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Procedure for the Testing of Nitrosamines in Centrally Authorised Products

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SAMPLING AND TESTING OF CENTRALLY AUTHORISED PRODUCTS

PROCEDURE FOR NITROSAMINE TESTING

Introduction

This yearly nitrosamine testing programme is aiming to test the presence of nitrosamine impurities in Centrally Authorised Products using a risk-based approach or selected randomly as discussed in Step 1.

This paper describes the operational procedure for post-marketing sampling and testing of Centrally Authorised Products (CAP) for nitrosamines as a yearly 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 Agreement Report to the EMA where the results of the Nitrosamine programme are summarised (ideally in year n+1).

The establishments in this procedure do not prevent the OMCLs from liaising with their National Competent Authority within the framework of their regulatory activity.

Year n-1: Planning of the 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 a list of products for nitrosamine testing 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 products per yearly programme.

The list of products is discussed via a teleconference between the EDQM, the EMA and the CAP Advisory Group, who may propose amendments to the list.

To increase the feasibility of the programme, the following steps are taken:

The nitrosamines group of experts and OMCLs are to be consulted at this stage to confirm the feasibility of the programme.

At the same time, EMA will check internally and with the Marketing Authorisation Holder of the product as applicable whether the product is manufactured or marketed, and if analytical procedures for the nitrosamines testing are available.

The EDQM will review the list taking also into account previous years' lists including leftovers to leverage synergies, explore acquired testing competencies and group similar products, if applicable. The EDQM will categorise the products on the list based on three criteria: 1) availability of an analytical procedure within the Network, 2) availability of an analytical procedure developed by the MAH and, 3) no analytical procedure available for the testing of the given product.

Step 2: **Final Adoption of the Product List for Nitrosamine Testing for the Year n**

The final list is normally adopted during the **February/March** (year n-1) meetings of the CHMP.

The final list will contain maximum 15 adopted products and a reserve list. The actual number of products tested in the programme is subject to the capacity of the Network and to the types of nitrosamines to be tested.

The EMA Secretariat provides the final adopted list to be tested to the EDQM and the CAP Advisory Group Members. 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 currently valid expert report, the qualitative and quantitative composition of all authorised strengths, analytical procedure(s) (together with the procedure validation report(s)) and limits used for the determination of nitrosamines submitted by the MAH during the call for review exercise and/or following actions defined during step 1, 2 and 3. The MAH is asked to confirm if reference standards are available. The MAH will also be requested to provide information on the marketing situation of the product and to nominate a contact person for the preparation of the electronic voucher at the time of the sampling phase of the product.

In addition, they will be asked to provide information whether the root cause of the nitrosamine impurity is known.

Documents received will be stored electronically at the EDQM in specific IT folders with restricted access.

Step 4: **Preliminary selection of testing OMCL(s)**

The EDQM sends out the list of products selected for nitrosamine testing to the EU/EEA OMCL Network as soon as this list is adopted by the CHMP.

The table listing the products for nitrosamines testing may also contain information on the outcome of the 'call for review' for all products (nitrosamines found or potential nitrosamine formation risk), if possible. If a procedure for nitrosamines testing is available by the MAH, this information will also be included in this table.

At this stage OMCLs are asked to express preliminary interest if they would like to perform nitrosamine testing on any of the products listed. They should also comment if they have experience performing nitrosamine testing on any of the products, and if they have an inhouse analytical procedure available, or if they have an interest to develop an analytical procedure.

Step 4A1: **Requesting samples and materials, Selection of Test Procedure, and Identification of Testing OMCLs**

Nitrosamines testing should be performed on one sample provided by the MAH (Control Test Sample, CTS) and three samples drawn from the market. Deviations from this modality is also possible, when there is a rationale behind the change.

The CTS sample always has to be provided at least in its primary packaging; testing of bulk sample without packaging is not recommended for this programme.

Ideally, market samples collected for the testing should be closer to their expiry date, but enough shelf-life should be left for testing (i.e. 6-7 months prior to expiry date). Deviations from this approach are accepted in justified cases, for example, if the targeted samples are not available.

Market samples are collected for the nitrosamines testing as per the sampling procedure described in PA/PH/CAP (05) 49 - General Procedure for Sampling and Testing of Centrally Authorised Products in its current version: preparation of electronic vouchers, identifying the inspectorates for sampling, sending the Official Sampling Request to samplers, receiving the samples at the EDQM, relabelling the samples.

By October year n-1 the latest, but preferably as early in the programme as possible, the EDQM will check with the preliminary selected OMCLs to confirm their participation in the programme. All available information can be provided at this stage (i.e. the analytical procedures and acceptance limits used for the determination of nitrosamines, if available).

The EDQM may at any time directly contact the MAHs to request clarifications or additional documentation, as deemed necessary, notably detailed and fully validated SOPs (in English).

For the testing of the product the analytical procedure of the manufacturer developed for the nitrosamines testing should be applied (to assess the robustness and feasibility of the analytical procedure). Alternatively, it is possible to apply a validated, inhouse procedure of the OMCLs either in addition to the manufacturer's procedure or in replacement of this procedure; in this latter case, a rationale should be provided to justify this approach. In some cases, the OMCL might decide to develop a new inhouse analytical procedure in course of a CAP Nitrosamine project.

When an inhouse procedure is used by the OMCL instead of an available MAH procedure, the OMCL should provide feedback on the quality and plausibility of the manufacturer's analytical procedure.

All OMCLs from the different EEA Member States with the required testing competency should be given the possibility to be involved in the programme applying the principle of voluntary participation.

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/IEC 17025, applying the complementary specific guidelines of the OMCL Network, operating in accordance with the requirements of

the European Pharmacopoeia and undergoing regular external assessment by peers within the OMCL Network or by an internationally recognised body are entitled to take part in this specific CAP programme);

b. Optimal allocation of the CAPs between the OMCLs of the EEA Network participating in this CAP programme.

Other criteria considered 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 OMCL(s) outside of the EEA OMCL network if pre-agreed with EMA;
c. When repeated testing is performed then the preference should be given to the OMCL(s) having performed the first testing.

The EDQM organises the sampling with the sampling inspectorates and the MAH with the necessary degree of urgency to obtain the market samples, CTS sample and suitable reference materials, standards, and any other key materials necessary for the testing.

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

The list of the products is presented at the CAP Annual Meeting (**Year n – 1**).

The programme including the list of all participating OMCLs is confirmed by the EDQM not later than the end of year n-1.

Step 6: **Dispatching documentation: Final Confirmation of OMCL Participation**

The documentation is sent electronically to the candidate testing OMCLs for review and definitive confirmation of their participation via the Active Collaboration Tool (ACT) platform. This is done for each product as early as possible, but preferably not later than January year n.

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 Active Collaboration Tool (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 procedure(s) 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.

When the Acknowledgement of Receipt of Confidential Documentation is signed and sent back, the OMCLs should indicate via email how many product units should be collected from the market (market samples) for the testing. From the MAH EDQM will request some additional number of units of the CTS sample compared to the number of the market sample units so the testing OMCL have additional units for the analytical procedure setup. The reference materials and other materials necessary would also be discussed between the EDQM and the testing OMCL via email.

Validation data of testing procedure(s) where available are also sent to the 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 procedures and to solve problems occurring during implementation of the test procedure.

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

Individual CAP Testing Agreements are prepared according to the PA/PH/CAP (05) 49 - General Procedure for Sampling and Testing of Centrally Authorised Products in its current version.

Step 7A: **Elaboration of Test Protocols**

By the time of the shipment of the materials to the testing OMCL, the EDQM will prepare a Test Protocol which will contain certain information (i.e. name of the product, project N°, pharmaceutical form, name of the active pharmaceutical ingredient, the name of the Marketing Authorisation Holder, number of samples to be tested, batch numbers, reference materials provided by the manufacturer).

If an analytical procedure of the Marketing Authorisation Holder is available for the nitrosamines testing, the Test Protocol might contain more information regarding the technique and the System Suitability Criteria.

The Test Protocol allows that after the testing, the participating OMCL will be able to elaborate a testing report in a format of their choice, containing the strategy/technique used, a summary of the test(s) performed, results obtained and a conclusion if the nitrosamines tested are below the acceptance limits. An evaluation of the MAH analytical procedure will also be provided together with the test results, when applicable.

Step 7B: **Dispatching Samples / Test Protocols**

Dispatching samples and sending test protocols follow the PA/PH/CAP (05) 49 - General Procedure for Sampling and Testing of Centrally Authorised Products in its current version.

Step 8: **Testing Phase**

Testing is the responsibility of the participating OMCLs. For each product to be tested a Cooperation Agreement (framework contract) is signed between the EDQM and the testing OMCL(s). PA/PH/CAP (05) 49 - General Procedure for Sampling and Testing of Centrally Authorised Products in its current version describes the general terms and steps for the preparation of the Cooperation Agreement.

When the manufacturer's analytical procedure is applied for the testing, OMCLs are not requested to revalidate the procedure(s), since the validation has already been done by the MAHs. They are, nevertheless, requested to demonstrate the successful analytical procedure implementation (compliance with the system suitability criteria and/or assay acceptance criteria included in the test procedures with supportive documentation, i.e. chromatograms) and to verify the parameters of the analytical procedure (i.e. sample work-up and formation of artefacts, MS parameters etc.).

In case of out-of-specification (OOS) situations, further action might be needed in accordance with the procedure in place at the OMCL; any subsequent action is the responsibility of the EMA.

When the obtained result is above the established acceptance limit, and the Nitrosamine impurity is not specified in the MAH dossier, the actions to be taken will be discussed between the EDQM, the EMA and the testing OMCL.

It might be decided to involve the MAH in the discussion on outcome of the testing.

Step 9: **Test Protocol completed**

The participants complete and send back the results compiled in the Test Protocol together with type chromatograms and any comments in due time. These documents should preferably be uploaded onto the ACT platform.

The report is due at the latest 90 working days after receipt of the test samples, the date of receipt being documented in the Individual CAP Testing Template. An extension of the testing period may be granted on a case-by-case basis when needed (i.e. delay due to the complexity of the project, inhouse analytical procedure is applied additionally, or inhouse analytical procedure is developed for the testing programme).

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

Step 10: **CAP Testing Reports**

An abridged report compared with the regular programme containing specific technical parameters of the analytical procedure used 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.

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.

Year n and beyond

Step 12: **Annual status reports and Annual Reports to EMA/OMCLs**

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

Annual reporting will be in line with PA/PH/CAP (05) 49 - General Procedure for Sampling and Testing of Centrally Authorised Products in its current version.