WHO Guidelines for post approval changes to vaccines

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Background

- **Post-approval change(**variation)**:** Refer to any change is made to an approved license application in product composition, manufacture process, quality controls, equipment, facilities or labels by the MA holder
  - happen frequently
  - to improve the quality, efficiency of manufacturing process, labeling items or marketing consideration
- Potential impact on the quality, efficacy or safety of the product
- Potential impact on the safe and effective use of vaccine

WHO Guidance

- Guidelines for national authorities on quality assurance for biological products (TRS 822 1992)
  - Significant changes to manufacturing establishment, source material, production process, QA procedures, or product specification should be reviewed and approval by the NRA.
  - Significant proposed changes in product indications, use or labeling should be evaluated and approved by the NRA
- Regulation and licensing of biological products in countries with newly developing regulatory authorities (TRS 858 1995)
  - Procedures for a renewal or variation in a product license should be clearly defined.
  - Significant variations (manufacture procedures, facility, specification, dosage form or labeling) must be submitted to the NRA for approval.
  - Demonstrate consistency or clinical data
  - New indication or dosage regimen (dose, route, frequency or timing).

WHO Guidance

- NRA assessment indicators for function of marketing authorization
- **Indicator MA7**: Requirements for variations to be submitted and assessed
  - **Sub-Indicator MA7.1**: Written guidelines for applicants with definition of types and scopes of variations and documentation required
  - **Sub-Indicator MA7.2**: Written guidelines for assessment based on type of variation

WHO Guidance

- WHO Guidelines for lot release (TRS 978):
- The format of the summary protocol should be amended in response to changes in the approved production process and should be approved by the NRA/NCL.
- Any changes to the template of summary protocol due to changes in the manufacturing process or testing should be traceable. The template should be a controlled document and the manufacturer should not change it without the approval of the NRA.

Request for WHO guidance

- Regulators facing difficulties of evaluation the changes
- Variety of changes: process, formulation, QC, equipment, reagent, facility, starting material, seed lot, cell substrate, scale of production, indication/age group, label, package insert etc.
- Different regulatory approaches?
- Comparability of the "new" product?
- Clinical trial and design?
- WHO provide guidance

WHO activities

- Set up drafting group
  - Roland Dobbelaer, Belgium (quit 2.2013)
  - Sara Gagneten, FDA, US
  - Sherri Boucher, HC, Canada
  - Mats Welin, MPA, Sweden
  - Swati Srivastava, CDSCO, India
  - Antonia Retno Tyas Utami, NADFC, Indonesia
  - Heidi Meyer, PEI Germany
- Meeting in November 2012
  - Outline of the guidelines
  - Development plan
- Consultation in April 2013

Structure

- Introduction and scope
- General considerations
- Reporting categories for quality changes
- Reporting categories for safety, efficacy and labeling items changes
- Procedures
- Special Considerations
- Abbreviation and glossary
- Appendix 1 Reporting categories and suggested review time lines
- Appendix 2 Post approval changes to the antigens
- Appendix 3 Post approval changes to the final products
- Appendix 4 Safety, efficacy and product labeling information changes

Introduction and scope

- **Definition of changes in this document**
  - Refers to any change made to an approved marketing authorization in product composition, manufacture process, quality controls, equipment, facilities or product labeling information by the MA holder (**variation)**
- **WHO's position**
  - Prior to implementing the change, the MA holder should assess the effects of the change and demonstrate through appropriate studies the lack of an adverse effect of the change on the quality, safety and efficacy of the vaccine
  - Regulation of changes to approved vaccines is one of the most important elements to ensure that vaccines of constant quality, safety and efficacy are distributed post authorization
  - Each country should establish the national guidelines
- **Scope:** Applies to the manufacture and distribution of approved prophylactic vaccines for human use.

General considerations

- In general, no change should be implemented by the marketing authorization holder without approval of the NRA unless it is exempted in the guideline
- The holder of a license for an approved vaccine should assess the effects of any change (e.g. manufacturing, labeling items, etc.) before distributing the vaccine with this change and decide whether submission of a supplement is required
- Manufacturing, quality control, safety, efficacy and labeling items changes are categorized using a risk-based approach into different types
- In defined circumstances (e.g. public health emergencies), national authorities may recommend use of a vaccine which is different from the approved use specified in that vaccine's label

Main principles

- Changes are categorized using risk-based approaches
  - Approval prior to implementation
  - No approval prior to implementation, retain information for audit
  - Administrative changes (acquisitions and mergers, company names or contact information be submitted directly to the NRA as a general correspondence)
  - New application
- Encourage pre-submission dialogue between applicant and NRA
- Recognition of the decision of other competent NRA
- Establishment the procedures and criteria: responsibility of national NRA
- If a quality change may have a potential impact on the quality, safety and efficacy of the vaccine, but is not included in the Guidelines then the NRA should be consulted for proper classification.

General considerations (cont.)

- Previous approval by another NRA
  - In the case where a change has been approved by another competent NRA, the NRA receiving the submission may
    - choose to recognize the decision or
    - make an independent decision based on their assessment.
  - Foreign approval documentation may accompany the required information to support the change
  - The responsibility of the final regulatory decision on the approval of the change still lies with the receiving NRA. NRAs should consider establishing procedures on the recognition of approvals for the same changes by other NRAs

Reporting categories for quality changes

- Based on the potential effect of the quality change on the identity, strength, quality controls, purity or potency of the vaccine, changes are categorized into major, moderate and minor; and are reported (require a supplement submission) in one of the following categories:
  - Major Quality Changes
  - Moderate Quality Changes
  - Minor Quality Change

- Minor changes may be implemented by the MA holder without prior review by the NRA, but are recorded and require GMP compliance

Reporting categories for quality changes (cont.)

Major quality changes

- Significant potential to impact vaccine safety and efficacy
- Require prior approval

Moderate quality changes

- Moderate potential to impact vaccine safety and efficacy
- Require prior approval

Minor quality changes

- Minimal potential to impact vaccine safety and efficacy
- Do not require approval
- When minor quality changes are related to a major or moderate change, then they should be included as part of the supplement for the major or moderate quality change

Reporting categories for safety, efficacy, and/or product labeling information changes

- Based on the effect of the changes on vaccine safety and effective use, changes are reported in one of the following categories:
  - Safety and efficacy changes
  - Product labeling information changes
  - Administrative product labeling information changes

- Product labeling information includes:
  - Prescribing information (package insert) for health care providers or patients,
  - Outer label (i.e., carton),
  - Inner label (i.e., container label).

Safety efficacy changes (cont.)

Safety and efficacy changes

- Generally, these changes affect the product labeling information and have the potential to increase the exposure levels of the vaccine, either by expanding the population that is exposed, or by increasing individual exposure.
- Require prior approval

Product labeling information changes

- Changes to the labeling information that have the potential to improve the management of risk to the population currently indicated for use of, or in any other way exposed to the vaccine
- Require prior approval

Administrative product labeling information changes

- Minimal potential to impact vaccine safety or efficacy
- Do not require approval but require annual notification

Reporting procedures

- The NRAs should establish written procedures for:
  - Submission of supplements and review time lines with action dates for the various categories
  - Communication and resolution of identified deficiencies; NRA should try to resolve the problems with the applicant via an information request letter
- When deficiencies are not resolved, the NRA may decide to issue a non-compliance notification by which the change cannot be implemented and product made with the change cannot be distributed.
- Required information to support the various quality changes is outlined and detailed in the appendices of the Guidelines.
- Procedures for different changes are recommended in the guidelines
- Accelerated procedures for urgent changes
  - Labeling information change
  - Public health reasons

Special Recommendations

- Comparability protocols:
  - A CP is a highly specific, well-defined plan for the future implementation of a quality change. The purpose of a CP is to allow for a more expedient distribution of product by permitting applicants to submit a protocol for a change, which if approved, may justify a reduced reporting category for the particular change at the time the comparability data is obtained and the change is implemented
- Multiple changes:
  - Multiple Major or Moderate Quality Changes for the same vaccine may be filed in a single submission provided those changes are related and/or supported by the same information. Any other category of changes (e.g., Minor Quality Changes and Administrative Label Changes) may be filed together with other submission whether or not they are related and/or support the same information
- Consistency samples: (may required by the NRA)
- Production documents: (should be available upon request)

Special considerations

- Adjuvants
  - Adjuvants are approved as components of licensed vaccines that consist of specific antigen/adjuvant combinations. Thus, each new adjuvanted vaccine is considered a new entity.
- Influenza vaccines
  - Annual strain changes in vaccine compositions based on WHO and NRA recommendations
    - Moderate quality changes with abbreviated review time
    - Other changes should follow normal procedures
- Bridging studies
  - Primary objectives: immune response and safety outcomes

Appendices

- 1 Reporting categories and suggested review time lines
- 2 Post approval changes to the antigens
- 3 Post approval changes to the final products
- 4 Safety, efficacy and product labeling information changes

Appendices

- For quality changes: (28 types for antigens, 32 types for final products)
  - Major,
  - Moderate and
  - Minor changes
- For safety, efficacy and labeling information changes: (16 examples)
  - Safety and efficacy change,
  - Labeling information changes
  - Administrative labeling information changes
- Suggested review time for different type of changes
  - Based on impact of the change and amount of required supportive data

Quality Changes

- These appendices consist of comprehensive listings of quality changes and provide recommendations for:

(a) the ***conditions to be fulfilled*** for a given change to be classified as either a major, moderate, or minor change.

(b) the ***supporting data*** for a given change, either to be submitted to the NRA and/or maintained by the market authorization (MA) holder; and

(c) the ***reporting category*** (e.g., Major, Moderate or Minor Quality Change).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
2. Change to an antigen manufacturing facility, involving:			
a. replacement or addition of a manufacturing facility for the antigen bulk, or any intermediate of the antigen	None	1-7,9-15	Major
	1-5	3, 7-12	Moderate
b. deletion of a manufacturing facility or manufacturer for an antigen intermediate, or antigen bulk	6-7	None	Minor

Conditions

1. This is an addition of a manufacturing facility/suite to an approved antigen manufacturing site.
2. Any changes to the manufacturing process and/or controls are considered minor.
3. The new facility/suite is under the same QA/QC oversight.
4. No changes have been made to the approved and validated cleaning and change-over procedures.
5. The proposed change does not involve additional containment requirements.
6. There should at least remain one site/manufacturer, as previously authorized, performing the same function as the one(s) concerned by the deletion.
7. The deletion should not be due to critical deficiencies concerning manufacturing

Supporting data ……1-12

Using Appendices

- For a MA Holder, when a quality change is planned the appendices should be consulted to determine the reporting category and supporting data requirements
- For the NRA, when a supplement is received the appendices should be consulted to determine if the change has been reported correctly and if all required supporting data requirements have been provided
- Changes, conditions and supporting data requirements are numbered to allow ease of reference and communication between the MA Holder and NRAs

Appendices 3 & 4 Continued

- MA holders should contact the NRA, if a change is not included in the table and it may have the potential to impact vaccine quality
- The NRA reserves the right to request additional information or material as deemed appropriate, or to define conditions not specifically described in this document in order to allow them to adequately assess the quality, safety or efficacy of a vaccine

Appendix on Safety, Efficacy and Labeling Information Changes

- The amount of safety and efficacy data needed to support a safety, efficacy and/or labeling items change may vary based on the impact of the change, risk/benefit considerations, and product specific characteristics

- This appendix provides a list of examples of changes in the various categories rather than a detailed table linking each change with the required supporting data

Appendix – Safety & Efficacy Changes

- Safety and Efficacy Changes are required for major manufacturing changes, clinical practice changes, and changes in safety and indication claims and require approval prior to implementation of the changes. In some cases safety and efficacy data comparing the approved vaccine to the vaccine produced with the change, may be required

- Some examples include
  - New dosage form
  - New dosing regimen, including concomitant administration with other vaccines.
  - Expansion of the age of indication

Appendix – Labeling Items Changes

- Do not require clinical efficacy or safety data or extensive pharmacovigilance data and require approval prior to implementation
- Some examples include
  - Addition of a new adverse reaction
  - Addition of a new warning or contraindication
  - Deletion of a strength due to safety reasons
- For urgent Labeling Items Changes, NRAs may establish a specific mechanism with applicants to allow for immediate implementation of an urgent change on a case-by-case basis.

Appendix – Administrative Labeling Items Changes

- Do not require supportive data or approval prior to implementation and may be reported in the Annual Notification Supplement.
- A list of examples is provided. Some examples include:
  - Change in MA holder contact information
  - Correction of typographical errors

Appendix –Suggested Review Time Lines

- Establishing review timelines allows manufacturer's to plan the implementation of changes.
- NRAs should establish review times based on their capabilities, the impact of the change and the amount of required supportive data.

Appendix – Example of Reporting Categories and Suggested Review Time Lines

Category	Supplement	Maximum Review Time
Quality Changes		
Major Quality Change	Prior Approval Supplement	6 months
Moderate Quality Change	Prior Approval Supplement	3 months
Minor Quality Change	Annual Notification	N/A
Safety, Efficacy and Label Changes		
Safety and Efficacy Changes	Prior Approval Supplement	10 months
Labeling items Changes	Prior Approval Supplement	5 months
Administrative Labeling items Changes	Annual Notification	N/A

These timelines are based on the those currently established by EMA, FDA and Health Canada

THANK YOU

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