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Sampling and Testing of Centrally Authorised Products – Procedure for Parallel Distribution Programme

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SAMPLING AND TESTING OF CENTRALLY AUTHORISED PRODUCTS

PROCEDURE FOR PARALLEL DISTRIBUTION PROGRAMME

Introduction

Parallel distribution is the distribution of a centrally authorised medicinal product from one Member State to another by a pharmaceutical company independent of the marketing-authorisation holder.

On 20 May 2004, notifications of parallel distribution of centrally authorised medicinal products became mandatory throughout the community, in accordance with Article 57(1)(o) of Regulation (EC) No 726/2004. The task of the European Medicines Agency (EMA) is to check compliance of products in the parallel distribution chain with the conditions laid down in Community legislation on medicinal products and in the marketing authorisation of the product. Parallel Distributed (PD) CAPs can be tested as part of the Parallel Distribution Programme. As part of this individual testing programme, each year a number of PD CAPs will be randomly sampled from the parallel distribution chain and tested. The number of products to be sampled and tested yearly should be maximum 10, unless otherwise agreed in writing.

This paper describes the operational procedure for post-authorisation sampling and testing of PD CAPs within the Parallel Distribution 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 overall CAP testing report covering the 5 year sampling and testing programmes performed on Centrally Authorised products (last year of the co-operation agreement). It should be read in conjunction with the General procedure PA/PH/CAP (05) 49 in its current version.

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

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

Step 1: **Proposed Programme**

In June (year n-1) the EMA Secretariat prepares a proposed list of PD CAPs selected on the basis of the number of notifications for parallel distribution received by EMA. The list of products will be established following risk-based considerations and will then be distributed to the OMCL Network beforehand.

Out of this list, samples will be randomly taken by samplers in year n depending on availability for 10 products (unless exceptional circumstances). The PD CAPs from this list that have not been sampled during a year will be reported to the next year's programme.

As such, every year additional products will be selected and added to the existing list of products selected in the past; thus, the number of products included in each yearly programme will continuously increase with time, offering more chances to get a sample.

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

The final programme is normally adopted during the July (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). 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 PD CAP products, asking them to provide EDQM by end October n-1 with the relevant information from the original application, as amended during the assessment of the application and by relevant variations (i.e. quantitative and qualitative composition of the finished product) including health and safety information about 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 a filled in and signed electronic voucher.
Section 1 of the Voucher is signed by the MAH or its agent and returned to the EDQM. By signing the Vouchers the MAH commits to rapidly replace the indicated amount of pharmaceutical units or less (whichever was practically sampled).
Section 2 of these documents is filled in by the EDQM, indicating the EDQM project number and the exact amount of pharmaceutical units needed.
Once the duly filled-in documents have been returned, they are kept at the EDQM until the initiation of the sampling operations.

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.

Each PD CAP is identified by an internal EDQM code (PD_CAP 20xx/Y) and its EU number. The EDQM coding system allows distinguishing 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.

In parallel, the EMA provides additional relevant information to the EDQM secretariat together with the list of PD products, such as the countries where the products are parallel distributed and the name and contact details of the parallel distributors.

Step 4: **Sampling**

The list of PD products and their marketing situation is distributed to the samplers by e-mail, so that they can check if products are available at the parallel distributor. Sampling operations can be performed from the time where the list of product is distributed until the end of September of the Year **n**.
Reminders will be sent out by the EDQM Secretariat twice a year to ensure that samplers regularly check if products are available at the parallel distributor. Every time a PD product is collected, the EDQM Secretariat will circulated an up-dated list.

Should a product be available at the parallel distributor level, the sampler will immediately inform the EDQM Secretariat, so that an Official Sampling Request, containing one Voucher, a Cover Letter, a Sampling Form (which includes essential information regarding sampling and a label check questionnaire tailored to the specificities of PD products) and a Shipment Cost Form, where applicable, is sent in electronic format as soon as possible.

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.

At least three different batches per product are required to be able to determine the authenticity of a product; this means that beside the market sample, the MAH will be asked to provide three different batches of the CTS, where possible. If fewer batches are available, the tests can still be performed but the results will be "less consolidated".

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 sampler immediately sends the completed Voucher directly to the MAH contact person or to the MAH's agent designated in Section 1.

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

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

Each PD product indicated on the list can only be sampled once. If, for a given product, several samplers contact the EDQM at the same time, only one Official Sampling Request will be provided. The choice of the country will be taken so that an equal repartition of the sampling operations can be reached at the end of the year.

In parallel to the shipment of the Official Sample Request sent to the sampling contact person, EDQM sends a request to the MAH to collect different batches of a Control Test Sample (CTS), necessary reagents/standards - where applicable and additional relevant documents (i.e. Certificates of Analysis).

Step 4A: **Receipt and dispatching of all Samples, Reference Materials and Reagents – where applicable**

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

Step 5: **Testing and reporting**

When the EDQM Secretariat is informed that a PD product can be sampled, the OMCL network is contacted so that a volunteer for testing can be identified as quickly as possible.

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).

Testing is the responsibility of the participating OMCLs. For each product to be tested, an Individual CAP Testing Template 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.

At the moment testing would be limited to authenticity testing with the possibility to include other parameters in a future step. Several options (based on different techniques available in OMCLs) are currently used to test for authenticity of a product. The decision about the testing strategy would be taken on a case-by-case basis by the testing OMCL in view of the product to be tested and the instrumentation available. Different cases have been analysed and recommendations for testing strategies were summarised in the position paper An "aide-

mémoire" for the testing of suspected illegal and counterfeit medicines, PA/PH/OMCL (06) 81 in its current version. The report is due at the latest 65 working days after receipt of the test samples, the date of receipt being documented on the acknowledgement of receipt for the samples.

The participants provide a testing report, in a format of their choice, containing at least, the object of the study (i.e. name of the product, project N°, pharmaceutical form, number of samples tested, batch numbers…), the strategy/technique used, a summary of the test(s) performed, results obtained and a conclusion on whether or not there are any reasons to question the authenticity of the product.

It is not possible for OMCLs to definitively determine the authenticity of a product, because ultimately only the manufacturer is in possession of exhaustive information on how a specific batch has been produced (e.g. sources of ingredients and packaging materials). For that reason OMCLs are encouraged to highlight similarities and differences between the tested sample and the original product in their reports, on the basis of their observed results.

An abridged report compared with the regular programme is set up by the EDQM within one month after the receipt of the results for a given product. Reports are issued on an ongoing basis and are distributed to the EMA and all OMCLs.

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.

The EDQM reports about the status of the programme during the CAP Annual Meeting (Year n) and provides an overview of the work performed in the Annual Report (Year n+1) sent to the EMA.

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. The Rapporteur and Co-Rapporteur receive the document for information on the overall outcome of the testing exercise.