OMCL Network of the Council of Europe
GENERAL DOCUMENT

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General procedure for Sampling and Testing of Centrally Authorised Products

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GENERAL PROCEDURE FOR SAMPLING AND TESTING OF CENTRALLY AUTHORISED PRODUCTS

Introduction

In accordance with Article 55 of Regulation (EC) N° 726/2004 of the European Parliament and of the Council regulating Centrally Authorised Products, the EMA (the Agency), is responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products.

- Furthermore, in accordance with Articles 57 c) and 57 r) the EMA has 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.

For this purpose, since 1999 the EMA has implemented post-marketing sampling and testing programmes aimed at supervising the quality of the Centrally Authorised Products available on the European market. The programmes are carried out on an annual basis in collaboration with the EDQM, who 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 relevant services responsible for sampling within the National Competent Authorities).

CAP Sampling and Testing activities are divided into 5 Individual Testing Programmes as described below:

1. Annual Programme: yearly sampling and testing programme performed on Centrally Authorised Products selected each year using a risk-based approach.
2. Generics Programme: sampling and testing programme performed on Centrally Authorised Generic Products using a common test method.
3. Biosimilars Programme: sampling and testing programme performed on Centrally Authorised Biosimilar Products associated to Biosimilar Products Groups tested using a common test method.
4. Parallel Distribution Programme: yearly sampling and testing programme performed on Centrally Authorised Products that are subject to parallel distribution.
5. Ad-Hoc API Programme: yearly sampling and testing programme performed on Active Pharmaceutical Ingredients on an ad-hoc basis.

This paper describes the operational procedure for post-authorisation sampling and testing of Centrally Authorised Products (CAP) as part of the Annual Programme. 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).

For Ad-Hoc testing a special procedure has been put in place whenever immediate action is required - PA/PH/CAP (16) 104, in its current version.

In case of possible deviation from authorisation dossier or regulations, such as Out-Of-Specifications results, appropriate verifications take place according to instructions in line with established Quality Management Systems and with the document PA/PH/CAP (16) 103, in its current version.

Subsequent actions to be taken based on the outcome of the testing lie within the responsibilities of the EMA.

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, in collaboration with the EMA Scientific Committees, a proposal of programme for the forthcoming year based on a risk-based approach (RBA). Products are selected on the basis of risk analyses and other specific considerations including random selection of additional products per yearly programme. Products subject to Official Authority Control Batch Release (OCABR) are not under the scope of the CAP programme. For discussing the lists of products, a teleconference might be organised by the EDQM involving the EMA and the CAP Advisory Group, who may propose amendments to the lists.

The parameters to be tested are based on the recommendations from the Rapporteurs and Co-Rapporteurs. They are provided to the EMA which will forward them to the EDQM.

Step 2: **Final Adoption of the Programme for the 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 and Healthcare (DBO) about the decision in a timely manner (list of products to be tested). The receipt of this list is confirmed by the EDQM in writing.

Step 3: **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 CAP products, asking them to provide the EDQM within 5 weeks with The current quality parts of the Common Technical Document (2.3 Quality overall summary and 3.2.S & 3.2.P of the Module 3 Quality)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 the validations respectively Module 2.3 – Summary of Quality, and the equivalent documents from sections 3.2.S & 3.2.P of the Common Technical Document – CTD) 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 controlled substance.

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 product up to the end of the 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 pattern (other than the usual channel) 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 currently approved in the original application as amended by any subsequent relevant variations" has to be included.

In case of products included later in the year (e.g. Ad Hoc testing), MAHs are contacted by EMA as soon as the decision for testing is taken.

The receipt of the documents is confirmed by the EDQM to the MAH after having ensured that the documentation is complete. In case 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 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.

The MAHs should ensure that all relevant complete and up-to-date detailed Standard Operating Procedures (SOPs) in English for the tests (also considering associated procedures) as well as the full validation is provided to the EDQM. The EDQM shall contact the MAH should suitable level of details not been achieved.

Each CAP is identified by an internal EDQM code (CAP 20xx/YY) and its EU number. The EDQM coding system allows users to distinguish between different dosage forms or strengths of a single product, thus ensuring easy traceability of the test samples.
Documents are stored electronically at the EDQM, DBO, in specific IT folders with restricted access.

Step 4: **Compilation of the Selected Test Methods and Preparation of the Test Protocols, Preparation of the Sampling Plan and Identification of Testing OMCLs**

These three procedures run in parallel between spring and the end of the year n-1 and can be divided into the following sub-steps.

Step 4A1: **Compilation of the Selected Test Methods and Preparation of the Test Protocols**

As the necessary documentation and information is being received, the EDQM compiles the Test Protocols and sets up the Testing Questionnaire (spring to September year n-1) by extracting the relevant information from the documentation received.

The Test Protocol contains a list of tests recommended by the Rapporteur/Co-Rapporteur plus the test methods from the marketing authorisation dossier (as amended) and other SOPs of relevance for testing. It also includes information about the composition and the release and shelf life specifications for the active substance and the finished product. These protocols will be used by the EDQM as first information for estimating the amount of pharmaceutical units required. During this process, the EDQM may at any time directly contact the MAHs for clarifications or additional documentation, as deemed necessary notably detailed and fully validated SOPs (in English).

Step 4A2: **Final Protocols**

All protocols have to be ready by the end of the year n-1. The EDQM in connection with OMCLs, may suggest changes in the choice and performance of tests based on scientific arguments (i.e. sterility/endotoxin determination, impurity profile of biologicals etc.) taking into account the feasibility at the OMCLs and the relevance of the test(s). Such suggestions are forwarded to the EMA for seeking endorsement/feedback from the Rapporteur/Co-Rapporteur.

Step 4B1: **Preparation of the Sampling Plan: Pre-selection of Sampling Countries**

For each product, the EDQM makes a first estimation of the amount of pharmaceutical dosage units required for the testing and identifies the relevant non-commercially available reagents/reference materials that will need to be provided by the MAHs. This procedure is run at the same time as the preparation of the Test Protocol. If necessary, this estimation of the required sample amount should be revised after discussion with the testing OMCLs once testing is assigned (see steps 4C).

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 equally sharing the sampling workload among the countries. Sales volumes are also taken into consideration. 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. Within each sampling country, samples should originate from a single batch to ensure comparability and adequacy of the results of the different tests performed. In general, market samples originate from 3 different batches (1 batch per sampling country).

However, for orphan drugs or other products with restricted indication(s), the general rules may be adapted on a case-by-case basis to take into account the specific market situation (this generally leads to a reduced number of batches to be tested).

[1] Because of the reduced size of its market Liechtenstein is not included in the sampling location(s)

Step 4B2: **The Sampling Questionnaire**

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 (Chemical, Non-chemical, EU numbers and special storage conditions) is also provided in the questionnaire. In August/September of the 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. 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, its sampling will be allocated to another Member State.

Step 4B3: **The Final Sampling Plan**

After receipt of the responses and by November of the year n-1 at the latest, the EDQM establishes the final Sampling Plan. A sampling timetable is prepared and sent to all sampling contact persons in the EEA OMCL Network for information.

The actual sampling phase should be initiated by the end of the year n-1 in order to start the active testing phase at the beginning of the year n.

Step 4C1: **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 (Chemical, Non-chemical, EU numbers and particular health and safety information, classification as controlled substance) is also provided in the questionnaire. It is obtained by compiling the information from the protocols established under step 4A. This document is sent in August/September of year n-1 to the OMCL Network to give the potential participants an overview of the analytical techniques and equipment required to test each product: OMCLs are asked to volunteer (within 1 month) to the testing taking into account the criteria listed in step 4C2. When completing the questionnaire, the OMCLs have the possibility to apply for testing of all parameters or of specific parameters only, depending on the equipment available in their laboratory. The OMCLs also have the possibility to comment on the selected parameters (a scientific rationale should be provided). The EDQM will forward the feedback received to the EMA, who will liaise with the Rapporteurs/Co-Rapporteurs in order to confirm whether a parameter could be skipped or added to the list of parameters initially selected.

Step 4C2: **Preparation of the Testing Plan**

The number of OMCLs to be involved in the testing of a product is defined per product type.

A distinction is made between **chemical** and **non-chemical** products (e.g: products from rDNA technology, biological products, immunological products). The assignment to one or the other type is made by the EMA and the EDQM based on the nature of the active substance and the testing methods used for each product. A specific testing scheme is systematically pertained to each type of product, unless specific circumstances apply.

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).

Priority criteria for product allocation to candidate OMCLs:

a. Availability of technical competencies/equipment (the OMCLs with quality systems that fulfil the requirements of ISO 17025, applying the complementary specific guidelines of the OMCL Network and having successfully undergone assessment by peers within the OMCL Network or by an internationally recognised body are entitled to take part in the CAP programme);
b. Optimal allocation of the CAPs between the OMCLs of the EEA Network participating in the CAP programme.

Other criteria taken into account for product allocation to candidate OMCLs are:

a. Internal work programme and staff resources allow the candidate OMCL(s) to perform the testing according to the defined timeframe of the CAP programme;
b. Candidate OMCLs belongs to the Supervisory Authority/Rapporteur country;
c. Candidate OMCL belongs to the Co-rapporteur country;
d. Candidate OMCL belongs to any other EEA country;
e. When repeated testing is performed then the preference should be given to the OMCL(s) having performed the first testing.

The preparation of the list of test parameters and analytical techniques (Testing Questionnaire) starts simultaneously to the preparation of the Test Protocols (step 4A1).

Step 4C3: **The Proposed Testing Plan**

The EDQM sets up the proposed list of participating OMCLs, taking into consideration the OMCL responses and the criteria given in step 4C2. The proposed Testing Plan is

established in October/November and sent to all concerned EEA OMCLs at least one week before the CAP Annual Meeting (year n-1).

Step 5: **Presentation of the Programme and Final Selection of Participants at the Annual Meeting**

The programme is presented at the CAP Annual Meeting.

The proposed Testing Plan is presented for approval and the final selection for the products not yet assigned is discussed.

The programme including the list of all participating OMCLs is confirmed by the EDQM not later than two weeks after the CAP Annual Meeting (year n-1).

In exceptional circumstances for specific tests a laboratory outside the OMCL Network may be involved in the programme. The same requirements in terms of confidentiality, absence of conflict of interest and Quality Management System as for any OMCL apply to this laboratory.

The EDQM sets up the annual programme timetable on a practicable sequence. The timetable is presented at the general CAP Annual Meeting in order to allow testing OMCLs to prepare their national work programmes.

Year n

Step 6: **The Sampling and Testing Programme**

The products included in the yearly programme are split into four operational working groups that are dealt with sequentially during the year. Hence, the two procedures for sampling and testing run in parallel during the first semester of the year.

Step 6A1: **The electronic vouchers**

For each project, an electronic voucher for rapid sample replacement is 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. The EDQM indicates in Section 1 of the e-voucher the name of the product, its strength, its pharmaceutical form, its EU number, the EDQM unique project number and the maximum amount of pharmaceutical dosage units required for the testing programme based on the parameters selected by the Rapporteur/Co-Rapporteur in their recommendations. Section 2 of the e-voucher is completed and signed by the MAH or its agent and the originals are returned to the EDQM. By signing the e-voucher, the MAH commits to rapidly replace the indicated amount of pharmaceutical units or the number of units which 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 e-vouchers have been returned, these are kept at the EDQM until the initiation of the sampling operations.

Sequentially during the programme, a Sampling Information Notice containing essential information, such as the anticipated sample size, is sent electronically 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 enough time to National Authorities to organise sample collection. For CAP products requiring storage and shipment under refrigerated conditions, a special note is made in the Sampling Information Notice e-mail. The EDQM offers a particular service for cold-chain shipment from the sampling location to the premises of the EDQM (provision of specific packaging material, coverage of costs), which have to be indicated by the Sampling Contact Person in advance by completing the Shipment Cost Form (available on the ACT platform, when applicable).

Step 6A2: **Sampling**

Once the signed e-vouchers are returned, Official Sampling Requests e-mails are sent by the EDQM to the nominated contact persons in the sampling Member States. E-vouchers are designed to enable replacement by the MAHs of the collected units. The Sampling Form, the electronic voucher and the Delivery Terms and Conditions sheet can be downloaded from the ACT platform using the link provided in the Official sample request e-mail. These documents are sent electronically month-by-month to allow management of the sampling phase from the end of the year preceding the programme (year n-1) to the end of the first semester of the year of the on-going programme (year n).

Each sampling Member State chooses an appropriate site within the distribution chain as closely as possible to patients on its national territory. Samples should preferably be drawn from a retail pharmacy or a hospital pharmacy. If not, sampling should be performed at wholesalers. Sampling at MAH warehouse level shall be performed only as the last resort. The choice of sampling location is dependent on the availability of the required product(s) and on the number of packs requested by the EDQM for appropriate testing in accordance with the pack size(s) available. The sampler/Member State's Agency completes and signs Section 3 of the e-voucher when taking the samples and clearly identifies the quantity of packs (tablets/units) actually sampled. Section 4 of the e-voucher is then completed and signed by the person responsible at the site where the samples are drawn (sampling location), confirming thus the quantity and type of samples drawn as well as the location. In case it is not possible to fill in electronically the e-voucher, it can be printed and manually completed. The responsible contact person at the sampling location will sign the e-voucher manually and a copy of it will be kept for traceability reasons. *Note:*

In order to avoid supply problems for life threatening products, the sampling contact person will, if necessary, ask the sampling location to increase stocks by the amount of pharmaceutical units to be sampled in advance of the sampling operation. In this case, the sampler should ensure that the samples are drawn from the original stock and not from the replacement stock.

The sampler sends the completed e-voucher to the MAH contact person or to the MAH's agent designated in Section 1. The samples drawn are transmitted to the EDQM under the required conditions of transport, together with the completed Sampling Form (which includes essential information regarding sampling and a label check) for traceability purposes and a copy of the filled in e-voucher – accompanying documentation can be uploaded on the ACT platform. Should this be the case, there is no need to send "paper versions" of these documents with the samples. The instructions indicated on the conditions of delivery sheet must be taken into consideration.

Upon receipt, the MAH replaces the sampled product as soon as possible, in the number and pack size indicated in Section 3 of the e-voucher, directly to the sampling location identified in Section 4 usually within one month unless another arrangement has been agreed with the sampling location.

An Official Sample Request e-mail is also sent to the MAH in order to collect a Control Test Sample (CTS) and all necessary non-commercially available reagents and standards. The MAH is asked to fill in electronically a Sampling Form that contains the list of samples needed and to provide the accompanying documentation (i.e. CoAs, SDS sheet…) by uploading these documents on the ACT platform. Normally a deadline of eight weeks for sampling is given.

Step 6A3: **Receipt of all Samples, Reference Materials and Reagents**

All incoming samples are registered and stored within the DRSL (Division of Reference Standards and Samples) at the EDQM according to an EDQM internal procedures.

The Sampling Contact Person or the MAHs are informed of the good reception of the samples/materials per e-mail by DRSL.

The storage conditions of the samples on their way from the manufacturer / sampling organisations to the EDQM must be verified and documented sufficiently: to this end, the electronic Sampling Form completed by the sampler/MAH should be made available on the ACT platform when samples are returned to the EDQM at latest.

Step 6A4: **Sample Preparation and Labelling**

The samples are labelled by DRSL/EDQM and prepared for dispatching to the testing OMCLs following the established general Testing Plan. 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 6B1: **Dispatching Protocols: Final Confirmation of OMCL Participation**

The test protocols (i.e. list of the selected tests to be performed plus copies of the related SOPs from the MAH, the composition and the release and shelf life specifications for the active substance and the finished product) are sent electronically to the candidate testing OMCLs for review and definitive confirmation of their participation. This is done for each product approximately at the same time as the sampling phase starts.

The receipt of the sending needs to be confirmed by the OMCLs by completing an "Acknowledgement of Receipt of SOPs for OMCLs" form on the ACT platform. All participants are asked to fill in this form including information on the testing location and the contact details of the person responsible for testing within the OMCL in order to facilitate later the shipment of the test material and subsequent communication during the testing phase. At this stage, requests for clarifications about testing methods can be addressed in the "Comments" section of the form. This form is also used by the OMCL to definitely confirm its participation in the concerned project.

Validation data of testing methods will be kept at the EDQM unless there is a written request by a participating OMCL. It should be made clear that no reassessing or verification of these data shall be carried out: they should only be informative to help OMCLs where necessary during performance of the testing programme to better understand the rationale of the methods and to solve problems occurring during transfer and setting up of the test methods.

Step 6B2: **Preparation of Product Testing Agreements**

Individual CAP Testing Agreement Templates defining the terms of collaboration between the testing OMCLs and the EDQM are issued by the EDQM and sent to the relevant OMCLs for each product once confirmation of participation has been received by the EDQM. These contracts have to be signed by an authorised representative of each party. The Testing Agreement defines the agreed practical conditions for testing and reporting (duration of the testing phase and funding) and cross refers to the official protocol and Results Data Sheet (see step 6B3 below). The EDQM, DBO prepares the templates which are then transmitted to Purchasing unit at the EDQM who is following it up according to internal procedures.

Step 6B3: **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 product. They actually 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 contains

tables to be filled in by the testing OMCLs with their system suitability and analytical results. The draft RDS should be provided to the concerned testing OMCLs ahead of the testing, in order to agree on the testing scheme proposed and on the system suitability criteria to be fulfilled. The OMCLs are encouraged to ask for further clarifications at this step; depending on the complexity of the methods; teleconferences with the MAH might also be organised.

Step 7: **Dispatching Samples / Results Data Sheets**

Samples are dispatched by the EDQM, DBO sequentially during the year according to the established timetable, unless unforeseen circumstances arise. The participants are informed in a notification e-mail about the shipment of the samples and are sent electronically the Results Data Sheet and accompanying documentation.

The participating OMCLs confirm the safe receipt of the samples, standards and data sheets and acknowledge any relevant information such as the storage conditions, handling etc. For that purpose, when the shipment takes place, a delivery note is sent to the recipients, together with an Acknowledgment of receipt form. The filled in Acknowledgement of receipt form is sent back to the Dispatch unit by the OMCL after having received the samples. A copy of this filled in acknowledgement of receipt is also addressed per e-mail to the Scientific Officer responsible of the project.

Upon reception OMCLs are also requested to perform a visual check of the materials received to ensure that they conform to the expectations. Particular attention is paid to the products requiring specific temperature conditions. Any deviation from the expected appearance is reported on the acknowledgement of receipt returned to the EDQM who will initiate the appropriate investigations.

Step 8: **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 that is provided to the OMCL(s) in order to support the costs incurred with the testing. The testing cannot be further sub-contracted, if not agreed in advance in writing by the two contract partners, i.e. the EDQM and the OMCL/Competent Authority. When two OMCLs are involved and in case 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. If needed, a teleconference within the MAH, the EDQM Secretariat and the participating OMCL(s) can be organised. 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, since the validation has already been done by the MAHs. They are, nevertheless, requested to demonstrate the successful

method transfer (compliance with the system suitability criteria and/or assay acceptance criteria included in the test procedures with supportive documentation, i.e: chromatograms) using the dedicated tables included in the Results Data Sheets.

Step 9: **Results Data Sheets Completed**

The participants complete and send back the Results Data Sheets together with type chromatograms and any comments in due time. These documents can be uploaded on the ACT platform.

Depending on the category of the product, the report is due at the latest 40 or 65 working days after receipt of the test samples, the date of receipt being documented in the Individual CAP Testing Template. As a rule, 40 working days are granted for testing chemical products and 65 working days are granted for testing non-chemical products. 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.

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

In case of out-of-specification (OOS) situations, further action is needed in accordance with the procedure in place for handling OOS results and in particular a failure investigation is required.

Step 10: **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 product. CTRs are issued on an ongoing basis and are distributed to the EMA and all OMCLs. The CTR is distributed to the MAH for comments by EMA. The Rapporteur and Co-Rapporteur receive the CTR and MAH comments for assessment. The Rapporteur feedback is conveyed to the MAH together with any requests for further actions, whenever deemed necessary.

Step 11: **Follow-up actions**

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 the responsibility of 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 12: **Annual status reports**

The EDQM reports about the status of the programme during the Annual Meeting of the concerned OMCL Network.

An Interim Report is sent to the EMA once a year (1st of June of year n, as indicated in the Cooperation Agreement established between the EDQM and the EMA).

In addition, the EDQM shall provide the EMA no later than 1st of December of year n a written update indicating which activities planned for year n were not performed as planned. This will be used by EMA for budget planning purposes.

Year n+1

Step 13: Annual **Reports to EMA/OMCLs**

An Annual Report and an Annual Financial Report are submitted to the EMA by 1st of September of the year n+1, to provide an overview of the previous year's testing programme and the summary of the costs associated to these activities, respectively. In case some projects are not finalised by the date, an extension of the deadline can be proposed by the EDQM, which must be endorsed by the EMA. Any outstanding activities not reported in the Annual Report and Annual Financial Report of the year n, shall be reported by the EDQM in the Final and Financial reports of the year n +1, following written agreements between both parties.

A Global Report to the EMA, the OMCLs and the Samplers is released by the end of November of the year n+1. It provides an overview of the products sampled and tested during the CAP programme, as well as information about the different partners that have contributed to this programme.

An overall CAP testing report covering the 5 years sampling and testing programmes performed on Centrally Authorised Products is set up by the EDQM and distributed to the EMA and the OMCLs by 1st of November in the last year of the co-operation agreement.

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 the 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 (05) 49 13R - General Procedure for Sampling and Testing of Centrally Authorised Products.

6th Revision (2022):

- Revision following the use of electronic documentation instead of paper versions.
- Change of the logo

♥ **Date of becoming effective** *(month and year)*: **January 2023**

Title of document: PA/PH/CAP (05) 49 11R - General Procedure for Sampling and Testing of Centrally Authorised Products.

5th Revision (2018):

- Revision following the signature of the 2019-2023 Co-operation agreement (Introduction: Reference to the 5 Individual Testing Programmes; Steps 12 & 13: written update with activities not performed, change in the deadlines,)
- Deletion of the Appendixes

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

Title of document: PA/PH/CAP (05) 49 10R - General Procedure for Sampling and Testing of Centrally Authorised Products.

4th Revision (2013):

- Step 8: 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 (05) 49 9R - General Procedure for Sampling and Testing of Centrally Authorised Products.

3rd Revision (2012):

- Step 4B1: inclusion of parallel distribution.
- Step 4B3: inclusion of the "sampling timetable"
- Step 6B1: additional information added regarding the A/R of SOPs (possibility to request further information about testing methods)
- Step 8: inclusion of the possibility to organise a teleconference.
- Update of the layout of the appendixes according to the new rules (i.e. logo)

- Update of Appendix VI in order to include the Shipment cost form
- Update of Appendix VII in order to delete information about the shipment cost form
- Update of Appendix VIII in order to simplify the questionnaire
- Update of Appendix X
- Update of Appendix XI in order to include a sentence as regards materials sent from non-EEA countries
- Update of Appendix XII in order to include a sentence as regards materials sent from non-EEA countries

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

Title of document: PA/PH/CAP (05) 49 9R - General Procedure for Sampling and Testing of Centrally Authorised Products.

3rd Revision (2012):

- Step 4B1: inclusion of parallel distribution.
- Step 4B3: inclusion of the "sampling timetable"
- Step 6B1: additional information added regarding the A/R of SOPs (possibility to request further information about testing methods)
- Step 8: inclusion of the possibility to organise a teleconference.
- Update of the layout of the appendixes according to the new rules (i.e. logo)
- Update of Appendix VI in order to include the Shipment cost form
- Update of Appendix VII in order to delete information about the shipment cost form
- Update of Appendix VIII in order to simplify the questionnaire
- Update of Appendix X
- Update of Appendix XI in order to include a sentence as regards materials sent from non-EEA countries
- Update of Appendix XII in order to include a sentence as regards materials sent from non-EEA countries

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Title of document: PA/PH/CAP (05) 49 6R - General Procedure for Sampling and Testing of Centrally Authorised Products.

2nd Revision (2010):

- Introduction and Step 1: Editorial (rephrasing) changes
- Step 3: EMA no longer provides an updated list of variation for the concerned products. Deletion of such information.
  Step 3: change of intervals for receipt of variation updates
- Step 4A1: change of definition of "Test protocol"

- Step 4C2: Update of the classification of the criteria for product allocation to candidate OMCLs
- Step 6A2: Correction of the sender of the Voucher to the MAH after sampling and inclusion of information regarding the sampling form
- Step 12: re-structuring of this chapter
- Step 13: inclusion of "global report"
- Update of Appendix VII following the suppression of Annex XI (Packaging recommendations)
- Editorial update of Appendix VIII and inclusion of a definition of severe cases of non-compliance in the label check
- Editorial update of the Appendixes
- Update of EMEA name to EMA
- Update of selection criteria of the products and suppression of Appendix II "Template for testing recommendations from Rapporteur/Co-Rapporteur" (Step 1)
- Inclusion of "Acknowledgement of receipt of MAH documentation" as Appendix II (Step 3)
- Inclusion of a description of the Sampling Questionnaire (Step 4B2)
- Inclusion of the "Shipment Cost Form" as Appendix IX and update of step 6A2
- Inclusion of the "Acknowledgement of Receipt of the Samples from Sampling Organisations" as Appendix XIV and of the "Acknowledgement of Receipt of Samples from the MAH" as Appendix XV and update of Step 6A3
- Inclusion of the "Cover Letter for Shipment of Samples to Testing OMCLs" as Appendix XVIII and update of Step 6B1
- Update of Appendix III following modification of the testing scheme for Insulins
- Update of Appendix VI in order to include the "Summary of Test Parameters" in attachment
- Update of Appendix VIII in order to include the label check
- Update of Appendix IX in order to include the label check of the samples
- Update of Appendix X – Conditions of delivery sheet
- Update of Appendix XI: Cover Letter for Official Sampling request to MAH
- "Product Testing Agreement" removed from the Appendixes
- Editorial update of the Appendixes
- Update of Appendixes numbering following the inclusion and removal of the several appendixes (see above)
- General harmonisation of the used terminology

♥ **Date of becoming effective** *(month and year)*: **December 2010**

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1st Revision (2007):

- Inversion of steps 4C1 and 4C2 in order to follow the chronological order of the process.
- Modification of the wording describing the quality management system requirements applicable to OMCLs involved in the CAP programme (Step 4C1) to make it in accordance with the document PA/PH/OMCL (06) 116 2R
- Modification of the timelines indicated under step 4A1, step 4B2, step 4B3.
- Introduction of the submission of the proposed testing plan to the CAP Advisory-Group for review and modification of the deadline for distribution of the proposed testing plan to the testing OMCLs (Step 4C3).
- Inclusion of a request for health and safety documentation regarding active substances and finished products to be tested alongside the technical documentation requested to the MAHs (steps 3 and 4C2). Request for special notification should the product be considered as a controlled substance within EEA Member States.
- Inclusion of the request for a visual check of the material upon receipt at the OMCLs (Step 7)
- Inclusion of PA/PH/CAP (04) 70 Rev 5 as Appendix III and modification of step 4C1 wording to include the notion of testing scheme.
- Modification of Appendixes numbering further to the inclusion of the new appendix III (see above)
- Update of EDQM name to EDQM & HealthCare
- Change in the name of EDQM Division IV to EDQM & HealthCare, Department for Biological standardisation and OMCL Network and HealthCare (DBO) and change in the name of Purchasing, Receiving and Dispatching Unit (PRDU) in Division of Reference Standards and Samples (DRS)
- Editorial update of the Appendixes
- General editorial modifications

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Reference document of this template: PA/PH/OMCL (08) 79 in its current version