHs. This step is performed ideally not later than **early Q1 of year n+2** to allow management of the sampling phase until the end of the first quarter of the year of the on-going programme (year n+2).

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

Step 7A2: 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 7A3: Sample Preparation and Labelling

The samples are labelled by the DRSL_ITEMS/EDQM and prepared for dispatching to the testing OMCLs following the established general testing repartition. The name of the product with the product strength together with the product identification number (CTS, Sample A, Sample B... etc), or in the case of reference materials/reagent the name of the material together with the project name are indicated on the labels.

Step 7B: Elaboration of Results Data Sheets

The EDQM designs the Results Data Sheets (RDS) for the Biosimilars programme based on the final INN Test Protocol. They consist of 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 8: 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 9: Testing Phase

Testing is the responsibility of the participating OMCLs. For each product to be tested, a Cooperation Agreement 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. The 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 the event of problems during

the testing phase the OMCL(s) will first contact EDQM and each other for assistance (this applies only if more than one OMCL is involved to perform the test parameter) and if necessary, EDQM will contact the MAH to request assistance. Any information concerning observations or changes in the test procedures which may affect all participants will be communicated via the EDQM.

When feasibility testing is performed, OMCLs are not requested to fully revalidate the methods stated in the INN Test Protocol, since the validation has already been carried out (e.g. compendial method, MAH method, OMCL in-house method) and their feasibility for the testing of the different Biosimilars groups checked by the Scientific Advisor. They are nevertheless requested to demonstrate successful method implementation (compliance with the system suitability criteria and/or assay acceptance criteria included in the test procedures with supporting documentation, i.e.: chromatograms) using the dedicated tables included in the Results Data Sheets.

Step 10: Results Data Sheets Completed

The participants complete and send back the Results Data Sheet together with type chromatograms and any comments in due time. Additional documentation can be requested by the EDQM. Each trade name product should comply with their respective approved specifications.

The report from the OMCLs is due 100 working days after receipt of the test samples, 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 Test Procedures in the 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 "Procedure for Handling out of Specification Results for CAP", PA/PH/CAP (16) 103 in its current version and, in particular, retesting using the MAH-approved method.

Step 11: CAP Testing Reports

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

1. A Biosimilars 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 all products included in the programme, summarising the compliance or non-compliance of the product, and providing analytical data for parameters with out-of-specification results.

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

The EMA distributes Individual Testing Reports to MAHs for information or comments.

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

Step 12: 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 13: Annual status report at Annual Meeting
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The EDQM reports about the status of the Biosimilars programme during the CAP Annual Meeting.

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.