Drafting Group on Stability of vaccines guidelines: Report of the 1st meeting

Paul Ehrlich Institute, Langen, Germany
7-8 February 2002
1. INTRODUCTION

The First Meeting of the WHO drafting group on Stability of vaccines guidelines was held in Paul Ehrlich Institute, Langen, Germany, on 7-8 February 2002. Participants of the drafting group on Stability of vaccines guidelines were Dr. Elwyn Griffiths, Dr. Roland Dobbelaer, Dr. Michael Pfleiderer, Dr. Ivana Knezevic and Dr. Maria Angeles Cortes (unable to attend this meeting).

The meeting was opened by Dr. Elwyn Griffiths, Coordinator, QSB, WHO, Geneva. Dr. Griffiths acknowledged that stability of vaccines present a very complex field since the majority of them cannot be well characterized by physico-chemical parameters and they are, by nature, very susceptible to inactivation by environmental factors. The fact that vaccines are intended for use mostly in healthy children makes regulatory issues, which includes vaccine stability, extremely important.

The importance of standardization is a main issue and the stability of standards need to be considered well in advance to be able to measure relevant parameters for stability of vaccines.

The Expert Committee on Biological Standardization at its 49 meeting (October 1997) was informed that the International Conference on Harmonization had prepared guidelines on stability testing of biotechnological and biological products. The Committee noted that biological and biotechnological products can be particularly sensitive to environmental factors, and that the analysis of their stability can require complex methodologies. The ICH guidelines outline a useful approach to the stability testing of such products, which include well characterized proteins and polypeptides, their derivatives and products of which they are components, as well as products isolated from tissues, body fluids or cell cultures, or produced using recombinant DNA technology. The need for specific WHO guidelines on stability of vaccines was emphasised by the Expert Committee on Biological Standardization at its 51st meeting in October 2000.

Dr. Manfred Haase welcomed the Group to the Paul Ehrlich Institute and endorsed their initiative to develop such important guideline since there is no document which specifically covers the broad field of vaccine stability.

The proposed agenda for this meeting includes 4 sections:
- review of the existing guidelines/papers relevant to the stability of vaccines (see below)
- discussion on major issues and proposals that need to be covered, concept
- drafting document - title, structure and format of the document
- next steps - plan of action

1 REVIEW OF EXISTING GUIDELINES/ PAPERS
I section: Review of existing guidelines and relevant papers

Dr. Haase mentioned that was a debate during the development of ICH Tripartite Guidelines on stability regarding the inclusion of all vaccines. It was decided they should not be included in the document. The ICH guidelines covers only vaccines based on well characterized proteins and polypeptides produced by rDNA technology. There was a concern that covering vaccines would delay finalisation of the document. This is the reason for narrow scope of ICH guideline on stability of biotechnological/biological products. It will be revolutionary if WHO will cover consideration of seed stability and other specific issues which are not considered in ICH guidelines (1, 2).

ICH:Q5C-biotech: page 4: section 5: “On the whole, there is no single stability-indicating assay or parameter that profiles the stability characteristics of a biotechnological/biological product. Consequently, the manufacturer should propose a stability indicating profile that provides assurance that changes in the identity, purity and potency of the product will be detected”.

This statement was discussed and group proposed to add toxicity to the above mentioned changes in the identity, purity and potency. The reversion of toxicity of toxoids or reversion to virulent state of live attenuated viruses need to be considered in stability indicating profile.

Structure in ICH guidelines stability of biotechnological/biological products:

1. Preamble
2. Scope
3. Terminology
4. Selection of batches (drug substance (bulk material), intermediates, drug product (final container product), sample selection criteria
5. Stability-indication profile (protocol, potency, purity and molecular characterization), other product characterization
6. Storage conditions (temperature, humidity, accelerated and stress conditions, light, container, stability after reconstitution of freeze-dried product
7. Testing frequency
8. Specification
9. Labelling

European Pharmacopoeia position on stability of vaccines was also discussed: "Maintenance of potency of the final lot throughout the period of validity shall be demonstrated by validation studies: the loss of potency in the recommended storage conditions is assessed and excessive loss even within the limits of acceptable potency may indicate that the vaccine is unacceptable. During developmental studies, the effectiveness of the antimicrobial preservative throughout the period of validity shall be demonstrated to the satisfaction of the competent authority. From the stability data generated for the vaccine it must be shown that at the end of the period of validity the degree of adsorption will not be less than for batches used in clinical testing."
Expire date. Unless otherwise stated, the expire date is calculated from the beginning of the assay. It applies to vaccines stored in the prescribed conditions”.

WHO: Brief review of requirements for stability testing in WHO guidelines for production and control of particular vaccines cover only stability as a part of lot release system and the potency and reversibility to toxicity were the parameters to evaluate stability of vaccines. These requirements vary in the content depending of the type of product. Currently, there is no WHO guidelines which covers a broad field of vaccine stability.

II DISCUSSION ON MAJOR ISSUES WHICH NEED TO BE COVERED IN WHO GUIDELINES

1. Main issues on stability of vaccines are:

a) Stability of intermediate products
   • testing vaccine by the end of shelf life, with 25 –30 different intermediates could be difficult approach

b) Cumulative Stability
   • For intermediates and final products a shelf life needs to be defined. Validation of this shelf life should cover the total age of the different intermediate components at the end of the shelf-life of the final product in which they are used.

c) Stability studies for licencing
   • accelerated stability studies and real time stability studies
   • changes in the formulation of vaccines already licenced
   • stability of combination vaccines

2. Stability with respect to different types of products

   • Bacterial vaccines
   • Viral vaccines
   • Highly characterized vaccines

   3. Stability profile

Stability profile depends of number of factors such as the way of manufacturing and complexity of intermediates and nature of excipients and in that sense each product need to be considered case by case.

   • What could be measured in addition to potency
   • Common tests for several groups of vaccines
   • how to measure stability indicating parameters and how to interprete these results
   • Stability programme for setting shelf-life (real time stability study)
   • Comparability of data in certain period of time

4. Design of stability studies
• Stability under the stress conditions (for mumps and polio it is difficult to define maximum loss of potency)
• specificity and accuracy of these tests

5. Stability of source materials (seeds)
• distinction between stable seed and non stable seed, how to measure genetic stability (e.g., mumps vaccine)

6. Stability of standards
• Standards – is reference vaccine enough
• do we need "new" standards for stability testing

7. Factors which could compromise stability
• heating and cooling several times, light deterioration, freeze drying

8. Safety and efficacy aspect
• how to measure potential toxicity in stability study
• is full characterization of the product enough
• What sort of stability data would be required to get approval for conducting clinical trials
• Clinical significance of the stability testing results and their interpretation- for new vaccines clinical data need to be considered and would be required to show clinically that vaccine is of the same efficacy by the end of shelf life as it was on the beginning
• there is a big difference between minimal clinical effective dose and optimal dose and there are a lot of factors which influence on this effective dose
• stability of GMO, genetic stability, immunological profile

9. Thermal stability and use of VVM

10. Stability of vaccines in post-marketing surveillance
• we can not expect completed stability data for licensure, some data might be completed as a part of post-marketing surveillance

11. Combination vaccines
• data on stability testing of the components presented in the form of tree

12. Excipients
Excipients in the final products: preservatives, stabilizers
• Albumin
- what does the expiry date of albumin for therapeutic use mean in relation to the the expiry date of albumin as a stabilizer (experience with recombinant albumin for human vaccines: antibodies to recombinant albumin have been shown and could cause a problem (similar story with interferon and factor VIII natural and recombinant).
The question is: Is it necessary to replace safe product with a product of unknown safety to meet theoretical safety consideration?
- what is the basis to define shelf life of albumin?

13. **Stability of complex vaccines**: complex manufacturing process and/or complexity of components, way of formulation /absorption (rotavirus for example)

- **CONCEPT OF THE DOCUMENT:**

1. General issues - for all vaccines
2. Specific issues – related to different types of vaccines
3. Special considerations for combination vaccines
4. Special considerations for GMO products

Stability need to be considered on different stages of vaccine production:

- Starting materials
- Intermediates
- Final products
- After reconstitution

Stability data required before licensure and licensure package need to be considered.

New products vs already licensed products with already evaluated antigens and/ or excipients (few subgroups under this) should be covered.

**CONCLUSIONS:**

1. Need to have stability of vaccines as a one document, including thermal stability (TS)
2. To address the issues of thermal stability to the TS group for consideration
3. Survey of stability data in the product summary file: to review all available stability data submitted for licensing to see type of data submitted and to develop questionnaire with parameters measured for stability indicating profile
4. To consider stability through different types of products

**III DRAFT - TITLE, STRUCTURE AND FORMAT OF THE GUIDELINES:**

- **Proposed title for the document:**
  - WHO guidelines on stability testing of vaccines

- **Proposed title for the Consultation:**
• Consideration on stability testing of vaccines

• How to categorize vaccines - inactivated, live attenuated or…
  • live attenuated, …or …will be based on survey results

INTRODUCTION:

1. **Purpose of the document** to help NRAs and manufacturers in planning, designing, performing and interpreting stability studies during development of vaccines as well as for licensure procedure and post-licensure surveillance of vaccines.

2. **The reason why vaccines deserve special consideration in addition to all pharmaceuticals:**
   • Stability of vaccine present a very sensitive field since majority of them cannot be well characterised by physico-chemical means.
   • Since the vaccines are given mostly to healthy children - regulatory issues are extremely important.
   • In the field of biologicals, including vaccines, the importance of standardization is a main issue and the stability of standards need to be considered well in advance to be able to measure reliably relevant parameters for stability of vaccines.
   • Clinical significance of changes seen in stability tests.

3. Stability as a stand alone doesn’t mean a lot and we cannot predict all potential problems, so we need to deal with the **groups of products** of particular vaccines.

**SCOPE:** all vaccines (definition in clinical) specific issues for several types of vaccines, special considerations for combination vaccines, for GMO (live cholera, dengui).

**ANNEX:** There is a need to develop annex of the document with the **List of tests which need to be considered in development of stability profile for particular products.**

**QUESTIONNAIRE:** need to be developed consulting Common Technical Document and reviewing manufacturers dossier (Roland-GSK, Florence – Aventis, France, Michael and Manfred - Chiron, Merck, Akira Homma-Brazil, Maria Angeles – Mexico, Chris Rolls-Australia, Reigel – Swiss Medic), and looking at the informations from pre-qualification procedure (Nora). Data would be anonymous. There is no need to review the results from these stability studies.

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**STABILITY OF VACCINES**
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<tr>
<th>SECTION</th>
<th>SUBSECTION</th>
<th>Resp. Officer</th>
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<td>1</td>
<td>INTRODUCTION</td>
<td>Purpose of the document, specificity of vaccine production and related stability issues, scope of the document</td>
</tr>
<tr>
<td>2</td>
<td>GENERAL PRINCIPLES</td>
<td>To write down few sentences about: - Starting materials - Intermediates - Final products - Combination - GMO - Clinical relevance - Setting shelf-life - Variation (changing the formulation) - Excipients and its shelf life</td>
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<td>3</td>
<td>DESIGN</td>
<td>-different approaches/ stress testing -testing frequency -evaluation of the results -protocol (sample selection etc.)</td>
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<td>4</td>
<td>SPECIFIC ISSUES FOR TYPE OF THE VACCINES</td>
<td>-types of vaccines and type of tests (specification) -old vaccines, novel vaccines and complex vaccines -Thermal stability -Combination vaccines</td>
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<td>REFERENCE PREPARATION</td>
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**IV  NEXT STEPS - PLAN OF ACTION**

- Summary of this meeting to be send to the members of this group. In addition to invite Florence Fuchs, Maria Angeles Cortes, Manfred Haase, Akira Homma, Chris Rolls to contribute in the development of the guidelines being involved in the proposed survey exercise. David Wood need to be involved in the development of this document addressing the questions from this meeting to be discussed/solved in thermal stability meeting: use of VVM. Summary to be sent to all of them within one month of the meeting.

- Develop questionnaire for the survey of stability data

- Drafting sections by the end April, (need to consider relevant documents such as “cell substrate guidelines”, WHO and ICH as well as the other relevant documents which will serve a basis for “References”) by members of drafting group and to send to QSB (Elwyn/ Ivana).

- Elwyn and Ivana to put together all sections and to make 1st draft which will be sent to all members of drafting group by 20 May.

- Survey of stability data to be done by the end of April/May
• Next meeting of drafting group – date and place to be agreed.

**List of available guidelines/papers relevant to stability of vaccines:**

4. Concept paper on the development of a Committee for proprietary medicinal products (CPMP) points to consider on stability and traceability requirements for vaccine intermediates - CPMP/BWP/4310/00
5. The role of Official Medicines Control Laboratories (OMCL) in the stability monitoring of vaccines. PA/PH/OMCL(2001)58
9. Requirements for Haemophilus Type b Conjugate Vaccines - WHO TRS 814 (1991)
11. WHO TRS 889