Drafting Group on stability of vaccines guidelines: Report of the 2\textsuperscript{nd} meeting

WHO, Geneva, Switzerland
16-17 June 2004
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Annex 1 Contents of the guidelines

I  Introduction

The First Meeting of the WHO drafting group on Stability of vaccines guidelines was held in Paul-Ehrlich-Institut, Langen, Germany on 7-8 February 2002, report of which has already been presented to the ECBS. However, the survey of stability testing of different types of vaccines was needed for further considerations of the guidelines.

On 16-17 June 2004 the second meeting on the stability of vaccines issues was held at WHO, Geneva. The meeting was opened by Dr. David Wood, Coordinator, QSB, WHO, Geneva. Dr. Wood acknowledged that stability of vaccines present a very complex field with a scientific basis often not well understood, since characterization by physico-chemical parameters often is difficult.

Dr. Ivana Knezevic, QSB, WHO, gave an overview on the process of drafting guidelines and proposed method of work in the assessment of the stability data collected for the purpose of this meeting. The intention of the second meeting was to review and assess stability data of different bacterial and viral vaccines and to identify relevant information to be included in the draft guidelines.

The aim is to prepare draft guidelines for broad consultation with the representatives from vaccine industry, NRAs and other experts involved in the evaluation of stability of vaccines in 2005. Key issues in the development of this guidelines will be presented to the ECBS at its meeting in 2004.

Dr. Haase (Germany) and Dr. Dobbelaer (Belgium) chaired the meeting and Dr Andreas Merkle (Germany) was appointed rapporteur. They provided an overview of the current approach for stability testing in Europe. Dr. Haase gave a short overview of the ICH guideline for biotechnological/ biological products highlighting that the useful principles should be considered in the development of WHO guidelines. In addition, specific issues related to vaccines, not considered in the ICH guidelines, should be discussed in the WHO document. However, WHO guidelines should have a broader scope, including the issues relevant for all vaccines. Dr Dobbelaer mentioned CPMP Concept paper on stability and traceability requirements for vaccines intermediates (CPMP/BWP/4310/00) as useful guidance developed to assist manufacturers in their development programs. The
The impact of long-term holding periods of vaccine intermediates is considered relevant for WHO guidelines.

The following points were discussed:

- Structure and content of the guidelines
- Design of stability studies (Live attenuated vaccines / inactivated vaccines)
- Scientific basis for thermal stability test
- Stability of source materials (seeds) and intermediates
- Stability of final bulk and final lot
- Stability of reference materials
- Safety aspect in stability studies / stability of vaccines in PMS
- Conclusions and next steps

II Structure and content of the guidelines

Drafting group agreed on the structure and content of the guidelines proposed at the first meeting of drafting group in Langen with some additional points such as potential extension of shelf life. A need for guidance for stability testing of reference materials was emphasized.

The following sections will be included in the guidelines:

1. Introduction
2. Glossary
3. Scope
4. General considerations
5. Design of stability studies (issues to be considered in the design of studies):
   - different approaches
   - testing frequency
   - evaluation of the results, including e.g., trend analysis
   - expression of results (quantitative results with confidence intervals, where applicable) and meaningful calculation (statistical)
- protocol (sample selection, matrixing, bracketing, position of test samples etc)

Vaccines to be included in the review of examples in this section:

- Viral - live attenuated (OPV, Yellow Fever, Smallpox, MMR)
- Bacterial (Oral Cholera, BCG, Oral Typhoid)
- Non live Viral (Rabies, IPV, JE, TBE, Hep A, Hep B)
- Non live Bacterial (DTwP, DtaP, conjugated vaccines)

6. Combination vaccines

7. Thermal stability

8. Labeling (including the use of VVM)

9. Stability of reference preparations

III. Conclusions of the discussion

Stability of vaccines guidelines aim on preventive vaccines used against infectious diseases, therapeutic vaccines are not considered to be in the scope.

Current understanding of the stability evaluation of vaccines is going beyond the thermal stability (accelerated degradation test) at the stage of final lot.

Real time, real temperature and real conditions studies are recommended to support shelf life of the vaccines.

Definition of intermediates should be developed and included in the glossary. Determination of shelf - life is recommended for all stages of production which includes source materials as viral / bacterial / cell seeds as well as intermediates (single harvest, monovalent bulk, final bulk).

Cumulative stability data should adequately support the use of intermediates up to the end of their approved storage time and conditions and up to the end of the shelf life in the finished product.

For inactivated vaccines, same principles as for live attenuated apply for but stability parameters are much more complex and include toxicity related parameters as well as potency tests.

Product specific list of parameters and testing frequencies should be included to give detailed guidance to manufacturers on how stability studies should be performed.
More detailed guidance on stability testing of international standards and reference preparations should be provided.

Stability of vaccines guidelines should include also tests to be performed for lot release and after reconstitution of the product.

Complete stability studies are not to be expected at licensure, but should be continued in PMS to confirm proposed retest period and other parameters.

IV List of participants:

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Dr David Wood, Coordinator, QSB
Dr Joele Daviaud, ATT
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Dr Carmen A. Rodriguez Hernandez, ATT
Dr Ivana Knezevic, QSB
Dr Sabine Kopp, QSM (Unable to attend)
Dr Scott Lambert, QSB
Dr Jin-Ho Shin, QSB
IV Questions to the ECBS on the selected issues of concern

Drafting group need the input from the Committee on the following issues:

1. Should shelf-life be assigned to all stages of production?
   a. Source materials (viral and bacterial seeds; cell seeds)
   b. Intermediates (single harvest, monovalent bulk, final bulk)

2. What should be the basis for assigning shelf-life for final lot?
   a. Real time real condition stability study
   b. Accelerated degradation test
   c. Other options

3. How to evaluate stability of reference preparations
   a. Long term stability study, with active monitoring at least once per year?
   b. Should shelf-life be assigned to:
      1. IS and RR
      2. Working standards?

4. What should be in the recommendations for particular vaccine in question (in TRS)?
   a. Recommendation for stability test for licensing and lot release
   b. Recommended use of vaccine after reconstitution
   c. Recommended parameters to be monitored in the stability study?
Annex 1 CONTENTS OF THE GUIDELINES

1. Introduction

1. The following text is written in the form of guidelines instead of recommendations in view the fact that vaccines represent a heterogeneous class of agents, and the stability testing will need to be adapted for the product in question. Guidelines allow greater flexibility than Recommendations with respect to specific issues related to particular vaccines.

2. WHO guidelines are scientific in nature and should provide principles for evaluation of stability based on the scientific evidence.

3. This guidance document is intended to assist Vaccine manufacturers and National Regulatory Authorities in the design, conduct and evaluation of stability of vaccines. Also, it could serve as useful information for the staff in immunization practice. Therefore, the lessons learned in immunization practice are also being considered.

4. Current understanding of stability of vaccines: focus on real time real temperature and real conditions stability data and limited value of accelerated degradation test. Concept in the past was based on the requirement for thermostability (accelerated degradation test). Therefore, in the requirement and recommendations for production and control of vaccines, stability was primarily considered as thermostability measured by potency test, at the stage of lot release. In this guideline, stability of vaccines is discussed with respect to two time points of vaccine manufacturing: licensing and lot release. Also, thermostability is discussed as a part of broader stability assessment, which includes different parameters in addition to potency.

5. Common issues for different classes of vaccines should be discussed in this document (live attenuated, inactivated, polysaccharide and conjugate etc).

2. Glossary

Terminology used within the context of the WHO guidelines on stability of vaccines:

Stability
Thermal stability
Intermediates
Accelerated degradation test
Shelf life
Maximum storage period
Single harvest
Monovalent bulk
Final bulk
Final lot
Intermediates
Storage period
Usage period

3. Scope

For the purpose of this document, vaccines are considered a heterogeneous class of medicinal products containing immunogenic substances capable of inducing specific, active and protective host immunity against infectious disease.

While the majority of vaccines are being developed for pre- and post- exposure prophylaxis, in some cases, they may be indicated for therapeutic use against infectious diseases, e.g., HIV, HPV etc. Both prophylactic and therapeutic vaccines for infectious disease indications are considered in this document.

Vaccines for human use include one or more of the following: micro-organisms inactivated by chemical and/or physical means that retain appropriate immunogenic properties; living micro-organisms that have been selected for their attenuation whilst retaining immunogenic properties; antigens extracted from micro-organisms, secreted by them or produced by recombinant DNA technology; chimeric micro-organisms; antigens produced in vivo in the vaccinated host following administration of a live vector or nucleic acid or antigens produced by chemical synthesis in vitro. The antigens may be in their native state, truncated or modified following introduction of mutations, detoxified by chemical or physical means and/ or aggregated, polymerised or conjugated to a carrier to increase immunogenicity. Antigens may be presented plain or in conjunction to an adjuvant, or in combination with other antigens, additives and other excipients.

Also included within the scope of this document are novel products such as DNA vaccines and live genetically engineered microorganisms used as vaccines themselves or as carriers for other antigens. However, therapeutic vaccines (e.g., viral-vector based gene therapy, tumor vaccines and anti-idiotypic vaccines such as monoclonal antibodies used as immunogens) are NOT considered here.
4. General considerations

Stability studies on medicinal products in general are conducted to determine or modify a maximum shelf-life, storage period or usage period\(^1\) of starting materials, intermediates, drug substance and drug products, under given environmental conditions (e.g. temperature, light, relative humidity, container/closure etc). Stability studies are an important part of the documentation to be submitted to the competent authorities in the framework of a Marketing Authorisation Application (Product License Application). In some cases, stability testing is also part of batch release testing (e.g. thermostability testing of live viral vaccines).

The purpose of stability studies is to guarantee that the medicinal product, at the end of its shelf life, storage period or usage period, still has the required characteristics supporting quality, safety and efficacy. Usually, the stability of a number of quality parameters (stability-indicating parameters) is studied but in some cases, pre-clinical and/or clinical studies may have to be included. The concept of stability may also be extended to genetic stability (e.g. stability of a recombinant genetic construct). The potential clinical implications of the observed changes must always be considered.

For biological medicinal products such as vaccines, a number of specific considerations have to be taken into account when designing stability studies. Such considerations include the inherent sensitivity of biological substances to changes in environmental conditions, the importance of tests reflecting the potency and their degree of uncertainty and the fact that, in general, a single parameter is insufficient to document stability and that a stability profile has to be set up. In addition, considerations of microbiological aspects such as bioburden or sterility of intermediates or finished products and effectiveness of antimicrobial agents may have to be addressed.

NRA should ensure that the appropriate stability studies have been performed at all stages of production and adequately support the proposed conditions for storage for licensing.

Stability of source materials and intermediates

- Source materials: no stability tests are recommended in ICH- or other guideline
- Stability expert reports provided by PEI focus on active ingredient & finished product level only.
- WHO requirements for e.g. polio include control of source material, control of cell seeds & control of virus MS + WS.
- Several biochemical / immunological parameters should be measured.
- Proposal for guideline: separate paragraph to explain problems, viral & bacterial cell seeds to be monitored, but no description of tests to be used.

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\(^1\) In this text, shelf-life is used for the finished product, storage period is used for starting materials and intermediates and usage period is used for the period of time that the finished (possibly reconstituted) product is used.
Stability of final bulk/ final lot should be determined, parameters to be measured defined and specifications set. Potency data should be generated using aged vaccines in addition to those stored at recommended temperature. Non-clinical and clinical performance may provide useful information with respect to the stability of final bulk/lots.

For lot release, a critical evaluation of production and control protocols would allow verification of the compliance with the stability specifications set in the manufacturer's dossier on a lot-to-lot basis.

Safety aspect in stability studies should also be considered and specifications defined at the licensing stage. Stability of vaccines should be monitored as part of PMS to confirm proposed retest period and other parameters. Guideline on stability testing of new drug substances and products Q1A (R2) should be considered for this issue.

This section should be expanded with the discussion on the following points: pre and post-licensing monitoring of stability (refer to ICH); cumulative stability; stability of reconstituted vaccines and assurance of stability during the shipment.

5. Design of stability studies (live attenuated / inactivated)

Parameters to be monitored depend on the class of product and will be discussed under the relevant sections.

For intermediates, maximum storage period and conditions should be clearly defined and adequately supported by stability data.

Cumulative stability data should adequately support the use of intermediates in the next stage of production at their approved maximum storage, time and conditions).

5.1. Live attenuated

Stability testing should be performed at different stages of production (single harvests, monovalent bulks, multivalent bulks, final bulk and final lot).

In particular, for multidose presentations, stability after reconstitution should be tested and documented to reflect in use stability. Stability should be adequately tested and documentation provided for each of the stages mentioned as appropriate for the product under consideration.

- Parameters: titre measured by potency, in some cases genetic stability should be considered as a part of stability study (e.g., OPV, rotavirus, mumps, rDNA constructs, etc.)

- Use of certain excipients such as albumin or other excipients of biological origin require traceability of their origin throughout the storage period of intermediates
and shelf life of the finished product. With respect to the safe sourcing, reference should be made TSE guidelines.

5.2. Non live vaccines

Same principles apply as above but stability parameters are much more complex and product specific and include toxicity related parameters as well as potency tests. Product specific list of parameters and testing frequency should be included.

6. Combination vaccines

This section will discuss requirements for stability data of each component of the combination vaccine with respect to the shelf life at the time of combination process. The issue of cumulative stability will also be considered.

7. Thermal stability test

Scientific basis for the requirement for thermal stability test has to be elaborated in the document. If appropriate, thermal stability tests should be performed for both live and inactivated vaccines. This test should allow recognizing trends by measuring relevant parameters of the vaccine in question (e.g., potency).

Factors, which could compromise stability, such as repeated heating and cooling, light, freeze-drying, should be defined for particular type of vaccine. Recommendation to manufacturers should be given with respect to the exposure of particular vaccine to the factors mentioned above in the design of stability testing programme.

Thermal stability test should comply with end of shelf life test.

With respect of intermediates, accelerated stability testing is useful only on a case-by-case basis.

8. Labelling

Details to be included in the label: expiry date, storage time and conditions, protection of light etc. Labeling (appropriate quality of label) should be adequate for the proposed storage (freezing etc).

Use of Vaccine Vial Monitors (VVM) should be discussed in this section, providing guidance to the NRAs on different types of VVM, the appropriate use and the interpretation of the information obtained by VVM.

This section is under development. The issues raised at the discussions on the recommendations for the production, characterization and establishment of International and other standards for reference materials of biological origin will be taken into account.

References

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