

OMCL Network of the Council of Europe

GENERAL DOCUMENT

PA/PH/CAP (05) 49 R11

General procedure for Sampling and Testing of Centrally
Authorised Products

Full document title and reference	General procedure for Sampling and Testing of Centrally Authorised Products, PA/PH/CAP (05) 49 R11
Document type	Terms of Reference / Procedure
Legislative basis	Not Applicable
Date of first adoption	12/2005
Date of original entry into force	01/2006
Date of entry into force of revised document	12/2018
Previous titles / other references	This document replaces document PA/PH/CAP (05) 49 R10
Custodian Organisation	The present document was elaborated by the OMCL Network/EDQM of the Council of Europe
Concerned Network	EU/EEA OMCLs – EU/EEA Sampling Organisations

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-authorisation 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 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.

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 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 EDQM within 5 weeks 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 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 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 included and 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 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 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.

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 EDQM. 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. Documentation is stored at EDQM, DBO, in an archive system 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 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 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 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.

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 submitted to the CAP Advisory Group for review and support, in case of difficulties. Further to the review by the CAP Advisory Group if needed, this list is sent to all concerned EEA OMCLs at least one week before the CAP Annual Meeting (n-1), along with the annual work programme.

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 Vouchers

For each product, Vouchers (usually 3) 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. The EDQM indicates in Section 1 of the Voucher 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 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 replace the indicated amount of pharmaceutical units or the number of units which was sampled in practice. Once the duly filled-in documents 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 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. A calculation of the required quantity of pharmaceutical dosage units is attached to the letter in order to make the request more transparent.

Step 6A2: Sampling

Once the signed Vouchers are returned and after the completion of Section 2 of these documents by the EDQM, indicating the EDQM project number and the exact amount of pharmaceutical units needed, Official Sampling Requests, containing a Cover Letter, a Voucher, a Sampling Form and a Shipment Cost Form, where applicable, and conditions of delivery sheet are sent by the EDQM to the nominated contact persons in the sampling Member States. Vouchers are designed to enable replacement by the MAHs of the collected units. A calculation of the required quantity of pharmaceutical dosage units (Summary of Test Parameters) is attached to the letter in order to make the request transparent. These documents are sent 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 Section 3 of the Voucher when taking the samples and clearly identifies the quantity of packs (tablets/units) actually sampled. Section 4 of the Voucher is then signed in his/her presence 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.

The conditions during transportation should be documented for products to be stored at 2-8°C. If needed, the EDQM may provide assistance in order to ensure that the storage conditions are maintained during shipment (provision of packaging material, cooling elements and data loggers for temperature control). EDQM offers the possibility to cover the cost of the shipment for products requiring a transport at 2-8°C. In this case, the sampler sends the filled in Shipment Cost Form to EDQM in advance.

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 immediately sends the completed Voucher directly 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 Voucher. 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 Voucher, directly to the sampling location identified in Section 4 usually within one month unless another arrangement has been agreed with the sampling location.

Safety features are included in the voucher template to avoid any misuse (non copiable paper).

In parallel to the shipment of the Official Sample Request sent to the sampling contact person, the MAH is addressed a Cover Letter and a Sampling Form in order to collect a Control Test Sample (CTS), all necessary non-commercially available reagents and standards and all additional relevant documents (e.g. Certificates of Analysis, Material Safety Data Sheets). EDQM states in this cover letter to the MAH that testing will be performed according to the methods described in the authorised dossier, relevant SOPs and authorised variations of the test methods.

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

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

An Acknowledgement of Receipt is sent by EDQM, DBO, upon receipt of the samples to the sampling organisations or to the MAH, as appropriate.

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 Sampling Form completed by the sampler is returned to EDQM together with the samples. If necessary, appropriate packaging materials, cooling elements and recording devices can be provided by the EDQM to the samplers. In any case samples should be forwarded to EDQM as rapidly as possible after sampling using courier companies if needed.

Step 6A4: Sample Preparation and Labelling

The samples are labelled by DRS/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 protocols are sent to the OMCLs to provide all details related to the testing. This is done for each product approximately at the same time as the sampling phase starts. The Cover Letter signifies that the shipment contains confidential information. In case the OMCL is not in the position to participate, it is asked either to destroy the documentation or to return it to EDQM.

All participants are asked to fill in the "Acknowledgment of Receipt of SOPs for OMCLs" 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 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

Product Testing Agreements defining the terms of collaboration between the testing OMCLs and the EDQM are issued by 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). A signed original is kept at EDQM, DBO. At the same time persons responsible for testing are informed about the expected time schedule of the testing phase.

Step 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 contain tables to be filled in by the testing OMCLs with their system suitability and analytical results.

Step 7: Dispatching Samples / Results Data Sheets

Samples are dispatched by EDQM DBO sequentially during the year according to the established timetable. With these are sent a Cover Letter , the Results Data Sheet and other relevant documentation (Certificates of Analysis, Material Safety Data Sheets...). The participants are informed in a notification about the shipment of the samples and are sent an electronic version of the Results Data Sheet.

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 an Acknowledgement of Receipt to be filled in is sent by EDQM along with the samples and the other documents . 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 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 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.

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 on

the acknowledgement of receipt for the samples. 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 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 June of year n, as indicated in the Cooperation Agreement established between EDQM and EMA).

In addition, EDQM shall provide the EMA no later than 1st 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 EMA by 1st 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. Any outstanding activities not reported in the Annual Report and Annual Financial Report by 1st September of the year n+1 shall be reported by EDQM in an Addendum no later than 1st October of the year n+1. The Addendum will include both the report of the outstanding activities and the associated costs, if applicable.

A Global Report to EMA, the OMCLs and Samplers is released by the end of October 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 year sampling and testing programmes performed on Centrally Authorised Products is set up by EDQM and distributed to the EMA and the OMCLs by 1st 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 EMA and 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 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 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**

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

♥ **Date of becoming effective (month and year): January 2008**

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