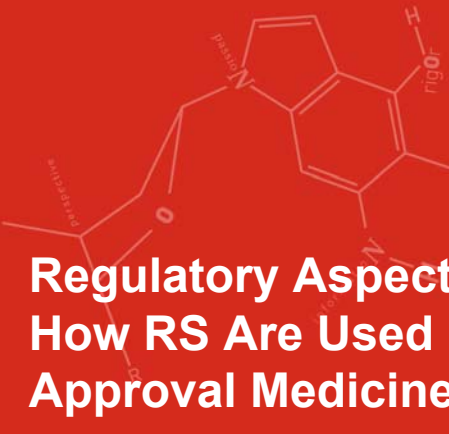


**13<sup>TH</sup> INTERNATIONAL SYMPOSIUM ON  
PHARMACEUTICAL REFERENCE STANDARDS**  
 Joint EDQM-USP Symposium organised by the  
 European Directorate for the Quality of Medicines & HealthCare (EDQM),  
 Council of Europe  
**13-14 March 2019, Strasbourg, France**



# Regulatory Aspects: How RS Are Used in Pre/Post Approval Medicines Framework


*Matthew Borer, Ph.D., Senior Research Advisor, Corporate Reference Standards*

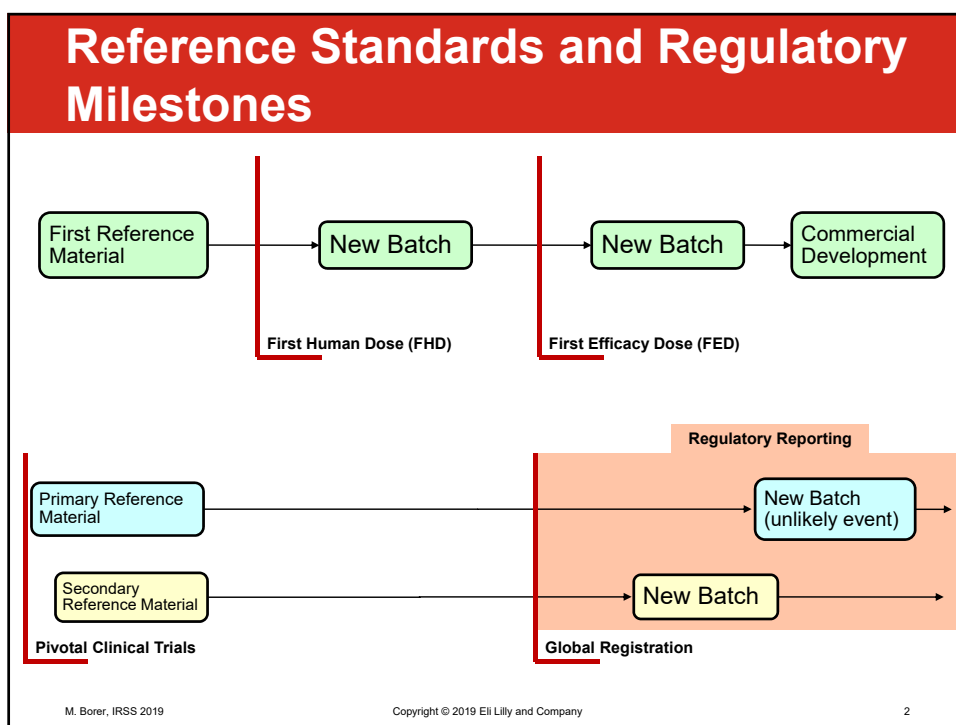
*Sally Anliker, Ph.D., Senior Research Advisor, Global Regulatory CM&C*

*Kim Dancheck, Consultant, Corporate Reference Standards*

*Erin Copeland Jones, Consultant, Corporate Reference Standards*

*David Lytle, Manager, Corporate Reference Standards*





# Lilly RS Quality System

*ICH Q12 "An effective Pharmaceutical Quality System (PQS) as described in ICH Q10 and compliance with regional GMPs are necessary for implementation of this guideline."*

## Global Quality Standard – Reference Standards

### Local Procedures

- Establishment and Maintenance
- Acquisition and Management of Materials and Components
- Production Records
- Finishing Operations
- Inventory Management
- Storage Facility Requirements
- Processing, Dispensing, Transferring, and Shipping
- Complaints and Withdrawals

## Content of Regulatory Submissions

## Disclaimers

- ◆ This presentation is focused on requirements associated with biologic reference standards
- ◆ Required regulatory submission content and expectations will differ for small molecules (typically less details are required)

## Reference Standard Information in Market Authorization Requests

- ◆ ICH M4: The Common Technical Document
- ◆ An agreement to organize the quality, safety, and efficacy information submitted to regulatory authorities in a defined format
  - Module 1 – Regional administrative information
  - Module 2
    - Quality overall summary
    - Non-clinical overview
    - Non-clinical summary
    - Clinical overview
    - Clinical summary
  - **Module 3 – Quality**
  - Module 4 – Non-clinical study reports
  - Module 5 – Clinical study reports

## Reference Standards - ICH

ICH Guideline	Expectation
ICH M4Q (CTD)	Information on Reference Standards or Materials placed in CTD Module 3 in 3.2.S.5 for drug substance and 3.2.P.6 for drug product
ICH Q6A (specifications for chemical products)	A reference standard must be characterized and evaluated as suitable for use in tests such as assay or identity using procedures that go beyond routine testing.
ICH Q6B (specifications for biologics)	Additional requirements beyond those for chemical products include preparation from lots representative of production and clinical materials, method of purification must be registered, and storage conditions provided.
ICH Q12	3.2.S.5 (drug substance reference standard) and 3.2.P.6 (drug product reference standard) sections of CTD identified as "established conditions" (EC) to be maintained via lifecycle

## Text from ICH...

### ◆ Q6A

#### 2.11 Reference Standard

A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. It should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing. For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and / or controlled, and purity should be measured by a quantitative procedure.

### ◆ Q6B

#### 2.2.1 Reference standards and reference materials

For drug applications for new molecular entities, it is unlikely that an international or national standard will be available. At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material. Where an international or national standard is available and appropriate, reference materials should be calibrated against it. While it is desirable to use the same reference material for both biological assays and physicochemical testing, in some cases, a separate reference material may be necessary. Also, distinct reference materials for product-related substances, product-related impurities and process-related impurities, may need to be established. When appropriate, a description of the manufacture and/or purification of reference materials should be included in the application. Documentation of the characterization, storage conditions and formulation supportive of reference material(s) stability should also be provided.

## ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- ◆ Scope covers drug substance, drug product, chemical and biological products, and drug-device combinations

**“This guideline provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner.”**
- ◆ Defines **Established Conditions** (EC) as “legally binding information (or approved matters) considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority.”
- ◆ In contrast, **“supportive information”** does not require a regulatory submission, if changed.

## Complexity with EC and Reference Standards

- ◆ Some of the reference standards information typically provided in the CTD is clearly EC
  - Protocol to manufacture and qualify new standards
- ◆ Some of the information is supporting
  - Characterization data for standards
  - History of standards used during development
- ◆ Careful management of the RS information in the CTD can facilitate lifecycle management
- ◆ **Register only the information required for each market and the level of detail required depending on product type**

# A Recommended Outline

## 3.2.S.5 Reference Standards or Materials

### ◆ Primary Reference Material

- *Describe the intended use of the Primary reference standard. Consistent with ICHQ7, the Primary RS should be reserved for use when characterizing Secondary reference standards. If an applicable Compendial reference standard is available, it is acceptable to refer to use of the Compendial RS as a Primary RS. In this case, the following sections are not necessary.*
- **Manufacturing Method**
  - *State if the reference material is obtained from typical production material. If the material undergoes additional purification, provide a description.*
- **Specifications of the Reference Material**
  - *Specifications must be established for the reference materials. The specification limits may be the same as for drug substance although purity specifications might be tighter if feasible (biologics must be similar purity). Some drug substance specifications will not be applicable to the reference standard.*
- **Analytical Procedures**
  - *This section should describe the methods used for reference standards specification tests. If the method is identical to one used for the drug substance, it is acceptable to refer to that section of the CTD.*
- **Container and Storage**
  - *A brief description of the reference standard storage container should be included. The storage temperature of the reference standard should be included.*

# A Recommended Outline

## 3.2.S.5 Reference Standards or Materials

### ◆ Secondary (Working) Reference Material

- *Describe the intended use of the Secondary Reference Material. Secondary reference standards are typically used as the “working standard” for routine Quality Control testing. Consistent with ICH Q7, the Secondary RM should be tested for suitability by comparison to the Primary RS.*
- **Manufacturing Method**
  - *State if the reference material is obtained from typical production material. If the material undergoes additional purification, provide a brief description.*
- **Specifications of the Reference Material**
  - *Specifications should be established for the reference materials. The specification limits may be the same as for drug substance although purity specifications might be tighter if feasible (biologics must be similar purity). Some drug substance specifications will not be applicable to the reference standard.*
- **Analytical Procedures**
  - *This section should describe the methods used for reference standards specification tests. If the method is identical to one used for the drug substance, it is acceptable to refer to that section of the CTD.*
- **Container and Storage**
  - *A brief description of the reference standard storage container should be included. The storage temperature of the reference standard should be included.*
- **Summary of Protocol for the qualification of a replacement secondary RS**
  - *Regulatory-level protocol required in several markets*

## A Recommended Outline

### 3.2.S.5 Reference Standards or Materials

#### ◆ Impurity Reference Material

- *If there are any reference materials for impurity compounds that are used in batch release testing of the drug substance, include information here. Information provided should be similar to above for Primary or Secondary RS but will be less detailed.*

## A Recommended Outline

Organize supporting information as separate documents in the CTD structure that will not be maintained during lifecycle. Examples:


#### ◆ Results

- *The Certificate of Analysis for the Primary and Secondary reference standards should be included here. Alternately, a table of test results can be included. Test results must include the specification tests and confirmation of adherence to specifications. Additional characterization tests may also be presented.*
- *Include representative figures such as chromatograms and spectra.*

#### ◆ GMP protocol for the qualification of a replacement Primary RS

#### ◆ History

- *A summary of the standards used throughout the development process can be included. Alternatively, this information could be placed into CTD section 3.2.S.2.6 Manufacturing Process Development*



# Change Management

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## Some Markets Require Reporting

- ◆ Include only the EC required for registration in each market
  - Avoid creating regulatory “footprint” to be maintained if not needed
- ◆ **Regulatory change provisions provide clues to what is EC**
- ◆ US FDA Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (July 1997)
  - New lot of, new source for, or different, in-house reference standard or reference panel resulting in modification of reference specifications or an alternative test method
  - Replacement of an in-house reference standard or reference panel according to SOPs and specifications in an approved application
- ◆ Canada Post-Notice of Compliance Changes: Quality Document
  - Qualification of a new lot of reference standard against the approved reference standard
  - Change to the reference standard qualification protocol
  - Extension of reference standard shelf life




## Reporting Markets, continued

- ◆ India Post approval changes in biological products:  
Quality safety and Efficacy Documents
  - Qualification of a reference standard according to an approved protocol
- ◆ JAPAN – Extensive expectations for EC to be registered and managed in lifecycle as partial change amendments (prior approval)
  - Both Primary RS and Secondary RS considered
  - Even simple changes can take a long time to implement

## Many Markets Do NOT Require Reporting

- ◆ European Union
  - Bosnia (EU identical market)
  - Israel (EU identical market)
  - Switzerland (uses EU variations guidance)
  - Turkey (typically consistent with EU)
- ◆ South Korea
  - Depending on EC registered
- ◆ Taiwan
  - Depending on EC registered
- ◆ Rest of World (dependent markets)
  - Depending on EC registered



# Regulatory Inconsistencies

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## Regulatory Inconsistencies

- ◆ Iraq
  - Primary RS required for importation testing (Iraq)
- ◆ Saudi Arabia
  - Expectation to receive a certain number of grams of RS regardless of the presentation (Saudi Arabia)
    - For a solution-based mAb RS, this could represent many years of the manufacturer's supply
- ◆ Several
  - Demand that the RS COA has at least 1 year of validity
  - Expectation that the RS will be within the first quarter of its valid use period

## Regulatory Inconsistency, Cont.

- ◆ Singapore (MIV-1), minor variation
  - New Biologic RS Implementation
    - Certificate of analysis of the proposed reference standard
    - Amended relevant CTD sections
    - A declaration that there is no change to the preparation and calibration/qualification protocols, if applicable
    - **Batch analysis data of the drug substance or drug product on at least two production batches using the currently registered and proposed reference standard**

## Regulatory Inconsistency, Cont.

- ◆ Australia –
  - Require pre-approval prior to implementing a new in-house reference standard (approval timing is 45 days after submission) if protocol was not included in the submission
- ◆ Russia
  - RS CoA needs to include more than “meets system suitability” but rather numerical results that show that individual impurity peaks are at an appropriate threshold (which could uncover lack of data supporting what levels are acceptable)

## Brazil: RDC 166/2017, Article 14

- ♦ XXII.- characterized reference chemical substance (CRCS): substance or mixture of chemical or biological substances in which the identity, quality, purity, content and power have been ensured by a characterization process;

- ♦ XXIII.- pharmacopeia reference chemical substance (PRCS): substance or mixture of chemical or biological substances established and distributed by official compendia recognized by Anvisa;

**Long story short:  
It is required to use a  
pharmacopeia  
reference standard for  
method validation OR a  
CRSC (which seems to  
be a synonym for the  
Primary RS)**



### RESOLUTION RDC No 166, OF JULY 24th, 2017

Provides about the validation of analytical methods and sets forth other provisions.

#### CHAPTER III REFERENCE CHEMICAL SUBSTANCES

Art. 14 For the validation of analytical methods, a Pharmacopeia Reference Chemical Substance (PRCS) made preferably official by the Brazilian Pharmacopeia or by other compendia officially recognized by Anvisa must be used.

§ 1 The use of a Characterized Reference Chemical Substance (CRCS) will be allowed with the presentation of a concluding characterization report for the lot being evaluated, including the technical reasons for selecting assays used and the pertaining rough data.

§ 2 Anvisa and the members of the Sanitary Surveillance National System may require samples of CRSC intended to evaluate the characterization process in the hypotheses of the previous paragraph and, with the emergence of the need of a fiscal analysis a CRSC sample must be provided intended to run the necessary tests.

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t. +55 11 5180-3499 f. +55 11 5183-4247  
[www.interfarma.org.br](http://www.interfarma.org.br)

## Brazil: RDC 166/2017, Article 15

- ♦ Art. 15 The characterization report, depending on the analyte, must contain data obtained from techniques applicable to the characterization of each chemical substance, as for example, thermogravimetry, fusion point, differential exploratory calorimetry, infra-red spectroscopy, mass spectrometry, nuclear magnetic resonance, elemental analysis (carbon/hydrogen/nitrogen), X-ray diffraction, optical rotation, chromatography methods, among others.

- § 1 In addition to characterization data the following information should be included in the report:
  - I.- substance lot number and expiration date used in the characterization;
  - II.- Brazilian common denomination or international common denomination;
  - III.- CAS number;
  - IV.- chemical name;
  - V.- synonym;
  - VI.- molecular and structural formula;
  - VII.- molecular weight;
  - VIII.- physical form;
  - IX.- physical-chemical properties;
  - X.- impurity profile;
  - XI.- manipulation and conservation care; and
  - XII.- analytical report proving identity, content and expiration date of the CRCS.
- § 2 For biological products, the characterization of material/reference standard must be performed using the appropriate state-of-the-art methods.

## Conclusion

- ◆ Reference standards are a critical aspect of ensuring product quality
- ◆ Global regulatory expectations for reference standards aspects of registrations are evolving
- ◆ Careful registration of “established conditions” can prevent over-committing to details that must be maintained through the product lifecycle
- ◆ Industry should encourage health authorities to adopt EU-like expectations for lifecycle
  - Leaves many aspects such as qualification of new secondary standards to quality systems rather than regulatory reporting
- ◆ Inconsistent regulatory expectations are a burden on the healthcare system

# Thank You!



## WHO standards: tools for regulatory convergence

Dr Ivana Knezevic, WHO

EDQM, 13-14 March 2019, Strasbourg

### Outline



1. WHO standards to assure quality, safety and efficacy of medical products including vaccines and other biologicals
2. Development and establishment of WHO standards
3. WHO roles in facilitating implementation of WHO standards into regulatory and manufacturers' practices
4. WHO standards as a basis for regulatory convergence
3. Opportunities for collaboration in the area of trainings

# “Together for a healthier world”

Dr Tedros Adhanom Ghebreyesus

Key Themes of WHO's  
13<sup>th</sup> General Programme of Work  
2019-2023



Health  
ization

## Mission

Promote Health - Keep the World Safe - Serve the Vulnerable

## Strategic Priorities

**Health Coverage:** 1 billion more people with health coverage  
**Health Emergencies:** 1 billion more people made safer  
**Health Priorities:** 1 billion lives improved

NEW Cluster

**Access** to Medicines, Vaccines and Pharmaceuticals (MVP)

Dr. Mariângela SIMÃO, Assistant Director General

at EB 2019

Roadmap on **access** to medicines and vaccines

[http://www.who.int/medicines/access\\_use/road-map-medicines-vaccines/en/](http://www.who.int/medicines/access_use/road-map-medicines-vaccines/en/)

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## World Health Organization (WHO)



WHO is a specialised agency of the UN serving as the directing and coordinating authority for international health matters and public health on behalf of its 194 Member States.

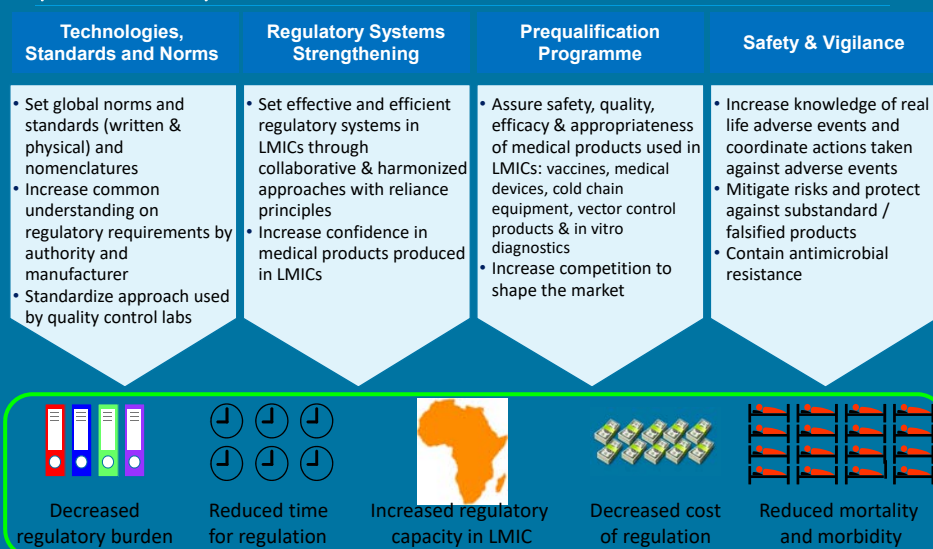
WHO is operating at 3 levels, HQ in Geneva, 6 regional offices and 150 country offices

Principle objective - *the attainment by all people of the highest possible level of health.*

WHO is responsible for providing leadership on global health matters, shaping the health research agenda, **setting norms and standards**, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.

Setting norms and standards and promoting their implementation is affirmed as **a core function** of WHO for the period 2014-2020.

## WHO Activities to assist Regulators: Focus on Access and Outcomes: Ensuring normative and technical excellence drives impact at country level



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## WHO Norms and standards for medicines



### International Chemical Reference Substances – ICRS

- primary reference substances
- for users of *The International Pharmacopoeia* to perform the physical and chemical tests described in the compendium
- established, distributed, stored since 2010 by EDQM
- released by WHO Expert Committee on Specifications for Pharmaceutical Preparations
- about 250 substances available at EDQM website



Slide kindly provided by H. Schmidt, MQA, WHO

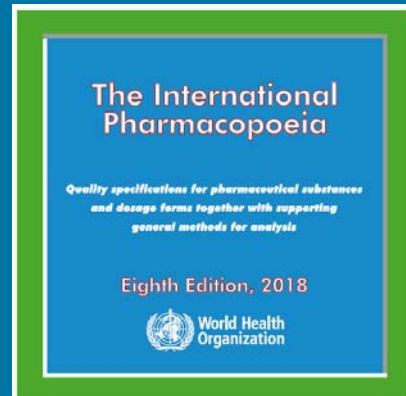


## WHO Norms and standards for medicines



### The International Pharmacopoeia

- focus on essential medicines
  - Model List of Essential Medicines (EML)
  - Invitations to submit EOI for product evaluation to WHO Prequalification Team - Medicines
  - WHO/UN specific disease programmes
- preferably not already described in other pharmacopoeias



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Schmidt, MQA,  
WHO

## WHO Norms and standards



### International Standards for Antibiotics (WHO ISA)

- primary reference substances
- to calibrate regional or national secondary standards that are subsequently used as references in microbiological assays of antibiotics
- established, distributed, stored since 2006 by EDQM
- released by WHO Expert Committee on Biological Standardization
- 23 reference substances available at EDQM website

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# WHO norms and standards for biologicals

Health  
nization

69<sup>th</sup> meeting of the ECBS (29 Oct-2 Nov 2018) -Executive Summary:

[http://www.who.int/biologicals/WHO\\_ECBS/en/](http://www.who.int/biologicals/WHO_ECBS/en/)

## Global written standards

**Total 97 docs (Recommendations/ Guidelines)**  
General docs that apply to vaccines & BTP: 10  
General documents that apply to all vaccines: 12  
Vaccine specific: 66  
BTP specific: 9

## Global measurement standards

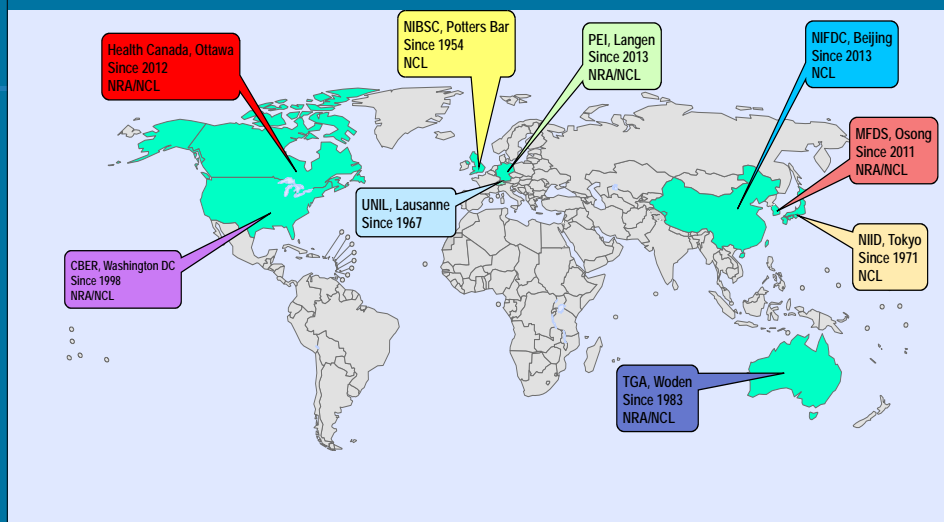


## Scientific evidence

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

Measurement standards:  
essential elements for  
development, licensing  
and lot release

## WHO COLLABORATING CENTERS IN THE AREA OF VACCINE RESEARCH AND STANDARDIZATION



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Data Source: World Health Organization



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## First-ever WHA Resolution on biotherapeutic

- WHA 67.21, 2014: "Access to BTPs including similar biotherapeutic products and ensuring their quality, safety, and efficacy"

Member States	WHO
To develop the necessary scientific expertise to facilitate development of solid, scientifically-based regulatory frameworks	To support MS in strengthening their capacity in the area of the health regulation of BTPs, including SBPs
To develop or strengthen, national regulatory assessment and authorization frameworks	To support the development of national regulatory frameworks that promote access to quality, safe, efficacious and affordable BTPs, including SBPs
To work to ensure that the introduction of new national regulations, where appropriate, does not constitute a barrier to access to BTPs/SBPs	To encourage and promote cooperation and exchange of information among MS in relation to BTPs/SBPs
	To convene the WHO ECBS to update the SBP GLs adopted in 2009 <ul style="list-style-type: none"> <li>• taking into account the technological advances for the characterization of BTPs; and</li> <li>• considering national regulatory needs and capacities</li> </ul>

## 18<sup>th</sup> International Conference of Drug Regulatory Authorities (ICDRA)



To provide drug regulatory authorities of WHO MS with a forum to meet and discuss ways to strengthen collaboration.

Held every two years, well established forum for NRAs, WHO and interested stakeholders to determine priorities for regulation of medicines.

- 18<sup>th</sup> ICDRA, Dublin, Ireland, 5-7 September 2018
  - Government officials and regulators from more than 100 WHO MS
  - Main theme: "SMART SAFETY SURVEILLANCE: A LIFE-CYCLE APPROACH TO PROMOTING SAFETY OF MEDICAL PRODUCTS"
  - General issues: Benchmarking, Reliance, Collaboration
  - Specific themes: Public Health Emergencies, Biosimilars, Advanced therapies etc
  - ICDRA recommendations:
[https://www.who.int/medicines/areas/quality\\_safety/regulation\\_legislation/icdra/en/](https://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/en/)

## WHO Guidelines for BTP including SBP

information available at <http://www.who.int/biologicals/biotherapeutics/en/>



- **For approval**

Originator Biotherapeutic (BTP)	Similar Biotherapeutic Product (SBP)
WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, adopted by WHO ECBS 2013 (requested by ICDRA 2010)	<ul style="list-style-type: none"> <li>• WHO Guidelines on evaluation of similar biotherapeutic products, adopted by WHO ECBS 2009 (requested by ICDRA 2006)</li> <li>• WHO Guidelines on evaluation of monoclonal antibodies as SBPs, adopted by the WHO ECBS 2016 (requested by ICDRA 2014)</li> <li>• Draft WHO Q&amp;A: Similar biotherapeutic products, adopted by the WHO ECBS 2018 (requested by ICDRA 2014)</li> </ul>

- **For post-approval management**

BTP licensed as generics	Post approval changes (variations) for BTP & SBP
Regulatory assessment of approved BTPs, adopted by WHO ECBS 2015 (requested by ICDRA 2010)	WHO Guidance on procedures and data requirements for changes to approved BTPs, adopted by WHO ECBS 2017 (requested by ICDRA 2014)

12/03/2019

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## Implementation of standards:

(requested by ICDRA 2010, 2014, 2016)

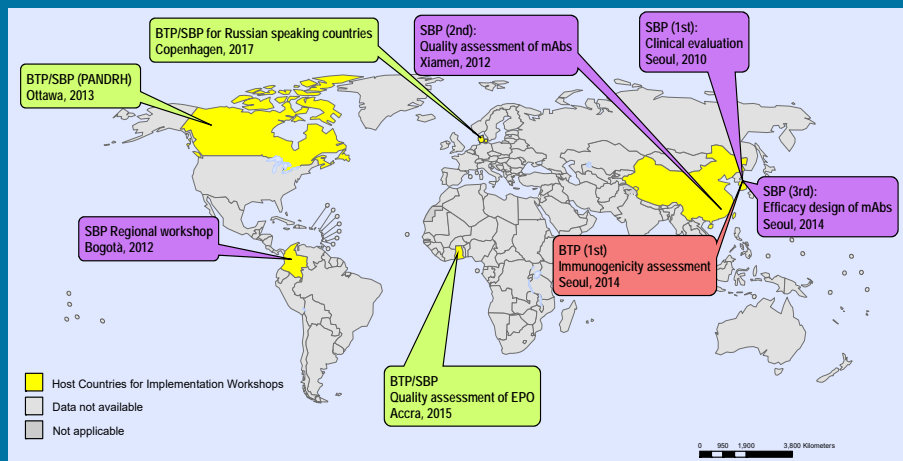


- **Implementation workshops** on the guidelines has become an increasingly important tool in achieving regulatory convergence.
  - WHO HQ & RO to Organize
  - Supported by Collaborating Centers, national regulatory authorities and WHO Regional Offices/Country Offices
  - Share experience among countries
  - Obtain information from countries
    - Their use and their capacity to follow the guiding principles in WHO documents
    - Their interpretation
  - Practice some of evaluation principles through case studies
- **Publications:** e.g. meeting reports, case studies, lectures, Q&A.
- **Collaborative activities** with other initiatives

12/03/2019

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## Implementation Workshop on BTP including SBP (2010-2017)



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Data Source: World Health Organization



## Implementation workshops for BTP/ SBP Guidelines



- Adopted: SBP by ECBS 2009; BTP by ECBS 2013

	Global level				Regional level		
Imp. workshop	1 <sup>st</sup> SBP	2 <sup>nd</sup> SBP	3 <sup>rd</sup> SBP	1 <sup>st</sup> BTP	SBP & BTP in AFR, Eng spk countries	SBP in EUR, Russian spk countries	SBP & BTP in EMR
When	Aug 2010	May 2012	May 2014		Sept 2015	July 2017	July 2018
(Co-) Host Where	MFDS Korea	NIFDC China	MFDS Korea		Ghana FDA Ghana	WHO EURO Denmark	WHO EMRO Oman
Participants	11 NRAs	16 NRAs	23 NRAs		16 NRAs	10 NRAs	19 NRAs
Main topic	Clinical study design: Eq vs NI	Quality assessment of mAbs	Efficacy study design on mAbs	Immuno-genicity assess of mAbs	Quality assessment of EPO		Strengthen regulation: Pre- & Post-licensure

## Publications: Outcomes of implementation workshops



When	Type & Topic	Publication
1 <sup>st</sup> WS for SBP 2010	Meeting report	<i>Biologicals</i> 39 (5), 2011
	Special lecture: Statistical considerations for confirmatory clinical trials for SBPs	
	Case study: Comparing equivalence and non-inferiority approaches	
2 <sup>nd</sup> WS for SBP 2012	Case study: The role of the quality assessment (of mAbs) in the determination of overall biosimilarity	<i>Biologicals</i> 42 (2), 2014
3 <sup>rd</sup> WS for SBP 2014	Case study: Efficacy study design and extrapolation: Infliximab & Rituximab	<i>Biologicals</i> 43 (1), 2015
1 <sup>st</sup> WS for BTP 2014	Special lecture: Immunogenicity assessment of BTPs: An overview of assays and their utility	<i>Biologicals</i> 43 (5), 2015
	Case study: Assessment of unwanted immunogenicity of mAbs: TNF antagonist & CD20 mAbs	
WS in AFR & EUR 2015, 2017	AFR Meeting report	WHO web, 2016
	Case study: The role and influence of the quality assessment of EPO	In preparation

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## ICDRA recommendations to WHO and collaboration with IPRP BWG



Activities/ Deliverables with IPRP	ICDRA recommendations
Template for Public Assessment Summary Information for biosimilars to assure consistency and transparency of the review process, 2016	<b>2010:</b> Develop a <a href="#">template</a> for Member States to share information on the scientific basis for licensing SBPs
Reflection paper on extrapolation of indications in authorization of biosimilar products, 2017	<b>2014:</b> Amend GLs on evaluation of SBP by providing <a href="#">additional information</a> , e.g. extrapolation of indication, evaluation of mAbs, acceptance of RBP, comparability exercise
Manual for regulatory reviewers: The basics of analytical comparability for biosimilar monoclonal antibodies, 2017 (English, Russian, Spanish versions)	<b>2014:</b> <ul style="list-style-type: none"> <li>Update norms, standards, and <a href="#">tools</a> to facilitate further development of expertise for regulatory evaluation of biologicals.</li> <li>Facilitate <a href="#">implementation</a> of existing GLs</li> </ul>
Establishment of IPRP BWG Regulatory Information Sharing Platform by 2018	<b>2014 &amp; 2016:</b> <ul style="list-style-type: none"> <li>Continually <a href="#">update information</a> regarding WHO standards for biologicals through regional and/or inter-regional networks and initiatives.</li> <li>Provide a forum for <a href="#">information-sharing</a> on collaborative efforts that leads to better access</li> </ul>

12/03/2019

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## Regulatory convergence: opportunities and challenges



1. Science based WHO standards for science based regulation - common Tools
2. WHO roles in regulatory convergence:
  - Set of definitions as a tool for common understanding in all member states
  - Provision of international standards for regulatory evaluation of biologicals
  - Educational and training tools for improving the expertise at NRAs - implementation workshops with lectures and case studies.
3. Many international and regional initiatives - an opportunity for update on WHO standards through regulatory, industry and Ph networks but also challenge:
  - DCVRN, PANDRH, AVAREF, ASEAN, APEC Harm. Center, IPRF, CoRE
  - IFPMA, IGBA, Medicines for Europe, DCVMN, BIO, DIA, CASSS
  - Pharmacopoeias, FIP
4. Successful collaboration with IABS: NGS, HCT, cell therapies
5. Opportunities for collaboration in the area of trainings: IPRP Biosimilars Working group and APEC CoE and RHSC - biotherapeutics including biosimilars

## Many thanks to...



...my team  
(NSB/TSN/EMP/WHO)

...members of WHO drafting  
and Working Groups

...colleagues from  
Collaborating Centers and  
Custodian Laboratories...

many individual experts

Further information and  
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Dr Ivana Knezevic

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Biological standardization  
website:

[www.who.int/biologicals](http://www.who.int/biologicals)

Dr Ivana Knezevic, WHO



## Establishment of Reference Standards for Biotherapeutics: A Regulator's Perspective

Evangelos Bakopanos, Ph.D.  
Senior Biologist/Evaluator, Monoclonal Antibodies Division  
CERB/BGTD/Health Canada

EDQM-USP  
13th International Symposium on Pharmaceutical Reference Standards  
March 13-14, Strasbourg, France

YOUR HEALTH AND SAFETY... OUR PRIORITY.



### Disclaimer

- The views expressed in this presentation are my opinion based on my experience as a reviewer/evaluator of biological drug submissions and do not convey official Health Canada policy.



## **Biologics and Genetic Therapies Directorate (BGTD)**

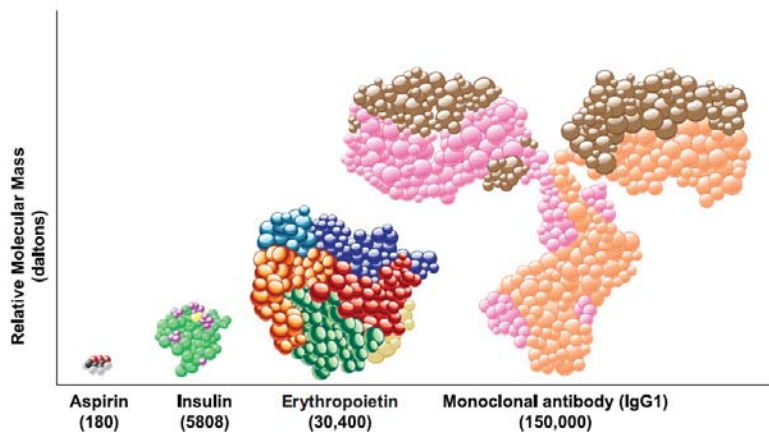
- Health Canada's BGTD is the Canadian regulatory authority of biological drugs and radiopharmaceuticals for human use in Canada.
- Centre for Biologics Evaluation
  - viral and bacterial vaccines
  - blood and blood products
  - cells, tissues and organs
- Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics
  - monoclonal antibodies
  - cytokines
  - hormones
  - enzymes
  - cell and gene therapies
  - radiopharmaceuticals

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## **Biological Drugs**

- Derived through the metabolic activity of living organisms
- Structurally complex
- Complex structure-function relationship
- Heterogeneous mixtures
- Sensitive to physical conditions
- Produced via complex & multistep manufacturing processes
- Inherent batch-to-batch variability
- Sensitive to manufacturing changes
- Multiple Critical Quality Attributes

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## Control Strategy

- The quality of the material made at commercial scale should be representative of the lots used in preclinical and clinical studies. (ICH Q6B)
- A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. (ICH Q10)
- Includes, but is not limited to:
  - GMP & Pharmaceutical Quality Systems
  - Raw material controls
  - Process validation
  - Control of critical process parameters
  - In-process control (IPCs) testing
  - Release & Stability testing
  - **In-house reference materials/standards (ICH Q6B)**

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## Intended use of In-house Reference Standards

- Comparative analytical methods:
  - Quantitative (e.g. calibrator for the measurement of biological activity)
  - Qualitative (e.g. comparator for purity testing)
  - Assay performance control to assess system suitability
- Lot release testing
- Stability testing
- Characterization studies
- Comparability assessments

## ICH Q6B

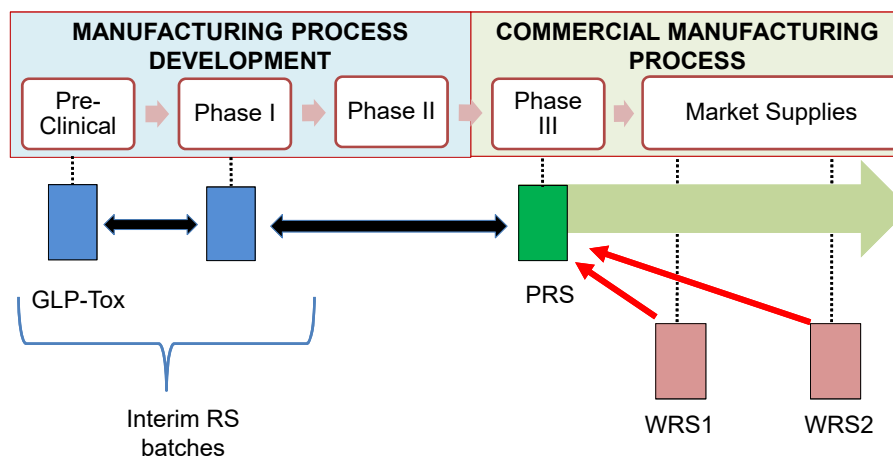
- **In-house Primary Reference Material/Standard:** At the time of submission, the manufacturer should have established an appropriately characterized material prepared by the manufacturer from lot(s) representative of production and clinical materials for the purpose of biological assay and physicochemical testing of subsequent lots, and against which in-house working reference material is calibrated.
- **In-house Working Reference Material/Standard:** A material prepared similarly to the primary reference material that is established solely to assess and control subsequent lots for the individual attribute in question. It is always calibrated against the in-house primary reference material.
- Where an **international or national reference standard is available and appropriate**, reference materials should be calibrated against it.

## ICH Q6B

- While it **is desirable to use the same reference material for both biological assays and physicochemical testing**, in some cases, a separate reference material may be necessary.
- Also, distinct **reference materials for product-related substances, product-related impurities and process-related impurities**, may need to be established.

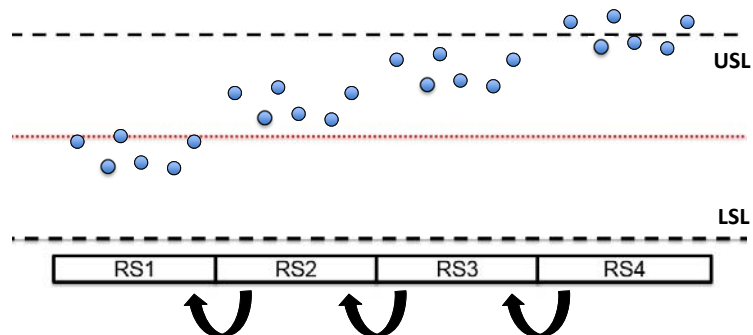
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## Example of an In-house Reference Standard Timeline



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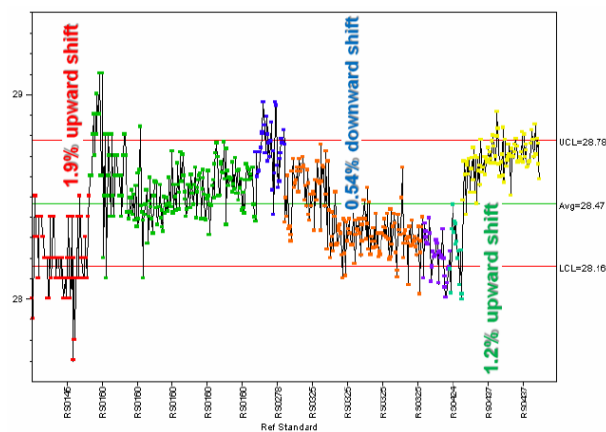
## Sequential RS Comparison



\* Simulated data

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## Example of Potency Shifts



Reference: WHO/BS/10.2143 - Working document QAS/10.381

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### In-house Reference Standards Program

- SOP(s) for the selection, preparation, qualification, requalification, stability monitoring, replacement and management all in-house reference standards used by Quality Control to determine the identity, potency, purity and other quality attributes throughout the product life cycle.
- Acceptance criteria for the qualification and requalification of in-house primary and working reference standards should be scientifically sound and justified.
- Traceability to any international or compendial reference standard, if available and **appropriate**.

### External Reference Standards

- WHO International Standards
- Pharmacopoeia Reference Standards (Ph.Eur., USP, etc.)
- NIBSC Reference Materials
- Not for clinical use in humans (i.e. **not biosimilar reference products**)
- Donated material
- Limited supply
- Each standard has a specific intended purpose
- Establish its suitability under actual conditions of use

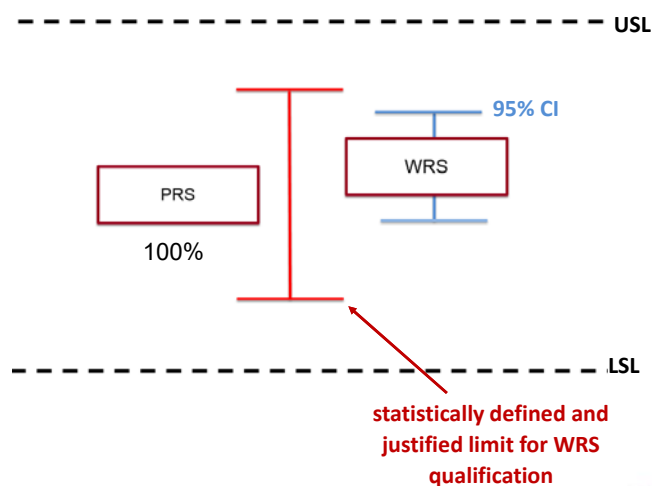
## ICH Q6B

- The results of biological assays should be expressed in units of activity calibrated against an international or national reference standard, when available and appropriate for the assay utilized.
- Where no such reference standard exists, a characterized in-house reference material should be established and assay results of production lots reported as in-house units.
- Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass.

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## No International or National Reference Standard

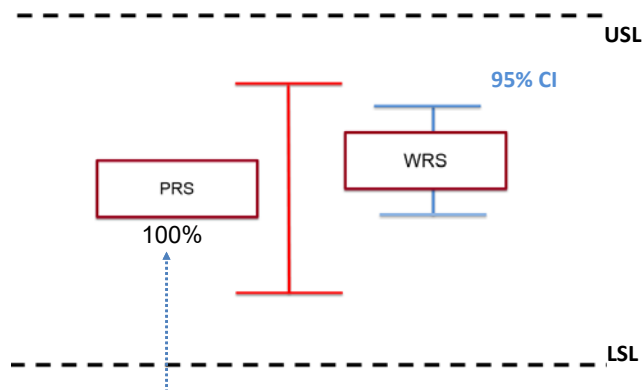
Product dosage/label in mass (mg)



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## Available International or National Reference Standard

Product dosage/label in mass (mg)



Use international or national standard (IU) to periodically monitor performance of in-house primary reference standard?

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## WHO International Standard for Infliximab

- Innovator product (i.e. biosimilar reference product) labelled in “mass” (mg).
- NIBSC developed the first IS for infliximab (anti-TNF product).
- Assigned potency values of 500 IU/ampoule of TNF neutralizing activity and 500 IU/ampoule of binding activity.
- Intended to support in vitro bioassay calibration and validation by defining international units of bioactivity.
- The proposed unitages are not intended to revise product labelling or dosing requirements.
- Not intended for determining the specific activity of products, nor to serve any regulatory role in defining biosimilarity.

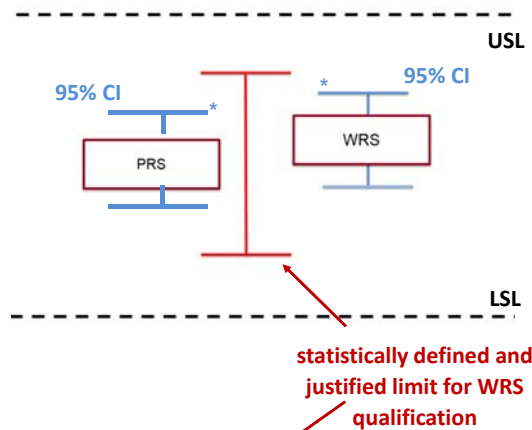
Reference: MABS 2019, VOL. 11, NO. 1, 13–25

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## Available and Appropriate International or National Reference Standard (IU)

Product dosage/label in IU



\* Must be within established precision acceptance criteria

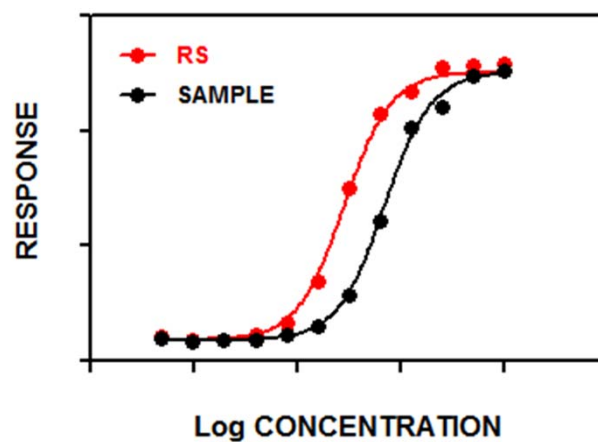
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## Potency Assignment

- The approach used to assign potency to in-house reference standards should be scientifically sound and justified with sufficient supporting data.
- Therapeutic use of products should be considered in establishing in-house reference standard qualification criteria.
- Number of replicates for the potency assay depends on intermediate assay precision, level of confidence, width of desired confidence interval, and the probability of data being outside that interval.
- If the potency value of a candidate in-house reference standard falls outside the established limit, question the suitability of the material.
- Where an international or national reference standard is **available and appropriate**, reference materials should be calibrated against it.

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## Relative Potency Assessment



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## USP Erythropoietin for Bioassays RS

- Biological activity of EPO shows a complex relationship between structure and function.
- The ratio of in vitro to in vivo activity is inversely correlated with type and degree of terminal sialylation.
- Highly sialylated products have a higher level of in vivo activity; thus, they have a relatively lower ratio of in vitro to in vivo activity.
- USP Erythropoietin for Bioassays RS is assigned a unitage that represents its activity in both in vivo assays and in vitro assays.
- The use of an in vitro assay to measure the biological activity of an EPO preparation requires a full understanding of the relationship between the EPO's in vivo and in vitro activity.

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## USP Erythropoietin for Bioassays RS

- If the ratios of in vitro to in vivo potency for the material being tested and the USP Erythropoietin for Bioassays RS are equivalent, then the USP Erythropoietin for Bioassays RS can be used directly in the in vitro assay to calibrate the material being tested.
- If the ratios are not equivalent, then the material being tested and the USP Erythropoietin for Bioassays RS have a different ratio of in vitro to in vivo potency, and the standard cannot be used with its assigned potency in the in vitro assay.
- Instead, this ratio determined for the material being tested should be used to assign a process-specific in vitro assay unitage to the USP Erythropoietin for Bioassays RS.
- The USP Erythropoietin for Bioassays RS, with its adjusted in vitro assay unitage, then can be used in the in vitro assay to transfer the unitage from the USP Erythropoietin for Bioassays RS to the material being tested.

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## ICH Q6B

- The results of biological assays should be expressed in units of activity calibrated against an international or national reference standard, when available and appropriate for the assay utilized.
- Where no such reference standard exists, a characterized in-house reference material should be established and assay results of production lots reported as in-house units.
- Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass.

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## Health Canada GMP guide (GUI-0001)

- Reference standards are available in the form of the current reference standards listed **in Schedule B to the Act**. When such standards have not been established or are unavailable, primary standards can be used. Secondary standards are verified against a Schedule B reference standard or against the primary standard and are subject to complete confirmatory testing at predetermined intervals.

### SCHEDULE B

(Section 10)

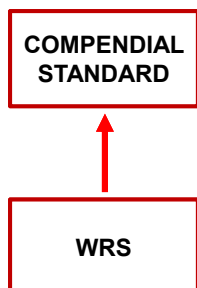
The most recent editions, including all errata, supplements, revisions and addenda, of the following standards:

Column I		Column II
Item	Name	Abbreviation
1	European Pharmacopoeia	(Ph.Eur.)
2	Pharmacopée française	(Ph.F.)
3	Pharmacopoeia Internationalis	(Ph.I.)
4	The British Pharmacopoeia	(B.P.)
5	The Canadian Formulary	(C.F.)
6	The National Formulary	(N.F.)
7	The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals	
8	The United States Pharmacopoeia	(U.S.P.)

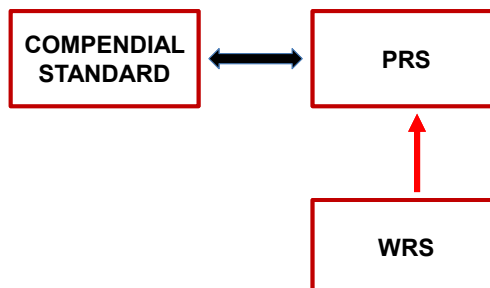
R.S., 1985, c. F-27, Sch. B; SOR/85-276; SOR/89-315; SOR/90-160; SOR/94-288; SOR/95-530, s. 2; SOR/96-96.

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**A**



**B**



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## Conclusion

- In-house reference standards are key elements of a product's control strategy.
- The use of two different tiers of in-house reference standards (as per ICH Q6B) help maintain consistent analytical test results and to preserve a reliable link between analytical data and clinical studies throughout the product's life cycle.
- Acceptance criteria for the qualification and requalification of in-house primary and working reference standards should be scientifically sound and justified.
- Where an international or national reference standard is available and appropriate, reference materials should be calibrated against it.

# Establishment of Reference Standards: Point of view of Japan

Tsuyoshi Ando PhD

Director

Division of Pharmacopoeia and Standards for Drug

Office of review management



Pharmaceuticals and Medical Devices Agency (PMDA)

## Topics

- Role of PMDA in JP RS establishment
- Definition of RS in JP
- Establishment of new JP RS



Pharmaceuticals and Medical Devices Agency (PMDA)

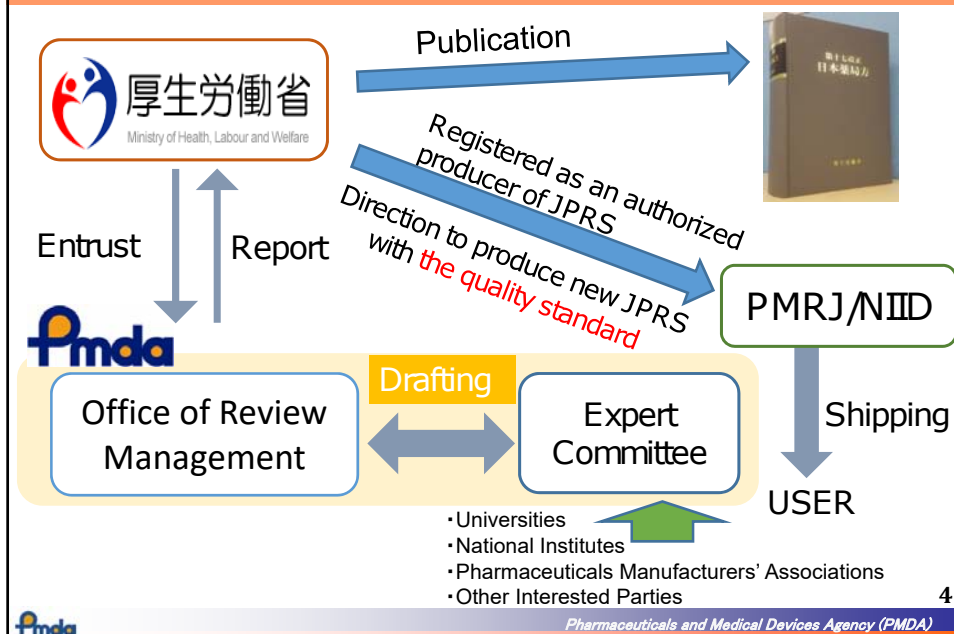
## Reference Standard

*"Generally, reference standards are standard materials used for quality tests of pharmaceuticals, prepared to constant quality, **assured its level of quality by official organization**, and supplied officially."*

*General Tests , Reference Standards <9.01> in*

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## Role in new JP RS establishment of PMDA



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## Reference Standards in JP17: Types and Use

- (1) Reference standards other than antibiotics are prepared and supplied by the Pharmaceutical and Medical Device Regulatory Science Society of Japan (PMRJ\*).

\*The current supplier of JP RS registered by the MHLW according to the Ministerial ordinance established by the Minister.

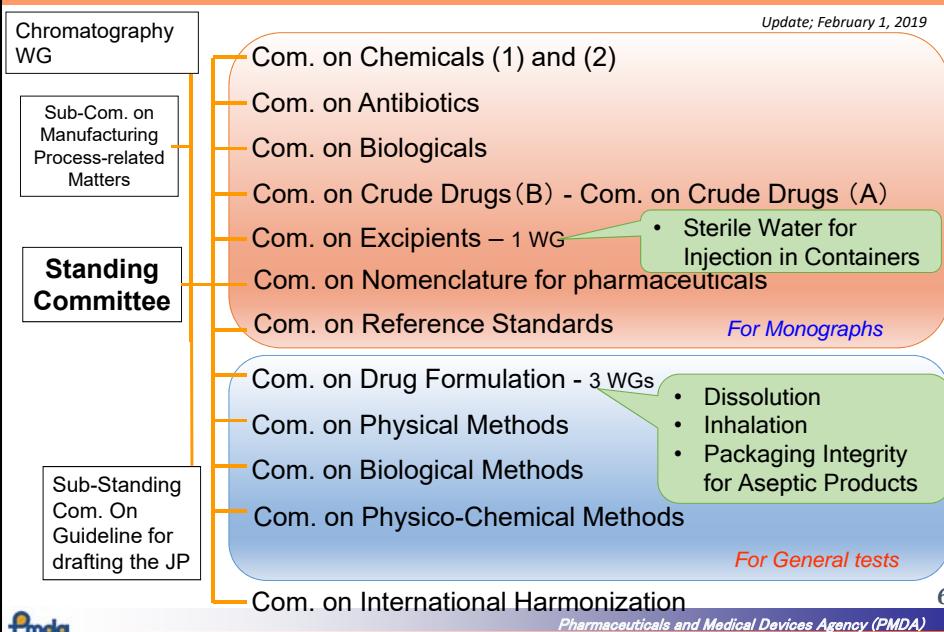
- (2) Reference standards of antibiotics are prepared and supplied by the National Institute of Infectious Diseases (NIID\*\*).

\*\*One of the research institutes under the MHLW

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## Organization of JP Expert Committees

Update: February 1, 2019



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## What's Quality Standards for JP

### ***Test items and their test procedures:***

*to be performed for obtaining necessary data for quality evaluation of the candidate raw material of RS*

e.g., List of the test items[RS of Chemical drugs]

- ✓ Structural formula of RS
- ✓ Molecular formula and molecular mass
- ✓ Chemical name, CAS registry number
- ✓ Description: Appearance
- ✓ Identification
- ✓ Specific physical and/or chemical values
- ✓ Purity
- ✓ Loss on drying or Water
- ✓ Assay
- ✓ Storage (Storage condition, Container)

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## Reference Standard in ICH Q6A

*A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. It should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing. For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and / or controlled, and purity should be measured by a quantitative procedure.*

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## Reference Standard in ICH Q6B

- ✓ *International or national standards*
- ✓ **In-house Primary Reference Material**  
An appropriate characterized material prepared by the manufacture from a representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots.
- ✓ **In-house Working Reference Material**  
A material prepared similarly to the primary reference material that is established solely to assess and control subsequent lots for the individual attribute in question. It is always calibrated against the in-house primary reference material.

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## JP Reference Standards

- ✓ Used for the tests of drugs specified in the JP and for the General Tests
- ✓ Used for Assay, Identification, Purity, calibration of apparatus and system suitability in monographs and in the General Tests

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## RS in JP17 General Information\*

1. Basic terms of reference standards
2. Classification of the JP reference standards by use
3. Names and uses of JP reference standards
4. Requirements for establishment of JP reference standards
5. Quality evaluation items required for JP reference standards
6. Reference materials specified in the JP
7. Precautions for the use of JP reference standards

\*General information: G9 Reference Standards, Reference Standards and Reference Materials Specified in the Japanese Pharmacopoeia

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Pharmaceuticals and Medical Devices Agency (PMDA)

## Point to consideration:

### establishment of new JP reference standards

- ✓ To adopt a relative determination (chromatography for a quantitative test, etc.) ➡ RS for Assay
- ✓ To appoint a comparison method for an identification (comparison of retention time in chromatography, etc.)  
➡ RS for Identification\*
- ✓ In a purity where a specific related substance or contaminant is analyzed ➡ RS for Purity \*
- ✓ If the system suitability cannot be adequately evaluated by conventional JP methods  
➡ RS for System Suitability \*

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\*: Unless using RS for the assay

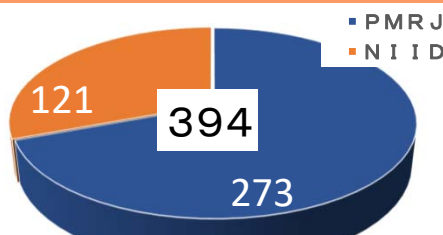
Pharmaceuticals and Medical Devices Agency (PMDA)

## Do not establishment of new JP reference standards

- ✓ Uncertainty, the continuous supply of the raw materials for the reference standard
- ✓ When a material utilized as standard has the use other for quantitative assay and can be obtained as a CRM, a reference material for other test or a reagent
  - ➡ Test Solutions<9.41>

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## The number of RS in JP17-1



The number of RS intended use in JP17-1			JP17-2*
Intended use	Number		
For Identification	7	+2	9
For Purity	3		3
For Apparatus Suitability	6	+1	6
For System Suitability	5		6
For Calibration of Apparatus	1		1
For Digestion Test	1		1
Not specified	371		378
Total	394		404

\* published in May 2019

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*Thank you for your attention*