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Monitoring of Stockpiled Medicines – Development of Technical Guidelines

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MONITORING OF STOCKPILED MEDICINES –DEVELOPMENT OF TECHNICAL GUIDELINES

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INTRODUCTION

Background

General considerations on monitoring of Stockpiled Medicines are addressed in the OMCL document PA/PH/OMCL (09) 05 "Stockpiling of Medicines – Monitoring – General Considerations" in its current version, first adopted at the Annual Meeting of the GEON in May 2009 in Vienna.

This document proposes to give a more technical approach to the establishment of a common monitoring programme which aims to provide confidence in the quality of stockpiled medicines, whether they are unlicensed or licensed products, to be used for a specified period of time beyond the approved shelf life.

Scope

When storing medicines for quick accessibility in case of emergency situations, there may be good reasons for extending the period during which the products are suitable for use, provided that the product remains within an acceptable quality (for decision-making on scientific grounds please refer to chapter "Support in decision making").

The scope of this document is to provide general technical guidance on the major issues, with respect to the OMCLs' contribution to the monitoring of stockpiled medicines (chemical and biological products), in order to propose, when scientifically justifiable, an extension of the period during which the products are suitable and safe for use.

The principles outlined below can also apply to Biologicals. However, in general they show higher variability and other considerations may have to be taken into account with regard to the continued use of the material. Many stockpiles of biological medicines are of vaccines or immunoglobulins for events that are expected to occur rarely if ever, such as outbreaks of eradicated diseases. The stockpiles may be held in ways different from those for chemical entities, and the assessment of their quality may be very different, for example in some cases being restricted to potency and visual appearance. In addition, the frequency of testing may be different and probably lower than for chemical entities. While this note may provide guidance for the assessment of stockpiles of biological medicines, the requirements should not be applied without careful consideration of their relevance for the material under question. For practical reasons this document does not give an exhaustive description of the elements involved in the management of stockpiled Biologicals, but only highlights items where specific adaptations are necessary due to the specificity of these products.

This guideline is not intended to be applied to medical devices. Nevertheless, it might be applicable to certain medical devices such as e.g. disinfectants.

Principle considerations

In order to monitor the quality of stockpiled medicines, an OMCL should conduct tests on samples and assess the data against the approved shelf life specifications. In the case of unlicensed products, the available data of pharmaceutical and other scientific sources should be used for the assessment.

Analyses performed by the OMCL should be carried out according to the marketing authorisation file, the European Pharmacopoeia or other standards regarding the quality, testing, storage, dispensing and designation of medicines.

For vaccines and blood products the selected test parameters for pre-use testing in connection with stockpiled medicines might differ from the OCABR guidelines applicable for the batch release, depending on the specific situation.

PLANNING FOR STOCKPILING AND QUALITY MONITORING

Preparation of the stockpile: Obtaining relevant information about the material to be stockpiled

The responsible body for stockpiling would need to collaborate with OMCLs in order to identify from the beginning the input of the OMCL in the stockpiling programme.

Care must be taken during the pre-procurement step of medicines to collect data, materials (i.e. reference samples of medicinal products, APIs, excipients, packaging materials) and other relevant information to conduct tests and assess the generated data. If the goal is to build a long term stockpile and there is a reasonable probability that an extension of the shelf life will need to be considered, extended real time stability data should be requested from the manufacturer (ideally from three batches) including a period after the approved shelf life. If the data is unavailable, the OMCL should test different expired batches provided by the manufacturer to investigate the possibility of eventually extending the period of use of the stockpiled product.

Storage of stockpiled medicines: minimum conditions to be requested

Ideally stocks should be stored in pharmaceutical premises under defined conditions. The storage conditions should be monitored by temperature/humidity recording loggers. These premises are normally subject to regular inspections by NCAs. Medicines are stocked in primary and secondary packaging, indicated in the MA file or equivalent documents prepared by the manufacturer (in the case of unlicensed products). Nevertheless, these products can also be stocked in different packaging designated for special storage purposes or for use in specific emergency situations.

Depending on the needs of the body responsible for stockpiling, stockpiles may be constituted of different types of materials (e.g. APIs, concentrated bulks, bulks, finished dosage forms). Moreover, the storage of stockpiled materials might fall under the remit of the bodies responsible for stockpiling or the manufacturer. When stockpiles are stored at the manufacturing site, the contract between the owner and the manufacturer should clearly state the details of the management and monitoring of the stocks.

Evaluation of information to establish monitoring needs

A risk based approach needs to be taken into account in order to determine the products that may be eligible for monitoring. The outcome of this risk based management should be clearly documented.

Different Member States may have different approaches when defining the risk profile. Elements to be considered include:

- Pharmaceutical form (with special attention to solutions)
- The amount of material available for the stock and the number of units dedicated for testing
- Products with release and shelf life specifications which differ (e.g. API content and impurities level)
- Products containing excipients whose physico-chemical properties might change during storage (hardening, hydrolysis of preservatives etc.)
- Review of the stability study of the MA file
- Quality of packaging for product protection
- Review of storage conditions (e.g. temperature, humidity) from inspection or monitoring reports
- Patient target population (children, adults, geriatric people)
- Availability of (approved) alternative products and life-threatening risks for patients (if product is not available or usable).

As a preliminary step, a scientific evaluation of the available stability studies performed by the MAH/manufacturer should be undertaken. Special attention should be paid to different parameters such as formulation, purity, API content etc.

Special care and a specific approach should be taken for stockpiled medicines without MAs, for products without initial stability studies according to ICH and for approved products without a labelled shelf life, for which nevertheless the manufacturing date is known.

Control of inventory and sampling strategy

For each product, an exact qualitative (e.g. manufacturing date, expiry date…) and quantitative inventory of the stock to be monitored should be available in order to be able to take and analyse samples at selected premises.

Specific appropriate national procedures could be put in place, in conjunction with the OMCL to sample the products in accordance with the respective instructions; special authorisations may be needed. The quantity of samples necessary for each analysis would have to be determined.

It must be taken into account that for samples which will be monitored over several years, the initial quantity of the stock should be known and a certain quantity of samples should be preserved for analysis. The samples for analysis should be located in the same controlled pharmaceutical premises as the stockpiles.

Further to the above "evaluation of information" and in the case of stability problems or inappropriate storage conditions, the totality of the stockpiled medicines or some specific parts of the stock may be removed from the monitoring programme. If this occurs the monitoring programme would need to be restructured taking into account the new situation.

Exchange of information

It is of importance to exchange technical information on the testing of stockpiled medicines within the OMCL Network, and stakeholders have to be involved, where relevant.

MONITORING OF PRODUCT QUALITY

The monitoring study performed by the OMCL is intended to verify the quality of the stockpiled medicines.

Monitoring programme

For each product (including different manufacturers) the batches or part of batches included in the monitoring programme should be clearly identified (name of the product, MAH/manufacturer, batch number, manufacturing date, expiry date, localisation and storage conditions, stock size).

Sampling plan

Samples must be representative of the batch or part of the batch stocked in the premises. Reasonable quantities of samples for testing have to be determined on the basis of case-by-case evaluation. Sampling should be planned just before testing (e.g. no earlier than 3 months before the testing). Careful attention should be paid to the transport of the samples.

If new batches are purchased, their quality should be evaluated before being added to the stockpile. Records and storage should ensure that batches procured at different times and with different expiry dates are identifiable and treated accordingly.

As an alternative the initial sampling of stockpiled medicines may be used for ongoing stability testing (1) with storage under ICH long term conditions (2). The continuous evaluation of possible changes of properties may be used for the proposal of re-test dates.

Testing plan

The following two steps could be put in place for the testing plan but other approaches are also possible. During the establishment of a testing plan the available information (storage history, location, extrapolation by statistical analysis from existing data (3), etc.) on the product should be taken into consideration.

The testing plan and the periodicity of the monitoring may evolve or be modified on the basis of extrapolation from existing data using statistical analysis and/or from on-going evaluation. Nevertheless in some cases, the limited quantities of stockpiled material may have an impact on the decision about the testing strategy and this should be taken into account.

Preliminary phase

In this phase, the OMCL performs tests of samples of all the batches (not expired or expired, in cases where no other material exists) selected and included in the monitoring programme if the number of samples permits. This preliminary control step could allow the withdrawal of all "out of specification" batches from the monitoring study.

In case of different storage conditions (i.e. well-controlled vs. uncontrolled, different climatic zones), one or more samples from a same batch might be included in the monitoring study to address a possible localisation effect on the stockpiled medicines' quality and preservation.

Monitoring phase

In this phase, a defined number of batches are selected in order to follow the real stability of the product.

For newly constituted stockpiles, the monitoring phase should start with batches as close as possible to their manufacturing date or as early as possible after procurement of the stockpiles. The monitoring phase should at minimum include also testing in the middle and at the end of the shelf life in order to have sufficient monitoring data. Based on the monitoring data, an extrapolation of the manufacturer's shelf life might be carried out by statistical analysis to propose, if needed, an extension of the period during which the products are suitable for use.

For already constituted stockpiles, among the batches controlled in the preliminary phase, a relevant number of representative batches per product (number of batches to be established in the sampling plan as near as possible to their authorised shelf life, and located at representative premises) are selected and followed up. These batches are controlled at pre-determined intervals (e.g. once a year) based on the knowledge of real-time stability data from expired batches and, if possible, extrapolation by statistical analysis from existing data. With this information and with the last monitoring data point, the period during which the products are suitable for use can then be extended, if justifiable.

If very old batches exist (older than the authorised shelf life) these batches could be added to the monitoring phase, in order to evaluate the quality of the product after its expiry date.

Parameters to be considered for testing or other evaluation

For initial control (quality control of the stock of the monitored product), physico-chemical analyses might be performed. For yearly monitored samples (quality assessment of the product year after year), depending on the dosage form, physico-chemical parameters and pharmaceutical-technological tests [such as assay, impurities, dissolution test (tablets, capsules etc.), pH (liquids), osmolality (infusions or eye drops), integrity of packaging, readability of labelling etc.] and microbiological controls (such as microbial contamination for oral or topical formulations, integrity of primary packaging material or sterility for parenteral medicines) could be planned.

Chemical pharmaceuticals are usually assayed by well understood physico-chemical methods that can be expected to give the same result over time. But for stockpiles of biological medicines, the parameters to be considered for testing might differ from others products. Biological pharmaceuticals are not fully defined and are usually assayed by complex biological methods that include a reference material closely resembling the material to be analysed. The selection of relevant assays to carry out for a defined product should be established based on the marketing authorisation (for licensed products) and/or with the help of the European requirements for Biologicals such as the OCABR guidelines and the European Pharmacopoeia monographs. Regarding reference materials, they could be as unstable as the stockpiled medicines themselves. The stability of International Reference materials is studied at the time of establishment and every effort is made to ensure that potency will not be lost over its lifetime. This is not necessarily true of lower order reference materials.

For other biological materials where the stability of the reference has been established, a replacement reference will be prepared before the original material is exhausted and will be calibrated against this old one. There will be unavoidable errors involved in the calibration of the new material against the old one. This should be taken into account in interpreting the results.

Depending on both the manufacturing process and the formulation of the biological product (intermediate products or final dosage form), a different approach may be conceivable for initial quality control testing and follow-up testing with the agreement of the body responsible for stockpiling. The OMCL may propose a strategy for the follow-up testing based on sound scientific judgement taking into account the knowledge of the product, any data generated previously and extrapolation by statistical analysis. In general the OMCL should focus on quality testing (*in vivo*[1] and/or *in vitro* potency, antigen content, bacterial endotoxins content and moisture for freeze-dried products), but in some specific cases additional safety testing is conceivable (e.g. sterility). For a freeze-dried product, the stock of the solvent intended for reconstitution should also be monitored with respect to physico-chemical and/or microbiological parameters (see above).

[1] For 3R reasons in vitro methods should be favoured whenever possible.

Reporting

For stockpiled batches, during the preliminary phase, test reports should be established for each tested sample.

For batches selected for the monitoring phase, a control chart with yearly results would allow the evolution of the different parameters to be followed in relation to the specifications.

Each year of the monitoring phase and for as long as the results of the selected batches are considered satisfactory, a yearly[1] extension of the period of suitability for use could be proposed. This proposal would clearly indicate the name of the medicine and the identification numbers of all stockpiled batches (or part of the batches) selected after the "preliminary phase" tests which could be considered for an extension of the period during which the products are suitable for use.

Support in decision making

The decision making and the responsibility for decisions on the future storage and the potential use of a stockpile lie with the owner/responsible body of the stock of the product. Nevertheless, the OMCL contributes to the decision making process through its knowledge of the product, and by the provision of concrete data collected through testing and possible extrapolation by statistical analysis. To support decision making, the OMCL may give recommendations and propose actions to the body responsible for stockpiling which then makes a decision and takes actions.

In the case of monitoring selected batches with satisfactory results, all the controlled batches from the preliminary phase might be eligible for extension of the period during which the products are suitable for use, for a defined additional time interval beyond the approved shelf life.

In the case that one or more of the monitoring products (batches) are found OOS with a relevant safety impact[2], the following step-by-step approach should be taken:

1. Investigation of the OOS (performed as described in the OMCL's own Quality System)
2. If the OOS is confirmed, the root of this OOS should be further investigated:
    a. OOS due to degradation during storage (known instability of the product)

       Possible Recommendations:

       - Destruction of the batch.

       Proposed Action:

       - It may be necessary to re-evaluate whether this product is really eligible for stockpiling (e.g. if samples of the same batch tested from different sites are also OOS).

    b. OOS due to degradation during storage but caused, for instance, by improper storage

       Possible Recommendations:

       - Destruction of the affected material.

[1] Other intervals are possible e.g. twice a year, every second year etc.

[2] Examples for OOS results with minimal safety impact after scientific assessment might be the deviation of hardness or colour of tablets.

Proposed Action:

- As this might only affect the products stored at a specific site, but not necessarily the whole batch, provided that it was properly stored at other sites (e.g. if the same batch from others sites comply with the given specifications), corrective action should be implemented to improve the storage conditions at the concerned site.

3. During the follow-up step, if one or more of the batches in the stockpile are found OOS

   Possible Recommendations:

   - After a scientific assessment of the results, the decision whether the monitoring study should be stopped.

   Proposed Actions:

   - In case of stopping the monitoring, the period during which the products are suitable for use should not be further extended, and preference should be given to the renewal of the stockpile.

4. In the case of the destruction of a batch, lack of supply might occur:

   Possible Recommendations:

   - A decision would have to be taken on a case-by-case basis, together with the regulatory authorities, as to whether the batch could be stored/used until a new supply became available. This decision (risk/benefit) might be influenced by several factors: results (e.g. level of degradation), safety concerns, dissolution/bioavailability, others.

5. For Biologicals different considerations might apply in case of an OOS situation:

   Possible Recommendations:

   - A case-by-case evaluation with a risk benefit analysis may be necessary for the final decision to destroy the batch, notably when the renewal of the stockpile is not possible (no existing manufacturer). Depending on the composition of the stockpile (intermediate products or final dosage form), an adapted usage of the product might be proposed by the OMCL and be considered by the body responsible taking into account the original requirements, e.g. for intermediate products: adaption of the formulation/blending of the final product taking into account the potency of the intermediate found during the last potency assay; for final dosage forms: use of the product as a booster only, or to adapt the volume of injection to the potency found during the last potency assay.

Quality management measures

As far as possible all tests conducted by the OMCL should be in accordance with ISO/IEC 17025 in its current version. However, in specific circumstances (e.g. for old biological stockpiles) the required and official tests may not be performed on a regular basis by the OMCL: consequently, with a justified exemption, the monitoring may not be conducted in total accordance with ISO/IEC 17025, provided that traceability of the decision is guaranteed. In case monitoring cannot be conducted completely in accordance with ISO/IEC 17025, the OMCL is invited to check (through the GEON) the possibilities of performing the test in accordance with ISO/IEC 17025 by another OMCL.

REFERENCES

(1) WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty seventh report (WHO technical report series).
(2) ICH Q1E (Evaluation for stability data).
(3) WHO/BS/06.2049: Guidelines on stability evaluation of vaccines.

ABBREVIATIONS

API – Active Pharmaceutical Ingredient
EDQM – European Directorate for the Quality of Medicines & HealthCare
GEON – General European OMCL Network
HMA WGPT – Heads of Medicines Agencies' Working Group on Product Testing
ICH – International Conference on Harmonisation
IEC – International Electro-technical Commission
ISO – International Organisation for Standardisation
MA(H) – Marketing Authorisation (Holder)
NCA – National Competent Authority
OMCL – Official Medicines Control Laboratory
OOS – Out of Specification
WHO – World Health Organisation.