OMCL Network of the Council of Europe

GENERAL DOCUMENT

PA/PH/CAP (12) 32 11R

General procedure for Sampling and Testing of Generic Centrally Authorised Products

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GENERAL PROCEDURE FOR SAMPLING AND TESTING OF GENERIC CENTRALLY AUTHORISED PRODUCTS

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, ethers, 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 an annual Centrally Authorised Products (CAP) test 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. This procedure is based on Article 57 c) and 57 r) of the Regulation (EC) N° 726/2004 of the European Parliament and of the Council regulating Centrally Authorised Products which give the EMA (the Agency) the responsibility:

- to coordinate the supervision, under practical conditions of use, of medicinal products which have been authorised within the Community.

- to coordinate the supervision of the quality of medicinal products placed on the market by requesting testing of compliance with their authorised specifications by an Official Medicines Control Laboratory or by a laboratory a Member State has designated for that purpose.

In addition, Article 55 of this regulation stipulates that the Agency shall be responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, **supervision** and pharmacovigilance of medicinal products.

For this purpose, the EMA has implemented post-authorisation sampling and testing programmes aimed at supervising the quality of the Centrally Authorised Products available

on the European market since 1999. The programmes are carried out on an annual basis in collaboration with the EDQM, which runs them on behalf of the EMA in collaboration with the EEA OMCL Network (Official Medicines Control Laboratories) and the EEA National Inspectorate Services (or other services responsible for sampling within the National Competent Authorities). Products included in the programme are selected through a risk-based approach.

Generic medicinal products authorised through the Centralised procedure can also be included in a specific CAP Generics programme. The EMA will decide when to initiate this procedure, which would normally be an integral part of an annual sampling and testing programme but could also be proposed on an ad hoc basis by the CHMP or the CVMP.

This paper describes the operational procedure for post-authorisation sampling and testing of Generics CAPs, when they are included in a specific 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). A flowchart is attached as **Appendix A**.

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 (excluding the appendices) are comments related to the steps described.

Year n-1: Planning of the Forthcoming Programme

Step 1: **Proposed Programme and Choice**

In **January** (year n-1) the EMA Secretariat prepares a proposal for the programme for the following year. The list of products to be tested can include CAP generics which may be tested as such in the regular CAP programme or be the focus of a Generics CAP programme.

A Generics CAP programme might be proposed whenever one generic of a product crops up on the risk-based list and several centrally authorised generic products (of the same originator product) are available. In addition, generic products frequently cropping up on the risk-based list should be taken into consideration and attributed a higher rank for triggering a Generics programme.

In general, a Generics programme is triggered when at least 4 products (1 originator + 3 generics) are available. Duplicates and informed consent forms of a product should also be included in a Generics programme.

A maximum of 2 generic programmes may be run every year.

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

The final programme 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**

This stage includes the two procedures described below and runs in parallel between spring and the end of year n-1 and can be divided into the following sub-steps.

Step 3A1: **Gathering of the Documentation and Information Package necessary to carry out the Yearly Programme**

Shortly after the adoption of the list of products, the EMA contacts the MAHs of the listed Generic CAP products, asking them to provide the EDQM within 1 month (**March, year n-1**) with the relevant information from the original application, as amended during the assessment of the application and by relevant variations (mainly Part IC.1 – Quality Expert Report, IIA, IIC, IIE, IIF including method validation data or Common Technical Document (CTD) Module 2.3 "Quality Overal Summary" and Modules 3.2.S (3.2.S.4.1, 3.2.S.4.2, 3.S.4.3) & 3.2.P (3.2.P.1, 3.2.P.5.1, 3.2.P.5.2, 3.2.P.5.3, 3.2.P.8.1, 3.2.P.8.2, 3.2.8.3) 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.

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.

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 receipt of the documents is confirmed by the EDQM to the MAH (cc: EMA) after ensuring that the documentation is complete (see **Appendix II**). In the event of outstanding replies, the EMA sends a reminder to the MAH. The updating of 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.

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. Such documentation should additionally include all relevant complete and up-to-date detailed Standard Operating Procedures (SOPs) preferably in English for the tests (also considering associated procedures). In addition, validation reports of the methods are provided to the EDQM. The EDQM must contact the MAH if the level of detail is insufficient.

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.

The EMA also asks the relevant Rapporteurs/Co-Rapporteurs to provide the recommendations of the critical parameters to be tested for each product. At this stage the EMA will briefly describe to the Rapporteurs/Co-Rapporteurs the main steps of the procedure (eg the role of the Scientific Advisor in the identification of the testing parameters and the selection of common testing methods; the fact that any discrepant results will be verified using each product's licensed methods) and will seek the preliminary agreement of the Rapporteurs/Co-Rapporteurs.

Step 3A2: **Establishment of the groups of products**

Whenever a Generics CAP programme is established, 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 and not dealt with individually.

A product group is a group of generic products which share the same characteristics (eg same API salt, same polymorphic form etc) and same manufacturing origin (eg same API manufacturer(s), same bulk finished product manufacturer(s)) so that they can be considered as identical. A product group should not include more than 3 trade name products. The products that will be part of the group are selected on the grounds of the parameters established in Step 5B1.

Groups are established on the basis of on the Part II/Module 3-related documentation provided by the MAHs.

The number of OMCLs that will be involved during the testing phase depends on the number of groups established.

Step 3B1: **Designation of the Scientific Advisor**

A Common Test Procedure based on the MA files concerned is prepared by a designated Scientific Advisor from the Network. The MA files will be made available to the Scientific Advisor during the **second quarter of year n-1** in order for the testing phase to start during the **first half of year n**.

The OMCLs with previous experience of testing the same or a similar product will be contacted by the EDQM and asked if they would like to propose one of their experts as Scientific Advisor. In the event of there being no candidates or more than one candidate, a decision is taken following a step-wise internal procedure.

Step 3B2: **Parameters to be tested, Compilation of the MAHs' Test Methods and establishment of a Common Test Procedure**

As the necessary documentation and information is received, the EDQM compiles all the quality documents and transfers them to the Scientific Advisor (**second quarter of year n-1**).

In parallel, the recommendations of the Rapporteurs/Co-Rapporteurs for the different trade name products are sent by the EMA at the same time as the MAHs are requested to provide the EDQM with the relevant data and quality documentation (**March, year n-1**). Since these might not be the same for all the registered sources, the EDQM will provide the Scientific Advisor with an overview of the recommendations received together with the quality documents. On the basis of the documentation available and taking into account the recommendations from the Rapporteur/Co-Rapporteur, the Scientific Advisor will prepare a proposal for the parameters to be tested on the finished products and on the active substance.

The Common Test Procedure (ie the group of methods – Ph.Eur., MAH and/or specifically developed in-house methods – used for the testing of all the generics and APIs) is established on the basis of the defined list of parameters to be tested. It will have to consider the following aspects: variety of the MA dossiers concerned including specifications, types of APIs, possible variations in the dosage form etc. Pharmacopoeial methods – when available - will also be considered in the establishment of the Common Test Procedure. As far as possible, the establishment of common procedures that are suitable for all finished products as well as for the different API salts should be sought.

The preliminary laboratory work on the establishment of the Common Test Procedure must include obligatorily a mandatory feasibility check of the pre-selected methods in the laboratory. It should be performed according to the principles of the OMCL guideline on Validation of Analytical methods in its current version and cover as wide a range of products as possible. It is the Scientific Advisor's responsibility to select and procure the samples to be used, with the assistance of the EDQM if needed. It is recommended that a back-up OMCL be available for this feasibility study.

A first version of the test procedure should be available by **September of year n-1** and the final test procedure by **December of year n-1**.
The Scientific Advisor should also define and identify the Common Test Sample 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.

Step 4: **Final Common Test Procedure**

The Common Test Procedure must be ready by **December of year n-1**. The final test methods are distributed by the EDQM to the EMA. The EMA will inform the Rapporteurs/Co-Rapporteurs.

Step 5: **Preparation of the Test Protocols, Preparation of the Sampling Plan and Identification of Testing OMCLs**

These three procedures run in parallel during the **2nd semester of year n-1** and can be divided into the following sub-steps.

Step 5A1: **Preparation of the Test Protocols**

Once the first version of the Common Test Procedure is available, the EDQM compiles the Test Protocols and sets up the Generics Testing Questionnaire (**September of year n-1**) by extracting the relevant information from the documentation received.

The Test Protocol encompasses the Common Test Procedure, information about the composition and the release and shelf-life specifications for the active substance and the finished trade name product(s). These protocols will be used by the EDQM as the first source of information for estimating the number of pharmaceutical units required and the amount of active substance.

Step 5A2: **Final Protocols**

The final test protocol must be ready by **December of year n-1** after endorsement/feedback for the Common Test Procedure by the Rapporteur/Co-Rapporteur or the relevant EMA body.

Step 5B1: **Preparation of the Sampling Plan: Pre-selection of Sampling Countries**

For each product, the EDQM makes an initial estimate of the number of pharmaceutical dosage units required for testing. This procedure is run at the same time as the preparation of the Test Protocol. If necessary, the estimate of the required sample amount should be revised after endorsement of the Common Test Procedure by the Rapporteurs/Co-Rapporteurs or the relevant EMA body.

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 States[1]: 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.

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

- No. trade name products = 1: three samples of the brand product concerned withdrawn.
- No. trade name products = 2: one sample for each trade name. The third sample will be taken from the product which is commercially available in the largest number of member states.
- No. trade name products = 3: one sample per each trade name is taken.
- No. trade name products ≥ 3: preference is given to the trade name products that are commercially available in a larger number of member states (MS). Three trade name products of the obtained list of products are withdrawn.

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

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.

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

Step 5B2: **The Sampling Questionnaire**

The Sampling Questionnaire consists of a table indicating the Member States where the products are marketed, a proposal for the sampling country(ies) and the estimated number of units to be sampled. General information regarding the products, EU numbers and special storage conditions is also provided in the questionnaire. In **September of year n-1**, the EDQM distributes this Questionnaire to the nominated contact persons of each National Authority, asking them to confirm within 1 month the availability on their respective market of the products tentatively allocated to each of them. This Sampling Questionnaire is also presented during the September (year n-1) meeting of the GMDP Inspectors Working Group for information. An initial estimate of the sample size may be given for information. In case of availability issues for a given product in one country, its sampling will be allocated to another Member State.

Step 5B3: **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** in order to start the active testing phase in the **1st semester of year n**.

Step 5C1: **The Testing Questionnaire**

The Testing Questionnaire consists of a table indicating the test parameters, analytical techniques and specific equipment (including particular reagents) required to test each product. General information regarding the products (EU numbers and particular health and safety information, classification as a controlled substance) is also provided in the questionnaire. It is obtained by compiling the information from the protocols established under step 5A. This document is sent to the OMCL Network as soon as the draft Common Test Procedure is available (during September of year n-1) in order to give the potential participants an overview of the analytical techniques and equipment required to test the generics. OMCLs are asked to volunteer (within 1 month) for testing taking into account the criteria listed in step 6C2.

Step 5C2: **Preparation of the Testing Plan**

The number of OMCLs to be involved in the testing is directly related to the number of products included in the programme, and more specifically to the number of groups.

In the framework of the CAP sampling and testing programme, a specific testing scheme is systematically assigned to each chemical product, unless specific circumstances apply. The testing scheme applicable to each category of products type is defined in **Appendix III** as well as some technical terms.

All OMCLs from the different EEA Member States should be given the possibility to be involved and the choice should be made on a voluntary basis (keeping in mind individual

technical competencies). One exception has to be considered: the OMCL with which the Scientific Advisor works will automatically be included for testing, as the experience gathered during the establishment and verification of the methods of the Common Test Procedure can be of added value for all the OMCLs participating in the testing exercise.

Criteria for product allocation to candidate OMCLs are those defined in Step 4C2 of the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

The preparation of the list of test parameters and Common Test Procedure (Testing Questionnaire) starts simultaneously with the preparation of the Test Protocols (step 5A1).

Step 5C3: **The Proposed Testing Plan**

Taking into consideration the OMCL responses and the criteria given in step 5C2, the EDQM sets up the proposed list of participating OMCLs. The proposed Testing Plan is submitted to the CAP Advisory Group for review and support in case of difficulties. Further to the review by the CAP Advisory Group, this list is sent to all EEA OMCLs concerned at least one week before the CAP Annual Meeting (n-1), together with the annual work programme.

Step 6: **Presentation of the Generics Programme and Final Selection of Participants at the Annual Meeting**

The entire Generics programme is presented at the CAP Annual Meeting.

The proposed Testing Plan is presented for approval.

The programme including the list of all participating OMCLs is confirmed by the EDQM no later than two weeks after the CAP Annual Meeting (year n-1).

Year n

Step 7: **The Sampling and Testing Programme**

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

Step 7A1: **The Vouchers**

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 weeks for returning them to the EDQM, see **Appendices IV and V** for templates (Cover letter and Vouchers, respectively). 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 Rapporteur/Co-Rapporteur in their recommendations. 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 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 (see **Appendix VI**) 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 7A2: **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 one Voucher, a Cover Letter, a Sampling Form and a Shipment Cost Form, where applicable (see **Appendices VII, VIII and IX**, respectively), 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

The most practicable approach is to request samples from the MAH 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 company. 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 person, a Cover Letter and a Sampling Form are sent to the MAHs (see **Appendices XI and XII**, respectively) with a view to collecting a Common Test Sample (CTS), in the case of the originator, and 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 Common Test Procedure developed for this specific purpose within the OMCL network.

Step 7A3: **Receipt of all Samples, Reference Materials and Reagents**

For detailed information, please refer to Step 6A3 of the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

Step 7A4: **Sample Preparation and Labelling**

For detailed information, please refer to Step 6A3 of the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

Step 7B1: **Dispatching Protocols: Final Confirmation of OMCL Participation**

For detailed information, please refer to Step 6B1 of the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

Step 7B2: **Preparation of Product Testing Agreements**

For detailed information, please refer to Step 6B2 of the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

Step 7B3: **Elaboration of Results Data Sheets**

For detailed information, please refer to Step 6B3 of the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

Step 8: **Dispatching Samples / Results Data Sheets**

For detailed information, please refer to Step 7 of 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, ie the EDQM and the OMCL/Competent Authority. 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.

OMCLs are not requested to revalidate the methods stated in the Common Test Procedure, since the validation has already been carried out (eg compendial method, MAH method, OMCL in-house method) and their feasibility for the testing of the different generic groups checked by the Scientific Advisor. They are nevertheless requested to demonstrate successful method transfer (compliance with the system suitability criteria and/or assay acceptance criteria included in the test procedures with supporting documentation, ie: 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 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 Test Procedure 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 11: **CAP Testing Reports**

The CAP Testing Report (CTR) is set up by the EDQM within one month after the receipt of all the results for a given trade mark product. CTRs are issued on an ongoing basis and are distributed to the relevant MAH, the EMA and all OMCLs. If issues have been raised during the testing phase, the CTR is distributed to the MAH for comments. The Rapporteur and Co-

Rapporteur receive the CTR and the comments are brought up with the MAH for further action, whenever deemed necessary.

An overall CAP testing report is prepared by the EDQM in parallel to the CTR 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.

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**

For detailed information, please refer to Step 12 of the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

Year n+1

Step 14: **Reports to EMA/OMCLs**

For detailed information, please refer to Step 13 of the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version.

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 11R - General Procedure for Sampling and Testing of Generic Centrally Authorised Products

3rd 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 entry into force: December 2014**

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♦ **Date of entry into force: December 2013**

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

1st Edition: (2012):

♦ **Date of entry into force: November 2012**

List of Appendices:

Appendices are provided for information purposes. Since they are general templates, these will have to be adapted to each individual product and may evolve from one year to another. However, the general structure of these templates is not likely to be significantly modified during the forthcoming yearly programmes.

Appendix A: **Flowchart: Sampling and Testing Programme for Generic Centrally Authorised Products**

Appendix B: **Cover Letter for Official Sampling Request to MAHs (originator)**

For the following appendices, please refer to the respective section in the "General procedure for Sampling and Testing of Centrally Authorised Products", PA/PH/CAP (05) 49 in its current version:

Appendix II: **Acknowledgement of Receipt of MAH Documentation**

Appendix III: **Testing Scheme per Product Type and Technical Terms**

Appendix IV: **Cover Letter to MAH for Vouchers Signature**

Appendix V: **Voucher**

Appendix VI: **Cover Letter for Sampling Information Notice**

Appendix VII: **Cover Letter for Official Sampling Request to the Sampling Contact Person**

Appendix VIII: **Sampling Form to Sampling Contact Person**

Appendix IX: **Shipment Cost Form**

Appendix X: **Conditions for Delivery of Samples to EDQM**

Appendix XI: **Cover Letter for Official Sampling Request to MAH**

Appendix XII: **Sampling Form to MAH**

Appendix XIII: **Acknowledgement of Receipt of Samples from Sampling Organisations**

Appendix XIV: **Acknowledgement of Receipt of Samples from the MAH**

Appendix XV: **Cover Letter for Shipment of SOPs to OMCLs**

Appendix XVI: **Acknowledgement of Receipt of SOPs for OMCLs**

Appendix XVII: **Cover Letter for Shipment of Samples to Testing OMCLs**

Appendix XIII: **Acknowledgement of Receipt of Samples and Materials by Testing OMCLs**

Appendix A: Flowchart: Sampling and Testing Programme for Centrally Authorised Products

				EMA		EDQM					
Related documents	Steps	Timetable	Flowchart	CHMP CVMP	Secr.	DBO	DRS	AdG	OMCL Network	Insp.	MAH
List of Potential Candidate Products	1	Year n-1 January	Proposed Programme and Choice of Product	R	E			GA			
List of Prod., List of Var., Letters to MAHs and (Co-)Rapp.	2	February	Final adoption of the Programme for Year n	D	E	I/E					I
Auth. Dossier, AOR, Test methods, List of Mark. Situation, Recomm from (Co-)Rapp	3	March	Preparatory phase								
	3A1 3B1	to	A: Gathering of documentation and testing recom. / B: Designation of the ScAdv.	I(A)	E(A)	R(A) R(B)		GA(A) GA(B)	I/FB(B)		E(A)
	3A2 3B2	June	Parameters to be tested & Compilation of MAH methods; Establishment of the groups; Preparation of CTP (1st version)		E(B)	R(A) R(B)			E(B)		
Auth. Dossier, AOR, Test methods, List of Mark. Situation, Recomm from (Co-)Rapp.	5*	July	Preparation of the test protocols and of the sampling and testing plans			GA/R					
	5A1 5B1 5C1	September	A: Preparation of Protocols / B: Preparation of Sampling Plan / C: Testing questionnaire	(FB)**	(I)**	R(A) R(B) R(C)		GA(C)		E(B)	
	5B2 5C2		Sampling questionnaire; EU/EEA OMCL Network		I(B) I(C)	R(B) R(C)		GA(B) GA(C)			
	5B3 5C3		National Insp. Services; Final sampling plan; Proposed list of Testing OMCLs = Testing Plan			R(B) R(C)			I/FB(C)	I/FB (B)	
Annual Programme	6	November	Presentation of Progr. and final selection of Testing OMCLs at the Annual OMCL CAP meeting			R(B) R(C)			I(C)		
			Confirmation of Programme			R(B) R(C)		GA(C)	FB(C)		
Time-table for sampling and testing		December	Annual Programme: final sampling and testing plans & Timetable		I(B) I(C)	R(A) R(B) R(C)	I(B) I(C)	I(B) I(C)	I(C)	I(B)	
CTP	4	December	Final CTP		I	R			GA		
	5A2		Final Protocols		I	R					

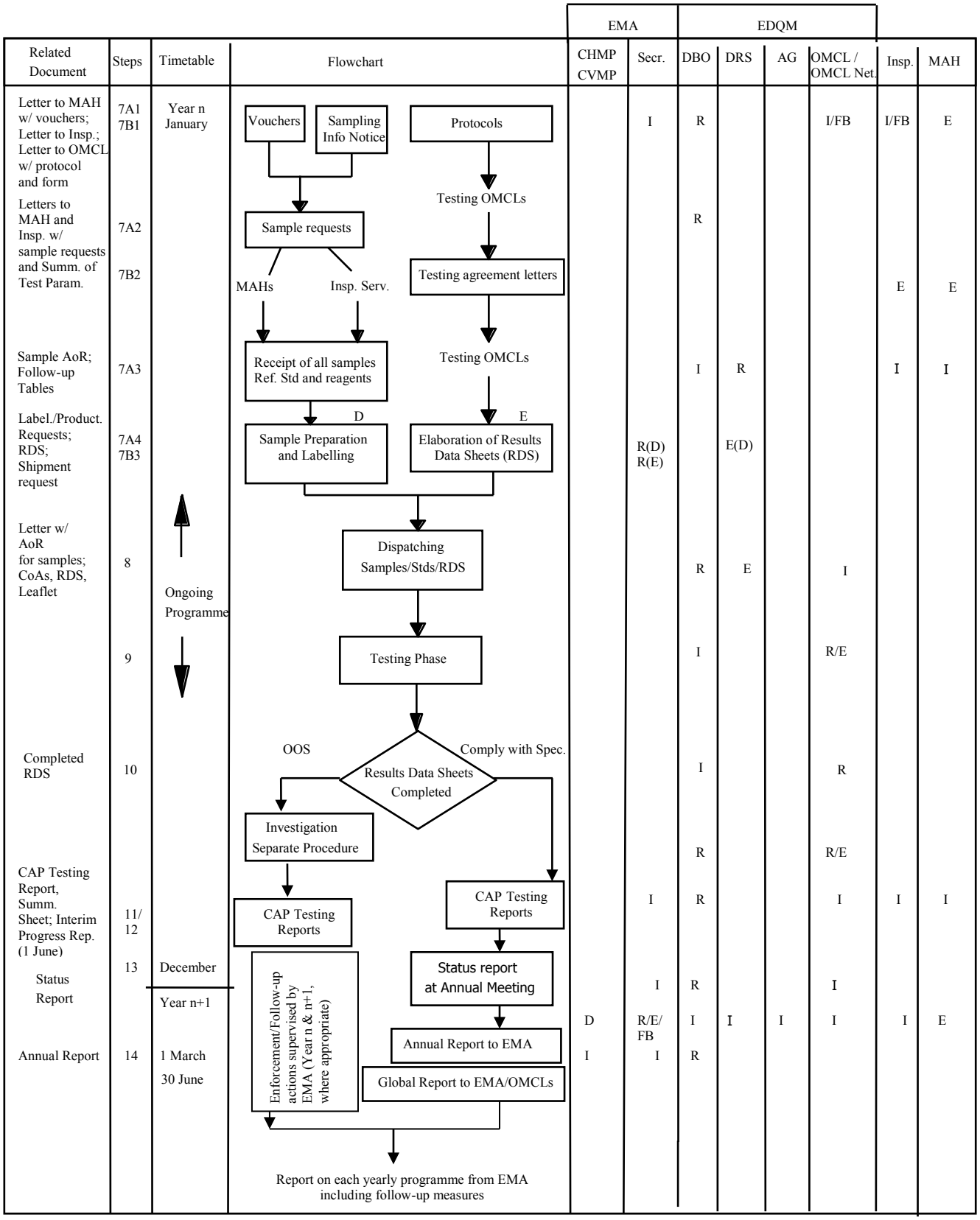
DBO: Department for Biological standardisation and OMCL Network and Health care at EDQM; AG: Advisory Group for CAP programme; OMCL Network: Official Medicines Control Laboratories of EU/EEA Member States; DRS: Division of Reference Standards and Samples at EDQM; CHMP/CVMP: Scientific Committees of the EMA; MAH: Marketing Authorisation Holder of the Product Under Control, Secr.: Secretariat of the EMA; Insp.: Inspectorate Services of the National Authorities

R: responsible for; D: decides; E: executes; I: is informed; GA: gives advice; FB: provides feedback. CTP: Common Test Procedure

* preparation of sampling and testing plans and testing protocols are parallel processes at this stage of the procedure

** In the event of a technical issue arising during the preparation of the test protocols, the (Co-)Rapporteur may be asked for feedback

Appendix A: Flowchart: Sampling and Testing Programme for Centrally Authorised Products



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Appendix B: Cover Letter for Official Sampling Request to MAHs (originator)

Department of Biological Standardisation, OMCL Network & HealthCare (DBO)
CAP Programme

Name
Address

RZ/PH/2012-06718L
ADM/ass

Strasbourg, date

RE: *Product name, strength, Form* testing exercise

Dear colleague,

The European Directorate for the Quality of Medicines and HealthCare (EDQM) and the European Medicines Agency (EMA) have a long history of cooperation in the marketing surveillance of Centrally Authorised Products (CAPs). In the context of the Generics CAP programme on *Product name, strength, Form*, the originator Commercial name® has been included in the testing campaign. As in regular CAP sampling and testing exercises, the testing phase will be performed by members of the Official Medicines Control Laboratory (OMCL) network and the coordination of sampling and testing lies within the responsibility of the EDQM where all documents and samples will be treated confidentially. Samples, reference material and relevant documentation needed to carry out the actual laboratory testing will be provided by the EDQM directly to the testing OMCLs.

The EDQM and EMA agreed that it would be beneficial for all stakeholders to perform in parallel to the Generics CAP programme the testing of corresponding MRP/DCP/Nationally authorised products.

Accordingly, you are kindly requested to provide the following samples (as detailed in the sampling form in attachment):

- Quantity of the same batch of Commercial name®, *strength, Form* (preferably xx form presentation), which will be used as Common Test Sample (CTS);
- Approximately quantity of xxx active ingredient with a purity degree that allows its use as working standard.

The product/reference materials must not expire before **date**; should this condition be problematic, please contact immediately the scientific officer in charge of the study, Scientific administrator.

In order to facilitate a swift and unproblematic transfer of the material to the EDQM, please read carefully the attached 'conditions of delivery sheet', which also includes specific shipment conditions from outside the European Union. Please return to us the completed sampling form containing essential information regarding sampling, storage/shipping conditions and other related documentation (such as certificates of analysis, special instructions for handling and Master Safety Data Sheets) together with the samples.

European Directorate for the Quality of Medicines & HealthCare (EDQM)
Address: 7 Allee Kastner - CS 30026 - F-67081 Strasbourg
Telephone: 33 (0)3 90 21 XX XX - Secretariat: 33 (0)3 90 21 XX XX -
E-mail: scientific.officer@edqm.eu - Fax: 33 (0) 3 88 41 27 71 - Internet: http://www.edqm.eu

We would be grateful if you could send the required amount of samples not later than **date** to the following address:

Council of Europe
European Directorate for the Quality of Medicines & HealthCare (EDQM)
DBO
To the attention of Scientific administrator
7 Allee Kastner
CS30026
67081 Strasbourg, France
Tel: (33) 3 90 21 XX XX
Fax: (33) 3 88 41 27 71

We thank you for your co-operation and assistance. Please do not hesitate to contact us if you have any questions concerning the sampling procedure.

Yours sincerely,

Scientific Officer Head

DBO, EDQM

1 sampling form
1 conditions of delivery sheet