NEW WHO Guidelines on Procedures and Data Requirements for Changes to Approved Biotherapeutics

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Content

• Background
  – What happened after publishing WHO guidelines for similar biotherapeutic products (SBPs; ECBS 2009)
  – Development and Consultation process

• Key message in the guidelines (ECBS 2017)

• Conclusion

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What happened after publishing WHO guidelines for SBPs, ECBS 2009

- 2nd implementation workshop for SBP GLs, China, 2012
  - Asked WHO to develop guidelines for changes of approved BTPs to resolve complexity and current challenges of global life-cycle management.
- APEC Harmonization Center workshop, Korea, 2014
  - found the detailed WHO guidelines for changes of approved vaccines (adopted by ECBS 2014) are very helpful so asked WHO to develop the same level of detail guidelines for BTPs.
- WHA 67.21, 2014: First-ever & New Resolution on BTPs
  - to support the development of national regulatory frameworks that promote access to quality, safe, efficacious and affordable BTPs
- 16th ICDRA, Brazil, 2014
  - requested WHO assistance in ensuring regulatory oversight throughout the life-cycle of BTPs.

Providing guidance to NRAs and manufacturers on regulating changes to already approved BTPs could contribute to assuring their continued quality, safety and efficacy throughout the life-cycle of BTPs as well as continuity in supply and access.
Development of WHO document: key events in 2014 - 2018

- 16th ICDRA recommendations, 2014

- Set up Drafting/Working group & Prepare the preliminary draft* (May 2016)
  - Consultation with critical reviewers and relevant experts (June 2016)
  - Working group meeting (Aug 2016): Scope, outline, and key issues

- 1st DRAFT (Sept 2016)
  - Report to the 67th ECBS (Oct 2016)
  - 1st public consultation (Oct – Dec 2016)
  - Informal consultation (April 2017)

- 2nd DRAFT (June 2017)
  - 2nd public consultation (July – Sept 2017)
  - Adopted: 68th ECBS (Oct 2017)

Published in the WHO Technical Report Series no. 1011, Annex 3 (May 2018)

*Note: The preliminary draft was the modified version of vaccine guidelines taking the nature of biotherapeutic products into consideration.
WHO Questions and Answers: SBPs

• 1\textsuperscript{st} implementation workshop for SBP GLs, Korea, 2010
  – WHO to assist NRAs in building and improving technical expertise in the evaluation of SBPs by providing some learning tools as well as opportunities for information and knowledge sharing, e.g. Q&As for WHO web site.

• 3\textsuperscript{rd} implementation workshop for SBP GLs, Korea, 2014
  – WHO to set up long term implementation strategy & use technical tools for implementation, e.g. information sharing via WHO extranet linking to publications, Q&As on guidelines.

• Informal consultation on SBPs, Geneva, 2015
  – Reviewed in detail the WHO 2009 GLs and GLs issued by EMA, Health Canada, US FDA etc
  – Agreed that all guiding principles in the 2009 GLs are still relevant and up to date. No need to revise document.
• Expert consultation on improving access to and use of SBPs, Geneva, 2017
  – WHO to review and provide clarification on the SBP 2009 GLs to reflect technological and analytical advances.
• Implementation workshop for Russian speaking countries in EUR, Denmark, 2017
  – Developing Q&As by WHO is supported for better clarity on principles in WHO GLs.

**Thus, developing Q&As document is more appropriate than revision of the guidelines for further clarifying and complementing some areas and points written in the guidelines. The points to be addressed with explanatory notes.**
WHA 67.21 & follow up

• WHA 67.21, 2014: First-ever Resolution on BTPs
  – WHO ECBS to update the 2009 GLs, taking into account the technological advances for the characterization of BTPs and considering national regulatory needs and capacities

• 69th ECBS 2018
  – approved the resulting Q&A document and recommended that it be posted on the WHO website rather than published in the Technical Report Series.
  – recognized that the 2009 GLs remained valid and did NOT therefore require revision at this point.
Questions asked by regulators in the workshops in the past 9 years were basis to develop the questions for this document.

- WHO Implementation workshops for BTP & SBP

<table>
<thead>
<tr>
<th></th>
<th>Global level</th>
<th>Regional level</th>
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<tbody>
<tr>
<td><strong>Imp. workshop</strong></td>
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<td>1st SBP</td>
<td>2nd SBP</td>
<td>3rd SBP</td>
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<tr>
<td><strong>(Co-) Host</strong></td>
<td>MFDS Korea</td>
<td>NIFDC China</td>
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<td><strong>Where</strong></td>
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<tr>
<td><strong>Participants</strong></td>
<td>11 NRAs</td>
<td>16 NRAs</td>
</tr>
<tr>
<td><strong>Main topic</strong></td>
<td>Clinical study design: Eq vs NI</td>
<td>Quality assessment of mAbs</td>
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Q&As document: content development

Q&As: 1. To provide clarity to questions that may arise in the use of WHO guidelines.
2. To be read in conjunction with relevant WHO guidelines.

<table>
<thead>
<tr>
<th>WHO SBP guidelines, 2009</th>
<th>Q&amp;As document</th>
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<tbody>
<tr>
<td>Scientific considerations and concept for licensing SBPs</td>
<td>Concept for licensing SBPs (4Qs)</td>
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<td>Key principles for the licensing of SBPs</td>
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<tr>
<td>Reference biotherapeutic products</td>
<td>Reference biotherapeutic products (6Qs)</td>
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<tr>
<td>Quality</td>
<td>Quality (12Qs)</td>
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<tr>
<td>Nonclinical evaluation</td>
<td>Nonclinical evaluation (8Qs)</td>
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<tr>
<td>Clinical evaluation</td>
<td>Clinical evaluation (12Qs)</td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>Pharmacovigilance (6Qs)</td>
</tr>
</tbody>
</table>
VI. Pharmacovigilance (6 Qs)

1. Will SBPs be as safe as originator products?

2. After an SBP has been approved, is the SBP required to show the maintenance of biosimilarity with its RBP?

3. Would it be beneficial to review/discuss post-marketing commitments from each NRA after extrapolation of indications?

4. If safety information of the RBP (i.e. as the result of adverse events) is amended, how would it be applied to SBPs that are already approved?

5. Can the SBP marketing authorization holder seek approval for a new indication, dosage form or route of administration that is different from the RBP?

6. Should cautions for the use of an SBP be the same with those for the licensed RBP?
WHO Guidelines for post-approval changes

WHO position

• The regulation of changes to approved BTPs is key to ensuring that products of consistent quality, safety and efficacy are marketed after they receive authorization or licensure.
• WHO guidelines are intended to serve as a guide for establishing national requirement for regulation of post-approval changes to BTPs.
• Implementation of new regulations should not affect product supply and access to products.
• NRAs are encouraged to apply the concept of reliance or work sharing or to use collaborative approaches when reviewing post-approval changes.
Changes: Essential for the continual improvement of the manufacturing process and for maintaining state-of-the-art control of BTPs (including SBPs) and often need to be implemented after the product has been approved.

NRAs and marketing authorization holders should recognize that:

– any change to a BTP has the potential to impact quality, safety and/or efficacy of the product; and

– any change to the information associated with the product (i.e. product labelling information) may have an impact on its safe and effective use.
Purpose

• To provide guidance on the
  – Procedure and criteria for the appropriate categorization and reporting of changes (main body); and
  – Data requirements to support the proposed changes (appendices).
• Appendix 1: Examples of suggested review timelines for changes in the various categories.
• Appendices 2, 3: comprehensive list of quality changes
  – The conditions to be fulfilled to classify a specific quality change as major, moderate or minor
  – The specific data requirements to support approval of a proposed quality change
  – The reporting category
• Appendix 4: e.g. of changes that affect to the clinical use of product and product labelling information
Terminology

- **Change**: a change that includes, but is not limited to, the product composition, manufacturing process, quality controls, analytical methods, equipment, facilities or product labelling information made to an approved marketing authorization or licence by the holder. Also referred to as “variation” or “post-notice of compliance change” in other documents.

- **Quality change**: a change in the manufacturing process, product composition, quality control testing, equipment or facility. Also referred to as ‘chemistry manufacturing and control (CMC) change’ in other documents.

- **Safety and efficacy change**: a change that has an impact on the clinical use of the BTP in relation to safety, efficacy, dosage and administration and that requires data from clinical or post-marketing studies, and in some instances clinically-relevant nonclinical studies, to support the change.
• Guidelines apply to biotherapeutic products that have received a licence or a marketing authorization
• The principles may also apply to quality changes that occur during development of a product and where comparability needs to be demonstrated.
  – In this case, the amount and type of data submitted for such products will be limited and will vary according to the nature of each product and its stage of development.
  – In addition, the legal status of investigational products varies from country to country, so it should be discussed with the NRA.
SCOPE: Inclusion/Exclusion

• Inclusion
  – all biologically active protein products used in the treatment of human diseases (e.g. plasma-fractionated products)
  – those intentionally modified by, e.g. fusion proteins, PEGylation, conjugation with a cytotoxic drug or modification of rDNA sequences.
  – protein products used for in vivo diagnosis, e.g. mAbs used for imaging
  – Low molecular weight heparins

• Exclusion
  – Prophylactic vaccines against infectious diseases (Annex 4, WHO TRS No. 993)
  – Gene and cell therapy products
General considerations

• Changes to approved biotherapeutic products or SBPs are categorized on the basis of a risk analysis which takes into consideration the complexity of the production process and product, the patient population, and the proposed changes.

Changes affect the manufacturing process or the control strategy

Evaluation of the impact of the changes on the quality, i.e. identity, strength, purity and potency

Changes affect the clinical use of a product or product labelling information

Evaluation of the impact of the changes on the safety and efficacy of the product

• Regardless of the impact on quality, safety and efficacy, all changes should be recorded and retained by the manufacturer.
Special considerations for SBPs

• Once licensed, no requirement to re-establish its biosimilarity to the RBP.
• Changes made on an SBP: same as other BTPs, i.e. comparability exercises to be conducted.
• Life-cycle management: same as other medicines, i.e. ensure their benefits outweigh their risks throughout their life-cycle.
• A major change in clinical use for an SBP: to be considered by the NRA on a case-by-case basis, e.g.
  • A new indication given to the RBP after approval of an SBP: not automatically be given to the SBP.
  • New safety information on the RBP added after the original approval of the SBP: labelling information of the SBP to follow the changes made for the RBP, unless it can be demonstrated that the new information on the RBP is not relevant to the SBP.
• In that context, it is important to emphasize that these data only could be obtained by having robust pharmacovigilance systems in place.
Procedure

- NRA should establish:
  - Procedures and criteria for adequate oversight of changes;
  - Written instructions regarding the submission procedures and timelines with action dates.
- Regulatory procedures:
  - Full review
  - Expedited review: Alternative regulatory procedures based on previous expert review and approval by the licensing NRAs.
## Comparison with requirements developed by other jurisdictions

- Approval required for moderate quality changes

  *(PAS*: Prior approval supplement; *S*: supplement; *N*: notification; *S/NDS*: Supplemental New Drug Submission; *NC*: Notifiable change; *D*: Days; *CBE*: Changes being effected)*

<table>
<thead>
<tr>
<th>Potential impact on Q, S, E</th>
<th>USA</th>
<th>EU</th>
<th>Canada</th>
<th>Japan</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>PAS 120 D</td>
<td>Type II, PAS 60 D</td>
<td>S/NDS, PAS 180 D</td>
<td>Partial, PAS</td>
<td>PAS 90-180 D</td>
</tr>
<tr>
<td>Moderate</td>
<td>S CBE+30</td>
<td>Type IB, N wait 30 D</td>
<td>NC, PAS 90 D</td>
<td>Minor, N wait 30 D</td>
<td>PAS 30-90 D</td>
</tr>
<tr>
<td></td>
<td>S CBE+0</td>
<td>Type IA$_{IN}$</td>
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</tr>
<tr>
<td>Minor</td>
<td>N (Annual report)</td>
<td>Type IA, N, 1yr</td>
<td>Level 3 N (annually)</td>
<td>Non-approval matters</td>
<td>Minor N (e.g. annually)</td>
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<td></td>
<td></td>
<td></td>
<td>Level 4 (On-site/GMP record)</td>
<td></td>
<td>With no impact (On-site/GMP record)</td>
</tr>
</tbody>
</table>
Comparison with requirements developed by other jurisdictions (cont.)

- Procedure for moderate quality changes
  - Issue: Replace the requirement to file a PAS by a type of filling like the US CBE-30 or the EU Type-1B. In these filing, the post-change product can be distributed after the default period without prior approval, i.e. the change can be implemented by the MAH without review of the supporting data.
  - **Note:** Agreement from consultations (2016-2017) & ECBS 2017
    - The NRAs confirmed that the supporting data for a Moderate change should be reviewed in order to confirm absence of negative impact of the change on the product. Furthermore, some Moderate changes could be the results of the downgrade of a Major change due to the execution of a comparability protocol. This highlighted the importance for the NRAs to review the supporting data for Moderate changes.
    - Thus, Moderate change should still require the filing of a PAS but with shorter review timelines compared to major changes.
Comparison with WHO vaccine GLs

- Procedure for quality changes

<table>
<thead>
<tr>
<th>VAC doc</th>
<th>BTP doc</th>
<th>Procedure</th>
<th>Maximum Suggested Review timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>Major</td>
<td>PAS</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate</td>
<td>PAS</td>
<td>1-3 months</td>
</tr>
<tr>
<td>Minor</td>
<td>Minor</td>
<td>Require notification to NRA</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>With no impact</td>
<td>Do not require notification to NRA</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- Minor changes divided into 2 categories
  - Minor
  - Changes with no impact: List of examples provided (section 6.4)

- Review Timeline
  - To be established by taking into consideration the country or regional situation, the capability of the NRA, the impact of the change and the amount of data required to support the change.
  - Suggested review timeline shown as examples; they are based on the experience of several NRAs and apply to situations where the NRA performs a full review.
  - Range provided (more flexibility)
    Guidance should encourage efforts to reduce timelines and harmonize requirements across countries/regions
Harmonization with ICH

• The principles of the guidelines are in line with relevant ICH guidelines.
• Issue: Including the concept of ‘Established conditions’ in draft ICH Q12
• **Note:** Agreement in informal consultation in April 2017 & ECBS 2017
  – Not to refer documents that are not yet finalized or approved. However, it was noted that these WHO guidelines are consistent with principles of draft ICH Q12, and development of ICH Q12 is considered important as it is complementary to the WHO guidelines.
Conclusion

- Guidelines incorporate life-cycle approach and sound science/risk management principles.
- The use of common categorization systems would facilitate consistent implementation of post-approval changes for biotherapeutics by stipulating criteria for appropriate reporting to NRAs.
- Facilitating the implementation of guidelines would
  - Lead to improved transparency, consistency and predictability in regulatory outcomes and decision making.
  - Promote collaboration and reliance on approvals from competent regulatory authorities.
  - Benefit regulators, industries, and patients globally by contributing to the sustainable supply of biotherapeutics.
Thank you

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