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EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS:

PROPOSED WHO GUIDELINES

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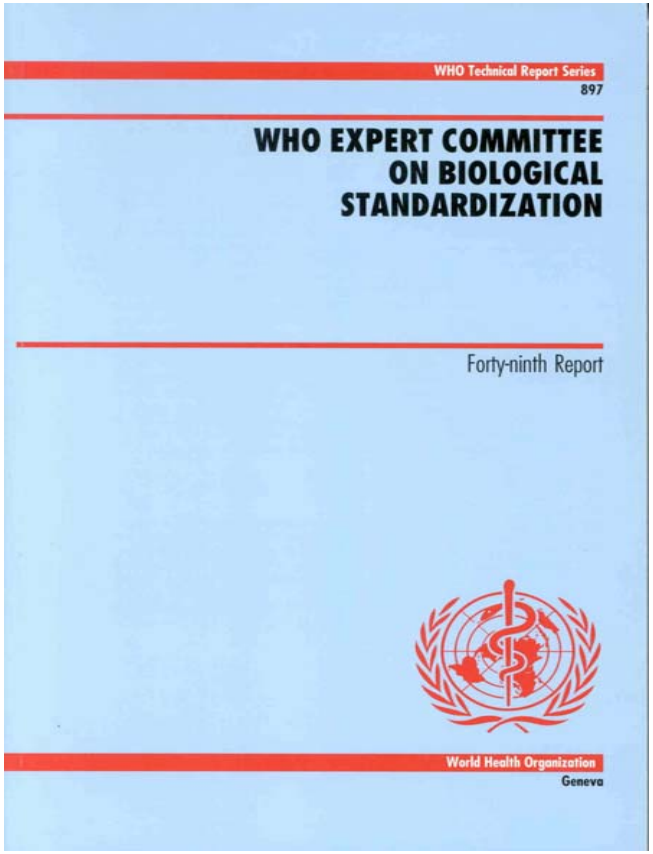
World Health Organization

Outline

- WHO Norms and Standards
- Implementation of WHO standards into National Regulations
- SBP in the context of Biological Standardization
- Key principles for evaluation of SBP
- Proposed WHO guidelines: next steps

WHO norms and standards

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

Measurement standards:
essential elements for lot release

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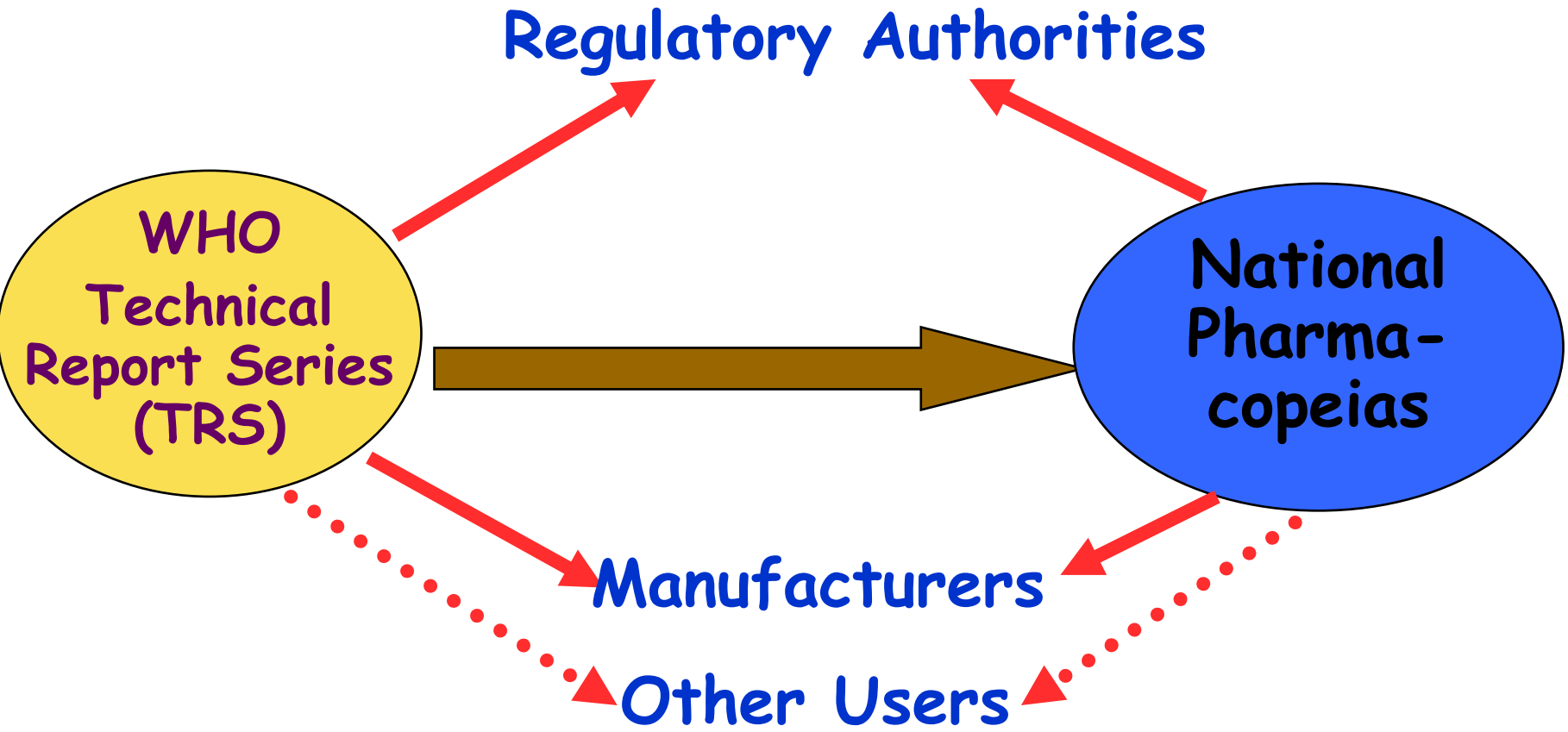
Expert Committee on Biological Standardization (ECBS)

Establishing WHO norms and standards for quality, safety and efficacy of biologicals

WHO core activity – reaffirmed for 2008-2013

WHO Written Standards
A tool for harmonization of specifications worldwide



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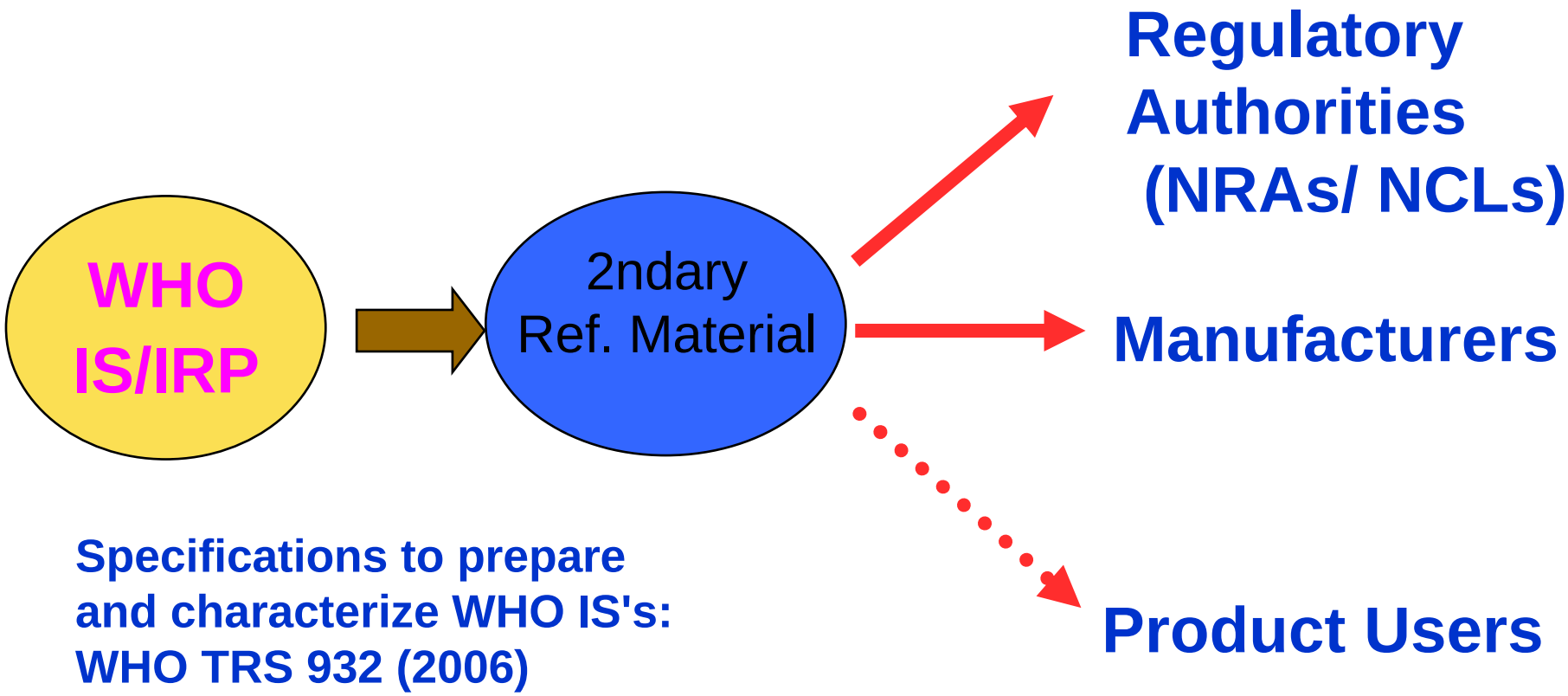
WHO Biological Reference Preparations
A tool for comparison of results worldwide



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

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What happens after adoption of WHO standards by the ECBS?

- Fully adopted by the NRAs/ NCLs and implemented into national regulation
- Adopted by NRAs/ NCLs with some modifications
- Implemented into manufacturers procedures
- Considered by National Pharmacopeias and, when appropriate, incorporated into general or specific monographs
- Used as basic requirements for prequalification

Proposed WHO Guidelines for Similar Biotherapeutic Products (SBP)

WHO guidelines: key events in the development

- Mandated by International Conference of Drug Regulatory Authorities, 2006
- WHO Consultation: 19-20 April 2007, Geneva
- Drafting group meeting:

March 2008, Bonn

- WHO Consultation:

May 2008, Seoul

- ECBS: Oct 08, Geneva
- Drafting group meeting:

Feb 09, Tokyo

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Consensus reached in April 2007

- WHO Consultation, 19-20 April 2007, Geneva
- Generic approach for pharmaceuticals does not apply to biotherapeutic medicines due to the complex nature of biologicals
- Divergent approaches for regulatory oversight of similar biologicals in different countries due to:
  - Different situation with innovative products (small vs big markets)
  - Different regulatory frameworks (eg option for "me too" products)
- WHO should develop a global regulatory guideline for biosimilar products
- Meeting report available at:

http://www.who.int/biologicals/publications/meetings/areas/en/index.html

WHO assistance to Member States

- Guidance for biological therapeutics - limited
- Options for similar biological products:
  1) Develop guidelines with key principles for evaluation of SBP focusing on general issues that apply to all products and leave space to NRAs to formulate national requirements;
  2) Assist with the implementation of the guidelines into regulatory and manufacturers practice through:
     - regional and national workshops involving regulators, manufacturers and other relevant experts;
     - Trainings, fora of experts to advise, other ideas?
  3) Consider guidance issued by other bodies – intention to complement them, not to create a conflict.

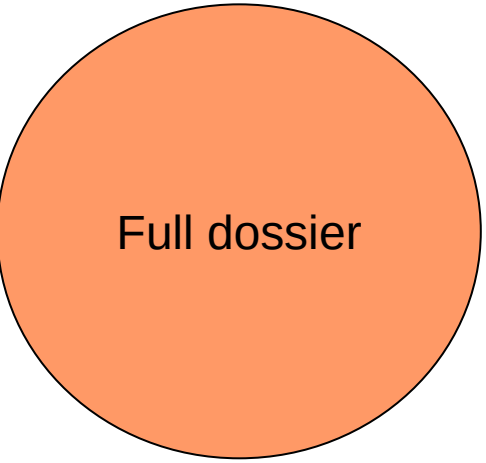
Draft WHO guidelines: 2008

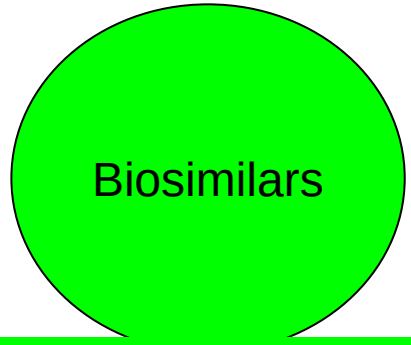
- First draft developed following drafting group meeting in March 2008
- Comments from regulators, manufacturers and other experts received and discussed in Seoul, May 2008
- Proposed changes incorporated and updated draft circulated for comments: June-October 08
- Proposed WHO Guidelines: presented to the ECBS 2008
- ECBS recommendations for further improvements

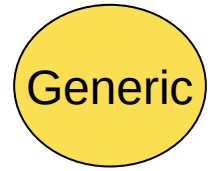
Definition of SBP

- SBP is a biological medicinal product developed to be "similar" in terms of quality, safety and efficacy (Q, S, E) to an already licensed, well established, reference medicinal product marketed by an independent applicant.
- two approaches (biosimilar and alternative) that might be used worldwide for proving similarity of products developed subsequently to the originator products.
- Key words: "developed subsequently" and "similar"

Licensure requirements- amount of data and applicability







Existing knowledge, full, comparative characterization, plus Comparative BUT reduced non-clinical, clinical data

Existing knowledge, full characterization, plus comparability of biological activity, clinical PK/PD, clinical efficacy and safety

For chemical entities only

Applicable to all biologicals

Pathways with reduced data applicable to some biologicals

Not applicable to biologicals

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Key issues in the evaluation of similar biological products

- Definition of "similar" biological product
- Proof of similarity – to what extent SBP should be similar to RMP?
- Comparability exercise - basis for evaluation of SBP
  - Reference product: rationale for its choice
  - Full analytical comparability vs comparability of CRITICAL parameters?
  - Clinical: non-inferiority vs equivalence?

Discussion point: examples to illustrate comparability studies for different products

Rationale for alternative approach

- Stand alone and Biosimilars approaches: two extremes
- For certain products with well known characteristics, simple structure: similarity in all aspects may not be needed
- Quality assessment on its own, without head-to-head comparison to the RMP BUT with full characterization of quality parameters
- Similarity in KEY aspects such as biological activity, PK/PD studies, efficacy and safety in humans

Prerequisites for reducing clinical data in alternative approach

1. Quality assessment
    1. Full characterization – key quality attributes defined; certain characteristics are known (publicly available information)
    2. Similarity in terms of biological activity demonstrated through head-to-head comparison with the RMP

2. Nonclinical testing - depends on
    - Extent of possible characterisation
    - Observed / potential differences
    - Clinical experience with substance class

Comparability/ Reference Medicinal Product (RMP)

- Main studies: use final formulation derived from final manufacturing process
- Reference product necessary for head to head comparison
- Same reference product for all comparative studies
- Purpose of comparability studies in CCA is to demonstrate similarity in terms of:
  - Biological activity
  - PK/ PD studies
  - Efficacy
  - Safety

Other relevant issues discussed

- Basic principles for evaluation and regulation of biological therapeutics
- INN – link between nomenclature and regulation of biological therapeutics
- Interchangeability and substitutability
- Patent, intellectual property and data protection
- Mechanisms for sharing the information

ECBS – Oct 2008

- Draft WHO guidelines presented to the ECBS and discussed in details
- The Committee affirmed that reduced data packages may be suitable to provide sufficient assurance for quality, safety and efficacy of certain biotherapeutic products
- The ECBS requested that a revised version of the document be prepared and submitted for public comments, and re-submitted to the ECBS in 2009.

ECBS recommendations

Clarifications and additional explanations on the following points requested:

1) Regulation of biotherapeutic products (licensing pathways)

2) Differences in the data packages provided for abbreviated pathways from those required for innovative product

3) Title and scope

Document applies only to well established, well characterized proteins derived by modern molecular methods. In particular, the ECBS advised that vaccines, plasma-derived products and recombinant clotting factors be excluded from the scope;

ECBS recommendations cont.

4) Quality assessment: comparability in terms of critical parameters (examples to be provided)

5) Design and specific requirements for clinical data to support licensing of similar biological products:
   - principles for reduction of clinical data;
   - design of comparative clinical efficacy studies;
   - size of safety database;
   - extrapolation of indication

6) Prescribing information (labeling, package insert)

Experience in countries where SBP are under development

- Regulators and manufacturers from India, China, S. Korea, Iran and other countries provided input to previous WHO meetings
- ICDRA meeting: Sep 2008, Bern
- Pharmacovigilance in Thailand
- Seminar organized by NICPBP in Beijing, Dec 2008: Chinese Regulators (SFDA and NICPBP) and manufacturers
- Tokyo, Feb 09: experience gained in Japan

Next Steps

- Drafting group meeting in Tokyo: 16 and 18 February 2009
  - Revision of the draft guidelines according to the ECBS requests
  - Review of examples
  - Consensus on key principles for evaluation of SBP and further revision of the guidelines
- Consultations with experts in 2009
- ECBS – Oct 2009

Many thanks

- To **WHO drafting group on biosimilars**:

1. Elwyn Griffiths and Kwasi Nyarko, Health Canada
2. Martina Weise and Hans-Karl Heim, BfArM
3. Yeowon Sohn, Jeewon Joung, KFDA
4. Emily Shacter, CDER, US FDA
5. Robin Thorpe and Meenu Wadhwa, NIBSC

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- **Many experts who provided advice on individual basis**