Post- Approval Changes WHO guidances & Examples

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Main Principles

- **In general, no change should be implemented by the market authorization holder without approval of the NRA unless it is exempted by the NRA (See some examples in the guideline).**
- **Based on the effect of clinical and labeling items changes on vaccine safety and efficacy, changes are reported in one of the following categories:**
  - Safety and Efficacy Changes
  - Labeling items Changes
  - Administrative Labeling items Changes

Three types of changes

- Generally safety and efficacy changes affect the vaccine product 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
- Changes to the labeling items 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 Labeling Items Changes
  - Minimal potential to impact vaccine safety or effectiveness
  - Do not require approval but require annual notification

1. Safety and Efficacy Changes

- They are changes that impact the safety, efficacy, dosage, administration and product content and require data from clinical studies to support the change. Safety and Efficacy Changes require supplement submission and approval prior to distribution of the product.

- Generally, Safety and Efficacy Changes affect the product information (labeling items) 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.

Safety and Efficacy Changes

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

Examples of Safety and Efficacy Changes

- The Safety and Efficacy Changes may be related to clinical use of the vaccine such as:
  - Addition or expansion of a safety claim or efficacy claim, including expansion of the population that is exposed;
  - Addition of a new route of administration;
  - Increase in the recommended dose and/or dosing range including the addition of a booster dose;
  - Co-administration with other vaccines or drugs; or
  - Deletion or reduction of existing risk management measures (e.g., contraindications, adverse events, warnings or cautionary text/statements, in the product label).

Examples of Safety and Efficacy Changes

- 1. Expansion of safety claims: Change due to increase of risk based on updated data from post-marketing clinical studies (confirmatory safety and efficacy studies or studies conducted in new populations), post-marketing surveillance, or studies of biodistribution, shedding or transmission.

- 2. Expansion or contraction of efficacy claims: New indications and usage (including reintroduction of a withdrawn indication) based on clinical studies demonstrating efficacy or lack of efficacy in specific populations.

Examples (cont.)

- 3. New route of administration, new dosage form, new strength, new dose, new dosing regimen, including concomitant administration with other vaccines.
- 4. Change in existing risk management measures, existing route of administration, dosage form and/or strength due to safety reasons.
- 5. Changes based on data from nonclinical studies.

WHO Guidance

- The type and scope of the supportive nonclinical and/or clinical safety and efficacy data are determined case-by-case based on risk-benefit considerations related to the impact of the changes, the vaccine attributes and the disease it is design to prevent and may be based on considerations such as:
    - Robustness of immune response elicited by the vaccine and availability of a correlate of protection (data establishing a threshold level of antibody needed to protect against the development of disease following exposure);
    - Availability of animal models and
    - Vaccine attributes (i.e., live vs. inactivated vaccines).

Required supporting data

- Detailed description of the proposed change;
- A description of the methods used and studies performed to evaluate the effect of the change on the vaccine's safety or efficacy;
- Amended product labeling items;
- Clinical studies (protocol, statistical analysis plan, and clinical study report);
- Clinical assay methods (SOPs) and validations;
- Pharmacovigilance plan; and
- If the clinical study was conducted to support a major quality change, the application should include information as required for Major Quality Changes.

2. Labeling items change

- Label Changes should be submitted for changes which do not require clinical efficacy or safety data or extensive pharmacovigilance (safety surveillance) data, and require approval prior to implementation. Label Items Changes require approval prior to distribution of the product with the labels bearing the change.

Examples of Labeling items change

- 1.Addition, strengthening, or clarification of text relating to contraindications, warnings, precautions, and adverse reactions of the package insert. These changes may include the provision of recommended risk-management actions (e.g., required testing prior to vaccination, specific monitoring, ensuring patient awareness of certain risks, etc.), or the identification of a specific sub-population as being at greater risk such as those with a concomitant condition, those taking concomitant medicine, or a specific age group.

- 2.Addition of an adverse reaction due to information reported to the applicant or the NRA.

Example (cont.)

- 3.The instructions for use including dosage, administration and preparation for administration revised to optimize the safe use of the vaccine.
- 4. An existing indication has been withdrawn in its entirety or altered for risk management purposes including reduction in scope, but without expanding the claims of the vaccine.
- 5. An existing route of administration, dosage form and/or strength has been deleted due to safety reasons.
- 6. A new drug interaction has been added, or an existing drug interaction has been better characterized, that alters the conditions of use in terms of risk management (e.g., a precautionary statement is added as the result of the new data).

3. Administrative Labeling Items Changes

- Administrative Labeling Items Changes should be submitted which do not require supportive data or approval prior to implementation and may be reported in the Annual Notification Supplement.

Examples of Administrative Labeling Items Changes

- 1. Minor changes to the layout of the label or revision of typographical errors without changing the content of the label.
- 2. Update of the MA holder contact information (e.g., customer service number, website addresses, etc.) or distributor's name.
- 3. Update of the existing information for referenced literature without adding or removing references.
- 4. Labeling changes made to comply with an official compendium.
- 5. Minor changes to the text to add clarity as it relates to maintaining consistency with common label phrase standards (e.g., change from "not recommended for children" to "not for use in children").

Requiring clinical data of major quality changes

- Change to an antigen manufacturing facility, involving
  - replacement or addition of a manufacturing facility for the antigen bulk, or any intermediate of the antigen (clinical data: Maybe)
  - deletion of a manufacturing facility or manufacturer for an antigen intermediate, or antigen bulk (condition 6,7) (clinical data: No)
    - There should at least remain one site/manufacturer, as previously authorized, performing the same function as the one(s) concerned by the deletion.
    - The deletion should not be due to critical deficiencies concerning manufacturing

- Data required:
  - Comparability of the approved and proposed antigen with respect to physico-chemical characterization, biological activity, and impurity profile. (N.B. **Occasionally**, the applicant may undertake bridging non-clinical or clinical studies, to support the quality data).

Requiring clinical data of major quality changes

- Changes to the cell banks, involving:
  - generation of a new Master Cell Bank(condition below. clinical data: Maybe)
    - The new MCB is generated from a pre-approved MCB or WCB.
- Changes to the seed lots, involving:
  - a new Master Seed Lot (MSL); or a Working Seed Lot (WSL) extended beyond an approved passage level (no condition. Clinical data: Yes)
  - generation of a new WSL (conditions and clinical data: Maybe)
    - The new cell bank/seed lot is generated from a pre-approved MCB/MSL.
    - The new cell bank/seed lot is at the pre-approved passage level.
    - The new cell bank/seed lot is released according to a pre-approved protocol.
- Data required:
  - Comparability of the approved and proposed antigen with respect to physico-chemical characterization, biological activity, and impurity profile.
  - Bridging clinical studies may be required where comparability is not adequately demonstrated.

Requiring clinical data of major quality changes

- Change in the description or composition of the final product , involving:
  - addition of a dosage form or change in the formulation (e.g., lyophilized powder to liquid, change in the amount of excipient, new diluent for lyophilized product). (no condition. clinical data: Yes)
  - change in the concentration of the active ingredient (e.g., 20 unit/mL *vs.* 10 unit/mL) (no condition. Clinical data: Yes. If condition 2,3, clinical: No)
  - addition of a new presentation (e.g., addition of syringes to vials) (No conditions and clinical data: No)
    1. Revised final product labeling information (as applicable).
    2. Characterization data demonstrating that the conformation and immunogenicity of the antigen is comparable in the new dosage form and/or formulation.
    3. The new concentration is bracketed by existing approved concentrations.

- Data required:
  - Supporting data or a request for a waiver of in vivo studies based on scientific evidence

Requiring clinical data of major quality changes

- Change involving a biological adjuvant:
  - change in supplier of a biological adjuvant(no condition. clinical data: Maybe)
  - change in manufacture of a biological adjuvant (Clinical data: Maybe)
  - change in specifications of a biological adjuvant (including the tests and/or the analytical procedures) (Clinical data: No)

- Data required:
  - Supporting nonclinical and clinical data, if applicable.

- Change in a component of a biological adjuvant system may require the filing of a new application for marketing authorization. Applicants are encouraged to contact the NRA for further guidance.

Risk-benefit analysis

- Different NRA may associate different procedures to a given type of change, but the procedures should be unambiguously defined.
- Prior to implement the change, the MA holder should **assess** the effects of the change and demonstrate through appropriate studies (validation and/or clinical or non-clinical laboratory studies) the lack of an adverse effect of the change on the quality, safety and efficacy of the vaccine.
- Dialogue between applicant and NRA is encouraged.