EVALUATION OF SIMILAR BIOATHERAPEUTIC PRODUCTS:

WHO APPROACH

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Outline

- Biotherapeutics in the context of WHO Biological Standardization
- Role of NRAs in assuring Q, S and E of biologicals
- Concept of proposed WHO guidelines for evaluation of SBPs
- Key principles for evaluation of SBPs
- WHO role in assuring Q, S and E of biotherapeutics
- Way forward
WHO norms and standards for biologicals

Global written standards

Global measurement standards

Scientific evidence

1) Standardization of assays
2) Further development and refinement of QC tests
3) Scientific basis for setting specifications

Reference preparations for biotherapeutics

Measurement standards: essential elements for development, licensing and lot release
WHO Written Standards
A tool for harmonization of specifications worldwide

National Pharma-Copeias
OR
NRA/NCL

NRA/NCL
Manufacturers
Product Users
WHO Biological Reference Preparations
A tool for comparison of results worldwide

WHO IS/IRP

Specifications to prepare and characterize WHO IS: WHO TRS 932 (2006)

2nd Ref. Material

National Control Laboratory

Manufacturers

Product Users
Recommended Regulatory Functions

- Marketing Authorization and licensing of activities: Approval of production facilities and approval of medicines for marketing
- Lot release: Approval of Biological Products on a lot to lot basis
- Access to laboratory testing as needed
- Regulatory Oversight of Clinical Trials: Authorization and monitoring of trials and evaluation of clinical data
- Postmarketing activities: Monitoring of safety and efficacy including surveillance of AEFI
Overall Strategy for NRA strengthening

Critical Control Functions

1. Licensing of products, manufacturers and distributors
2. Laboratory testing and lot release (where required)
3. Inspections of manufacturing sites and distribution facilities
4. Control of clinical trials
5. Control of advertising and promotion
6. Post marketing surveillance of quality and safety

Identify weaknesses

Take corrective measures

Establish solid foundations

Secure strong political will & commitment, both human & financial, for NRA functions
TOTAL POPULATION MONITORED THROUGH WHO* NRA ASSESSMENTS AND FOLLOW UP: 1997 - 2008

1997

Not monitored;
5 580 M;
96%

Monitored;
226 M;
4%

2008

Not monitored;
427 M;
6%

Monitored;
6 233 M;
94%

*World Health Organization
Source: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st December 2008
Cumulative values
Role of NRAs in the regulation of SBPs

- One of the responsibilities of an NRA is to set up appropriate regulatory oversight for the licensing of SBPs that are developed and/or authorized for sale in their country.

- Decision making regarding the licensing of SBPs should be based on scientific evidence.

- Stepwise approach: Comprehensive characterization and comparison at the quality level are the basis for possible data reduction in the non-clinical and clinical development.

- The reduction in data requirements is only possible for the non-clinical and/or clinical parts of the development program.

- Significant differences between the SBP and the RBP during the comparability exercise would be an indication that the products are not similar.
Development of WHO guidelines on SBPs: key events in 2007 and 2008

- Mandated by ICDRA in 2006 and the Expert Committee on Biological Standardization (ECBS) in 2007
- Drafting group meeting: March 2008, Bonn
- WHO Consultation: May 2008, Seoul
- ICDRA: Sep 2008, Bern
- Seminar organized by NICPBP in Beijing, Dec 2008: Chinese Regulators (SFDA and NICPBP) and manufacturers
Outcomes of the consultations in 2009

   1. Experience gained in Japan
   2. Meeting of the WHO drafting group

2. IABS/HC workshop: 13 - 14 July 2009

3. WHO Consultation: 15 - 16 July 2009
   1. Focus on clinical evaluation of SBPs
   2. Review of the development of SBPs in the countries
   3. Comments received during the 1st round of public consultation

4. WHO drafting group meeting: 17 July 2009
   1. Review of experience in countries where SBPs are under development
   2. Further improvements of the proposed guidelines.
Improvements of WHO Guidelines following July 2009 Consultation

1. Agreement on the scope
2. Definitions
3. Clarification of key principles for licensing SBPs
4. Reference product
5. Clarification of the principles for Q, S and E evaluation
6. Statistical considerations (equivalence vs non-inferiority)
7. Interchangeability and substitutability
8. Roles and responsibilities of NRAs
Concept of WHO Guidelines

1) Provide key principles for evaluation of SBPs as a basis for setting national requirements;

2) Leave space to NRAs to formulate additional/more specific requirements;

3) Living document that will be developed further in line with the progress in scientific knowledge and experience

4) Assist with the implementation of the guidelines into regulatory and manufacturers practice through:
   - Global, regional and national workshops involving regulators, manufacturers and other relevant experts
   - Trainings, advisory groups

5) Consider guidance issued by other bodies – intention to complement them, not to create a conflict.
Licensure requirements—amount of data and applicability

- **Full dossier**
  - (Stand alone approach)
  - Applicable to all biologicals

- **Similar Biotherapeutic Products (SBPs)**
  - Existing knowledge, full, comparative characterization, plus Comparative BUT reduced non-clinical, clinical data
  - Applicable to well characterized biologicals only

- **Generic**
  - For chemical entities only
  - Not applicable to biologicals
Key definitions

- **SBP** is a biotherapeutic product which is “similar” in terms of quality, safety and efficacy (Q, S, E) to an already licensed reference biotherapeutic product (RBP).

- **RBP** is used as the comparator for head-to-head studies with SBP in order to show similarity in terms of Q, S and E. Only an originator product that was licensed on the basis of a full licensing dossier can serve as an RBP. *It does not refer to measurement standards such as international, pharmacopoeial or national standards or reference preparations.*

- **Comparable** means absence of any relevant differences at the level of Q, S or E between SBP and RBP.

- **Non-inferior** means not inferior to a comparator in the parameter studies. A non-inferiority clinical trial is a trial which has the primary objective of showing that the response to the investigational product is not clinically inferior to a comparator by a *pre-specified margin*.

Important to note that biotherapeutics which are not shown to be similar to a RBP should not be described as "similar", nor called a "SBP".
Key principles for the licensing of SBPs

- **SBPs are not generic medicines** and many characteristics associated with the authorization process and marketed use of generic medicines generally do not apply.

- **Stepwise approach**
  - Demonstration of similarity of SBP to RBP in terms of quality is a prerequisite for the reduction of the non-clinical and clinical data set required for licensure.
  - If major differences are found in the quality, non-clinical and clinical studies, the product should not be considered as "similar" and, therefore, other options for its further development should be considered (e.g., stand alone).

- **Effective regulatory oversight is critical for assuring Q, S and E of SBPs**
Reference Biotherapeutic Product (RBP)

- RBPs should have been marketed for a suitable duration and have a volume of marketed use
- RBPs should be licensed based on a full Q, S and E data set
- The same RBP used throughout the development of the SBP
- An SBP should not be considered as a choice for RBP
- The active substance of the RBP and the SBP must be shown to be similar
- The dosage form and route of administration of the SBP should be the same as that of the RBP
- NRAs may need to consider establishing additional criteria to guide the acceptability of using a RBP licensed or resourced in other countries
Quality

- Development of an SBP
  - Thorough characterization of a number of representative lots of the RBP
  - Engineering a manufacturing process that will reproduce a product that is highly similar to the RBP in all critical product quality attributes

- The quality comparison showing molecular similarity between the SBP and the RBP provides the underlying rationale for predicting that the clinical safety and efficacy profile of the RBP should also apply to the SBP
  - So that the extent of the non-clinical and clinical data required with the SBP can be reduced

- To evaluate comparability
  - The manufacturer should carry out a comprehensive physicochemical and biological characterization of the SBP in head-to-head comparison with the RBP
Non-clinical evaluation

- General principles:
  - Address pharmaco-toxicological assessment of SBP
  - Should be conducted with the final formulation intended for clinical use
  - Minimum: head-to-head comparative toxicology studies
  - Additional NC data depend on the specificities of a product

- In vitro studies
  - Methodology: Receptor-binding studies, cell-based assays, etc
  - Purpose: Establish comparability of biol/pharmacodynamic activity of SBP and RBP

- In vivo studies
  - General principles
    - Comparative in nature
    - Performed in relevant species
    - Employ state of the art technology
  - Endpoints
    - Biological/pharmacodynamic activity relevant to the clinical application
    - Non-clinical toxicity as determined in at least one repeat dose toxicity study with a relevant species and including toxicokinetic measurements
Clinical evaluation

- Designed to demonstrate comparable safety and efficacy of the SBP to the RBP
- Clinical comparability exercise: stepwise procedure that should begin with PK and PD studies followed by the pivotal clinical trials

Efficacy studies
- No dose-finding studies
- Demonstrate in adequately powered, randomized, and parallel group clinical trial (ICH E9 and E10)
- Equivalence or non-inferiority studies may be acceptable for the comparison of efficacy and safety of the SBP with the RBP
- Equivalence/non-inferiority margins have to be pre-specified and justified

Safety
- Usually, safety data obtained from the efficacy trials will suffice
- Comparison with the RBP should include type, frequency and severity of AEs
Clinical evaluation – cont.

- **Extrapolation**
  - **Prerequisites**
    - Similarity shown in a sensitive model
    - Mechanism of action/receptor the same
    - Safety and immunogenicity sufficiently characterized in the evaluated population

- **Pharmacovigilance**
  - Focus on (rare) serious AEs in all approved indications
  - Pharmacovigilance system should be in place at the time of marketing authorization
  - Post-marketing report to be evaluated in a scientific manner including frequency and causality of AEs
Consultation process continues

1. Public consultation: 1st round closed on 15 July 2009

2. Public consultation: 2nd round: from end July to 7 October 2009
   (http://www.who.int/biologicals/en/ under "Highlights")
   – direct link to the document:

   http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/BS2110Dft_guidelines_Final_HK_IK_29July_09.pdf

3. Submission to the ECBS in Oct 2009

4. Consultations with regulators, manufacturers of SBPs and other experts in 2010 and 2011
Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Comments proposing modifications to this text MUST be received by 9 October 2009 and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Quality Safety and Standards (QSS). Comments may also be submitted electronically to the Responsible Officer: Dr Ivana Knezevic at email: knezevici@who.int.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/IMD/PUB/04.1).
Experience in countries where SBP are under development

- Regulators and manufacturers from EU, Canada, USA, Japan, India, China, S. Korea, Thailand, Cuba, Brazil, Iran and other countries provided input to previous WHO meetings;

- Variety of approaches in evaluating SBPs are in place;

- In most countries comparability in terms of quality and non-clinical assessment could be done BUT no comparability in clinical evaluation;

- Example from a large country in great expansion: "None-innovative new drug study approach" - product developed through stand alone approach with some comparability in physico-chemical parameters.

Need for strengthening expertise in designing and evaluating data from CTs;
WHO role: way forward

1. Facilitate development and approval of SBPs of assured quality, safety and efficacy at affordable price;

2. Provide guidelines as a basis for setting national requirements;

3. Assist WHO Member States in implementing guiding principles for evaluation of SBPs in the regulatory and manufacturers' practice;

4. Share information and knowledge;

5. Consider further assistance to regulators and manufacturers
   1. Database or list of RBPs
   2. Prequalification of SBPs
Many thanks

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