Setting Pharmacopoeia standards for biotherapeutic products – WHO policy

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Essential Medicines and Health Products Department

World Health Organization

IT'S THE CORE OF WHO'S CORE BUSINESS

The Constitution requires WHO “to develop, establish and promote international standards with respect to biological and pharmaceutical products”.

This has been done for more than 60 years now

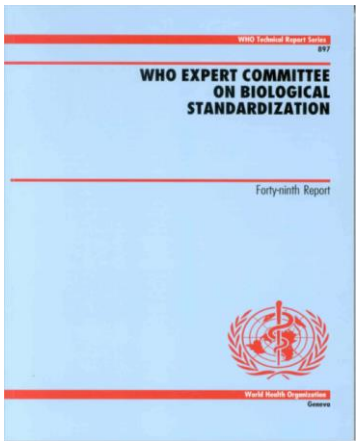
The norms and standards are established by Expert Committees

WHAT IS A WHO EXPERT COMMITTEE?

- Official Advisory Body to Director-General of WHO
- Established by World Health Assembly or Executive Board
  - **WHO Expert Committee on Specifications for Pharmaceutical Preparations**
    Secretary: Dr Sabine Kopp
  - **WHO Expert Group on International Non-proprietary Names**
    Secretary: Dr Raffaella Balocco
  - **WHO Expert Committee on Biological Standardization**
    Secretary: Dr David Wood

LINK WITH WHO GOVERNING BODIES

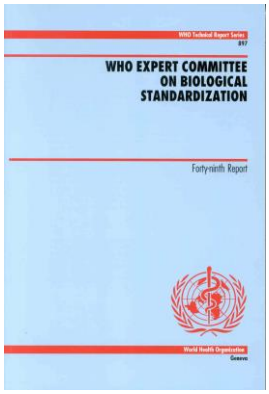
WHO Expert Committee reports are presented to the Executive Board



WHO GLOBAL STANDARDS AND NORMS

– ROBUST, DURABLE and RESPONSIVE TO PUBLIC HEALTH NEEDS

Global written standards
Tools for appropriate regulation of quality, safety and efficacy



Global measurement standards
Tools for product development, licensing and lot release

INNs
A single name for a substance for use globally

Cover a wide range of BIOLOGICAL AND BIOTHERAPEUTIC SUBSTANCES

Key drivers of WHO policy for biologicals

The WHO biologicals standards portfolio extends to over 70 written standards and 300 reference preparations

Current global public health priorities

- Responding to public health emergencies of international concern
- Access to biotherapeutic products
- Strengthening regulatory systems

World Health Assembly Resolutions

- **Resolution on biotherapeutic product (BTP)**
  - Adopted by 67th World Health Assembly in May 2014: **WHA67.21**

http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R21-en.pdf

- **Resolution on Regulatory System Strengthening**
  - Adopted by 67th World Health Assembly in May 2014: **WHA67.20**

http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R20-en.pdf

WHA 67.21: Urges Member States

- to develop or strengthen, as appropriate, national regulatory assessment and authorization frameworks, with a view to meeting the public health needs for biotherapeutics (BTPs), including similar biotherapeutic products (SBPs);
- to develop the necessary scientific expertise to facilitate development of solid, scientifically-based regulatory frameworks that promote access to products that are affordable, safe, efficacious and of quality, taking note of the relevant WHO guidelines that may be adapted to the national context and capacity;
- to work to ensure that the introduction of new national regulations, where appropriate, does not constitute a barrier to access to quality, safe, efficacious and affordable BTPs, including SBPs;

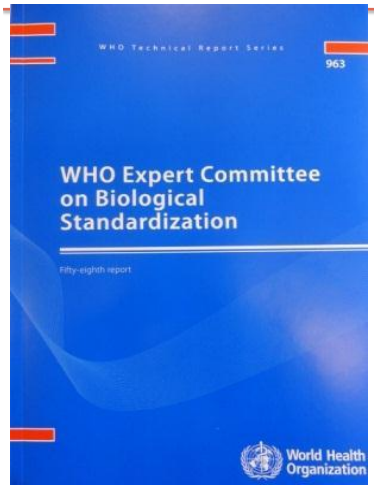
WHA 67.21: Requests WHO

- to support Member States in strengthening their capacity in the area of the health regulation of BTPs, including SBPs;
- to support, as appropriate, the development of national regulatory frameworks that promote access to quality, safe, efficacious and affordable BTPs, including SBPs;
- to encourage and promote cooperation and exchange of information, as appropriate, among Member States in relation to BTPs, including SBPs;
- to convene the WHO Expert Committee on Biological Standardization to update the 2009 guidelines, taking into account the technological advances for the characterization of BTPs and considering national regulatory needs and capacities and to report on the update to the Executive Board;
- to report to the Sixty-ninth World Health Assembly on progress in the implementation of this resolution.

WHO written standards for biotherapeutic products

World Health Organization

WHO written standards for biotherapeutics



1) Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by rDNA technology; TRS 987 (2014) Annex 4
2) Guidelines on the evaluation of similar biotherapeutic products; TRS 977 (2009), Annex 2
3) Regulatory assessment of approved rDNA biotherapeutics; TRS 999 (2016) Annex 3

www.who.int/biologicals

Lifecycle of a written standards project

- Evaluation of need for a global standard and endorsement by the ECBS
- Consultation process with regulators, industry and other experts:
  - different opinions and views - great enthusiasm or resistance
  - from initial misunderstandings, consensus developed with stakeholders on definitions, guiding principles, and technical requirements
  - WHO Collaborating Centers and many experts from various areas of product development, regulation and use
  - collaboration between WHO programme areas
  - Publication of drafts for public comment
- Establishment of global standard by ECBS
- Implementation workshops by WHO

Recent and ongoing activities: WHO written standards for biotherapeutics

	2014	2015	2016	2017
BTP				
Regulatory reassessment for approved BTPs				
SBP				
mAb SBP				
Post-approval changes for BTPs				

Development stage – scientific consultations

ECBS submission

Implementation workshop

Implementation workshops for BTP/ SBP Guidelines

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

Imp. workshop	1st SBP	2nd SBP	3rd SBP	1st BTP	SBP & BTP in Africa Region
When	Aug 2010	May 2012	May 2014		Sept 2015
Host Where	MFDS Korea	NIFDC China	MFDS Korea		Ghana FDA Ghana
Participants	NRAs from 11 countries + Industry	NRAs from 16 countries + Industry	NRAs from 23 countries + Industry		NRAs from 16 countries + Industry
Main topic for case study practice	Clinical study design: Eq vs NI	Quality assessment of **mAbs**	Efficacy study design on **mAbs**	Immunogenicity assessment of **mAbs**	Quality assessment of **EPO**

Implementation workshops for BTP/SBP GLs: Case studies & Publications

When	Topic of simulated case study	Publication
1st WS for SBP 2010	Special lecture: **Statistical considerations** for confirmatory clinical trials for SBPs	*Biologicals* 39 (5), 2011
	Comparing equivalence and non-inferiority approaches	
2nd WS for SBP 2012	The role of the **quality assessment (of mAbs)** in the determination of overall biosimilarity	*Biologicals* 42 (2), 2014
3rd WS for SBP 2014	**Efficacy study design and extrapolation**: Infliximab & Rituximab	*Biologicals* 43 (1), 2015
1st WS for BTP 2014	Special lecture: **Immunogenicity assessment** of biotherapeutic products: An overview of assays and their utility	*Biologicals* 43 (5), 2015
	Assessment of unwanted immunogenicity of mAbs: TNF antagonist & CD20 mAbs	
SBP & BTP in Africa Region 2015	The role and influence of the **quality assessment of EPO**	In preparation of a publication in a scientific journal

WHO reference standards for biotherapeutic products

World Health Organization

WHO GLOBAL MEASUREMENT STANDARDS
for biotherapeutics

Lifecycle of a standardization project

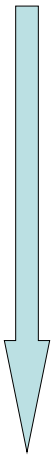
- Evaluation of the need for a global standard
  - input from stakeholders
- Endorsement of the project by ECBS
- Performance of the project
  - by a WHO Collaborating Center
- Establishment of global standard by ECBS, assignment of unitage
- Provision of measurement standards by WHO CC

WHO COLLABORATING CENTERS
Helping to implement WHO's mandate for biotherapeutics

NIBSC, UK

Whilst Biologicals continue to be dependent of Bioassays, the use of Bioassays units in labelling, dosing and release specifications has shown a progressive evolution. At least 5 different situations have existed and continue to exist.

Manufacture, formulation labelling and dosage is done in Bioassay units	Coagulation factors
Manufacture and formulation is done in mg. Finished product complies with a bioassay and is labelled and dosed in units	Erythropoietin
Manufacture, formulation and dosage is done in mg. API and/or finished product complies with a bioassay as specified in release specification, but not included in label	Filgrastim MAbs
Manufacture, formulation and dosage is done in mg. Product is never bio-assayed, but dosing is done in Units based on an agreed conversion factor	Insulin
Product is a pure mg product, with no bioassay being used or referred to	Somatropin



The existence of Bioassay units is ***not*** intended to:

-change labelling requirements for any currently licensed products

-Change the approach taken to labelling of future products

-Set or dictate standards for the specific activity or relative biological activities of licensed products by comparison with the reference standard

Reference Standard	Reference Medicinal Product
Roles	***Roles***
Reference standard between labs and across time *Defines unitage but not specific activity* *Controls the performance and system suitability of bioassay systems*	*Biosimilarity-defining characteristics of purity, specific-activity and identity* *Allows extrapolation to clinical data*
Properties and characters	***Properties and characters***
Between-sample homogeneity *Predicted and monitored stability* *Unitage assigned by international collaborative study and formally adopted by convention/agreement* *Defined acceptable product characteristics (moisture, oxygen, containers etc)* *Compliance with relevant requirements for establishment of a reference standard*	*Representative of licensed innovator product* *Labelled content is derived from a higher order standard* *Labelled content is measured batch to batch but not formally assigned as in a standard and is actually a statement of compliance with test requirements*

In summary, the reference product and the reference standard are different entities, with only limited overlap in both form and function

- the reference product serves to define the quality criteria that the candidate must meet, a function that the reference standard does not serve

- the reference standard serves to control, define and calibrate the performance of the test measurement system, a function that the reference product cannot serve

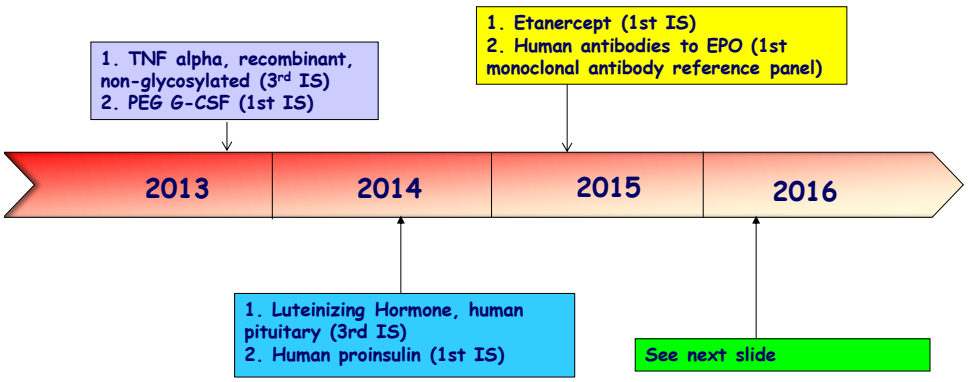
Way forward

WHO Informal Consultation on International Standards for Bio-therapeutics Products: future direction
21-22 September 2015
Geneva

- WHO will proceed cautiously with a standardization program for biotherapeutics as they gain Market Authorization through the Bio-similar route

- There should be overt recognition, however, of the concerns and potential impacts on affected stakeholders, and the need to consider very carefully the potential use and extent of applicability of these standards

Development of measurement standards for biotherapeutics, 2013 - 2016



New project proposals to be considered at ECBS 2016

- **Parathyroid hormone 1-34, recombinant, human,**
  Endorsement of a new project to develop the 2nd International Standard for parathyroid hormone 1-34 — WHO/BS/2016.2296 Rev 1
- **TAFI (thrombin activatable fibrinolysis inhibitor)**
  Endorsement of a new project to develop a proposed International Standard for TAFI — WHO/BS/2016.2296 Rev 1
- **Vascular endothelial growth factor (VEGF) antagonists**
  Endorsement of a new project to develop proposed International Standards for VEGF antagonists — WHO/BS/2016.2296 Rev 1
- **ErbB/HER family of receptor tyrosine kinases**
  Endorsement of a new project to develop 4 proposed Reference Reagents for the biological activities of monoclonal antibodies to ErbB/Her receptor family — WHO/BS/2016.2296 Rev 1
- **Antibody assays for immunogenicity assessment of biotherapeutic products**
  Proposed WHO Reference Antibody Panels — WHO/BS/2016.2296 Rev 1

WHO INNs for biotherapeutic products

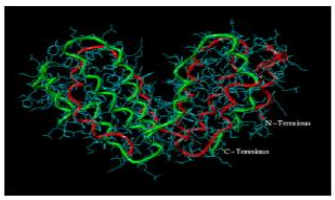
World Health Organization

INNs

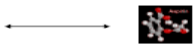
- Unique name
- Distinctive in sound and spelling
- Not liable to confusion with other names in common use
- Formally placed by WHO in the public domain
- Can be used without any restriction to identify pharmaceutical substances

BIOLOGICALS ARE COMPLEX

- The complexity of substances
- The



Interferon beta



Aspirin

- The emerging of new types of substances (new policies?)

INN IS SIMPLE

"Simplicity is the ultimate sophistication"

Leonardo Da Vinci

INN Policies for biotherapeutics

- General policies for non-glycosylated compounds
- General policies for glycosylated compounds
- General policies for fusion proteins
- General policies for pegylated substances
- General policies for cell therapy products (CTP)
- General policies for gene therapy products (GTP)
- General policies for monoclonal antibodies
- General policies for blood products
- General policies for immunoglobulins fractionated from plasma
- General policies for skin substitutes
- General policies for transgenic substances

A historical conclusion

The first international biological reference preparation, 1925

NIBSC AND BIOLOGICAL STANDARDIZATION 1900-2000

STANDARDS FOR INSULIN

Insulin was discovered in 1921 by Banting and Best in Toronto and its important use in the treatment of diabetes was immediately apparent as was the problem of correct dosage. Dale visited Toronto in 1922 in order to prepare the MRC for the responsibilities of controlling the production of therapeutic insulin in the UK. The Canadians had generously given the parent to manufacture insulin to the MRC. Heroic efforts had been made by the Toronto team to extract insulin but to measure the potency of the final product they only used the rabbit unit i.e. the quantity just sufficient to lower blood sugar levels and produce hypoglycaemic convulsions in a normal rabbit. Dale knew that valid measurements would only be obtained by comparison with a standard preparation of insulin.

An international conference on biological standardization was held as part of the 1923 International Conference on Physiology in Edinburgh. Cushny, Professor of Pharmacology at Edinburgh was chairman of the meeting and insulin was the main subject for

Charles Best (left) & Frederick Banting, August 1921.

Yours very truly,

First International Standard for Insulin, 1925.

Banting and Best with one of the first de-pancreatised dogs to have its life prolonged by insulin injections: they are photographically superimposed onto another photo of their laboratory in Prof. Macleod's Department of Physiology, University of Toronto. Prof. Collip, University of Alberta also worked with them and helped to refine the preparation of insulin.

Banting and Macleod were awarded a Nobel Prize in 1923. Banting gave half of his cash award to Best and Macleod gave half to Collip. Best worked with Dale at Hampstead on the action of insulin and histamine in 1925 and '28 and Dale made a number of visits to Canada; they became life-long friends.

This ampoule is exhibited with Dale's letter (see next page) in NIBSC but no evidence has been found that it is the actual ampoule rolled across the table to Macleod. More likely it is one of the batch of ampoules that became the first International Standard for Insulin in 1925.

17

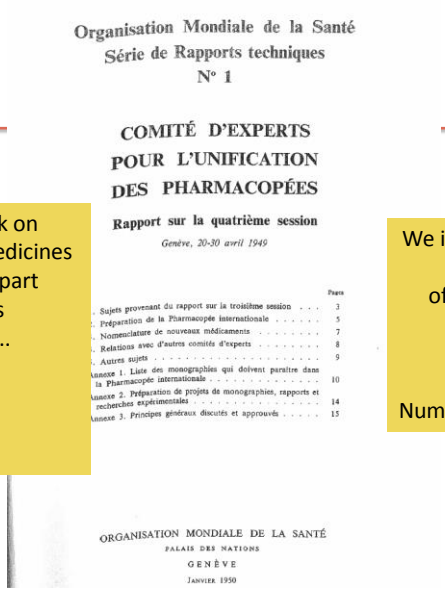
Hazel Davies (Australia), diagnosed with type I diabetes in 1921, photographed 2 years before she celebrated her 100th birthday

HIS/EMP | WHO norms and standards – promoting quality and innovation for health products

World Health Organization

WHO's normative work on biologicals, diagnostics, medicines and vaccines has been part of our core business since the very start….

WHO Technical Report Series Number 1



Organisation Mondiale de la Santé
Série de Rapports techniques
N° 1

COMITÉ D'EXPERTS POUR L'UNIFICATION DES PHARMACOPÉES

Rapport sur la quatrième session

Genève, 20-30 avril 1949

Pages

1. Sujets provenant du rapport sur la troisième session . . . 3
2. Préparation de la Pharmacopée internationale 5
3. Nomenclature de nouveaux médicaments 7
4. Relations avec d'autres comités d'experts 8
5. Autres sujets 9

Annexe 1. Liste des monographies qui doivent paraître dans la Pharmacopée internationale 10

Annexe 2. Préparation de projets de monographies, rapports et recherches expérimentales 14

Annexe 3. Principes généraux discutés et approuvés 15

ORGANISATION MONDIALE DE LA SANTÉ
PALAIS DES NATIONS
GENÈVE
JANVIER 1950

We intend to continue the good work of our predecessors….

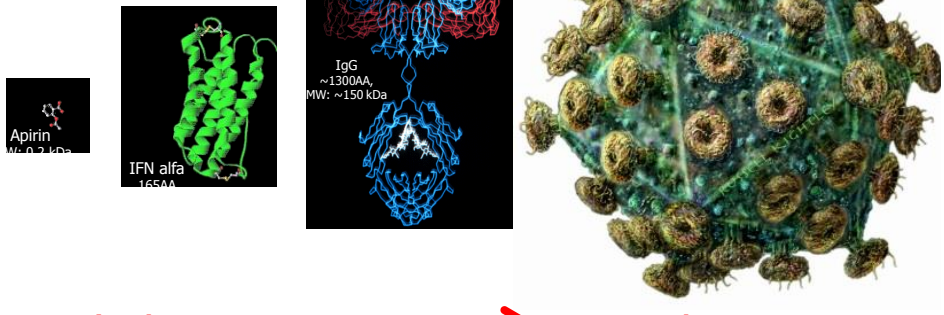
WHO Technical Report Series Numbers 1000, 100x, 10xx?

Biological standards

Peter Jongen
Medicines Evaluation Board, The Netherlands
Chair of PhEur Expert group 6

Disclaimer: Personal views only, meant to initiate further discussion. Does not necessarily reflect view of MEB, PhEur or EDQM

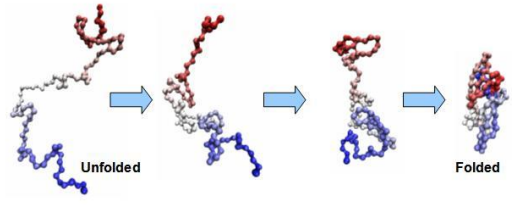
Chemicals versus Biologicals



Simple → ***Complex***

Bioassay when applicable

- When potency cannot be adequately measured by chemical and physical analysis
- Need for bioassay depends on
  - Complexity of product
  - Availability of technologies and knowledge to characterise relevant properties of the product



Expectations from a bioassay (extracted form ICHQ6B)

- Biological activity = specific ability or capacity of a product to achieve a defined biological effect
- Potency in Units (U / IU) quantitative measure of biological activity linked to products' relevant biological properties
- Correlation between the expected clinical response and the activity in the biological assay established in pharmacodynamic or clinical studies

ICH Topic Q 6 B
Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

ICH regulatory guideline (9Q6B)

- A relevant, validated potency assay should be part of the specifications for a biotechnological and biological drug substance and/or drug product.
- For complex molecules, the physicochemical information may be extensive but unable to confirm the higher-order structure which, however, can be inferred from the biological activity. In such cases, a biological assay, with wider confidence limits, may be acceptable when combined with a specific quantitative measure

Examples of procedures used to measure biological activity include: (ICH Q6B)

- Animal-based biological assays, which measure an organism's biological response to the product;
- Cell culture-based biological assays, which measure biochemical or physiological response at the cellular level;
- Biochemical assays, which measure biological activities such as enzymatic reaction rates or biological responses induced by immunological interactions.
- Other procedures such as ligand and receptor binding assays, may be acceptable.

Examples of bioassays:

- measuring appropriate marker for activity
- in-vivo:
  - assay measuring increase reticulocyt in mice for erythropoietin
  - glucose lowering effect of insulin in rabbits
  - in vivo: rat growth by somatropin
  - challenge assays for inactivated vaccines

- in vitro:
  - cell proliferation assays for G-CSF
  - clotting mechanism based assays for clotting factors and heparins
  - enzymatic acitivity assays for therapeutic enzymes
  - Inhibition of enzyme activity e.g. anti IIa and anti Xa assays for heparins
  - ligand and receptor binding assays

Bioassay: general design

- In vitro* biological or in vivo biological response
  * also enzymatic, immunochemical, microbial assays
- Comparison with standard preparation (relative assays)
- Test at same time under identical conditions
- Inherent variability >> subject to random error>> calculate error for each test

- Several approaches in PhEur :

Biological activity in PhEur monographs 1

- Potency in Definition section & potency test description
  - Lower limit for specific activity (IU/mg) or Upper and Lower limit for specific activity
  - Exceptionally: "as approved by the competent authority"

  Also: 80-125 % of stated potency (potency test result)

  Examples: Interferons, CSF's, erythropoietin, FSH

- Role of potency test for product control may change in time/course of product development

Biological activity in PhEur monographs 2

- Quantitatively defined potency in production section
  - Specified lower limit for specific actvity (IU/mg).
- No bioassay description
- No bioassay in assay section ⟹ no request for bioassay in batch control!
- Examples:
  - Somatropin: validated bioassay based on growth promotion as approved by the competent authority
  - Glucagon: During the course of product development, it must be demonstrated that the manufacturing process produces a product having a biological activity of not less than 1 IU/mg using a suitable validated bioassay
  - Teriparatide During the course of product development, it must be demonstrated that the manufacturing process produces a biologically active protein using a suitable bioassay as approved by the competent authority.

Biological activity in PhEur monographs 3

- Quantitatively defined potency in definition section
  - Mass and Unit equivalence **defined by convention**
    - Eg: *"by convention for the purpose of labelling insulin glargine preparations 0.0364 mg of insulin glargine is equivalent to 1 unit."*
- No bioassay in assay section ⟹ no request for bioassay in batch control!
- Examples:
  - rH insulin and analogues (no reference to bioassay)
  - Salmon Calcitonin (no reference to bioassay)
  - Somatropin (reference to bioassay result in production section)

Balancing the need for a bioassay

- Complexity substance
- Avialability of suitable assay(s)
- Aim of the bioassay in monograph
  - verification of conformation or quantification response
- Options to address biological activity
- Balancing selecitivity, precision, relevancy for clinical activity, costs and ethics

- Only when really needed
- Enhanced characterisation may abolish necessity bioassay

Which bioassay to be adopted in PhEur

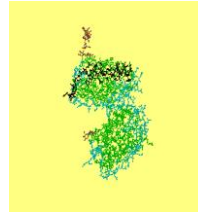
- Proposal from companies
- As approved by authorities
- Theoretically and metrologically sound
- When alternatives exists chose best option

Considerations when describing compendial bioassays

- Detailed or general description
- Detailed: advantage for new users possible disadvantage for users applying different conditions
- Detailed: reduce potential sources of variation
- Avoid patented cell lines and commercial single source reagens
- Harmonise statistical evaluation

Level of detail: example assay PhEur assay Interferon beta 1a

- Principle: IFN beta1a has ability to protect cells against cytopathic effect viruses
- Compare with appropriate IS for IFN beta 1a, result in IU
- "suitable method based on following design."
- Established cell line sensitive to cytopathic effect of a suitable virus and responsive to interferon: 2 examples "shown to be suitable"
- minimum number for concentrations and replicates
- Control cells
- Quantitative determination cytopathic effect by "suitable method"
- "usual statistical methods" fe 5.3 (quantal responses)
- Requirements for estimated potency and confidence limits



Level of detail: example assay Etanercept (draft monograph)

Principle: etanercept inhibits biological activity of TNF-α in cell based assay. Compare with etanercept BRP, result in IU.

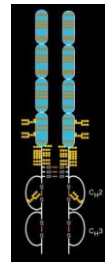
"The following procedures has been found suitable"

- TNF-α + etanercept dilutions induce apoptosis in histiocytic lymphoma cell line U973; Capsase-Glo 3/7 assay
- Incubation cells with mixtures etanercept dilutions and TNF-α; Caspase activation measured with luminogenic substrate

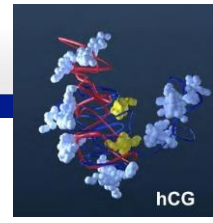
"The following indications are given as example."

- Medium, dilutions, TNF-α solution, plate preparation, cell preparation, controls, caspase-glo 3/7 assay
- System suitability
- Calculation by four-parameter logistic curve model (5.3)

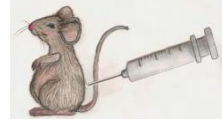
Requirements for estimated potency and confidence limits, and specific activity (defenition section)



Level of detail: PhEur assay rec follitropin



- Principle: enlarging ovaries of rats treated with chorionic gonadotrophin (Steelman Pohley)
- Compare with appropriate IS for rh-FSH, result in IU
- Female rats, requirements for age and weigth, # of groups, size of groups
- Recommendations for doses administrated, i.e. compositions, concentrations, volumes, injection schedules
- Quantitative determination effect by weighing
- "usual statistical methods" fe 5.3 (quantal responses)
- Requirements for estimated potency and confidence limits
- Alternative approaches ?



PhEur (bio)assays written in stone?

Ph.Eur. General Notices

- **Alternative methods**. The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative.

Replacement established in-vivo assays

- Promote the use of in vitro assays for batch control
- Delevelop alternative assay suitable for all products
  - Large collaborative effort (successes in the past)
- Or: develop in house in vitro alternative assay(s)
  - In vivo procedure in pharmacopoeia provides link to IU of product specific standards

- EU Directive 2010/63/EU on the Protection of animals used for scientific purposes

Reference standards in PhEur bioassays for biotherapeutics

- International standard or ref prep calibrated in IU (FSH, IFN's, filgrastim)
- BRP expressed in IU (EPO)

  Always a direct link to International unit

- If no IS or BRP exists the manufacturer must have established an appropriately characterised in-house biological reference material.
- **Compendial reference should standardise the biological activity (not necessarily a specific product)**

European Pharmacopoeia biological reference preparation (BRP) (chapter 5.12).

- *European Pharmacopoeia biological reference preparation (BRP)*. A substance or mixture of substances intended for use as stated in a monograph or general chapter of the European Pharmacopoeia. BRPs are either secondary standards calibrated in International Units or primary standards, which may be used to define a European Pharmacopoeia Unit (Ph. Eur. U.). Other assigned contents may also be used, for example, virus titre or number of bacteria.

BRP's

- Established through Biological Standardisation Programme
- Interlaboratory studies sometimes BSP in cooperation with other organisations
- Reports endorsed by participants, BSP Steering Cie, EP expert group. Standards officially adopted by PhEur Commission
- Establishment reports published in Pharmeuropa Bio & Scientific Notes
- Leaflet provides relevant information (instructions for use, assigned content, measurement uncertainty, validity etc.)
- To be used as specified in the monograph

BRP establishment, an example: etanercept

- 2013 start monograph elaboration (P4 BIO) based on data package provided by manufacturer
- P4 BIO 5 labs (OMCL, EDQM) involved in bioassay ('learning phase')
- 2014: bioassay found suitable. Minor modifications. Start BSP138 project (PL: Dr. M. Wadhwa)
- Joint WHO/EDQM study part of WHO IS establishment study: 12 labs using PhEur method
- 2015 outcome study reported, BRP study report based on 12 labs.
- Selection preparation and potency assignment BRP and recommendations for System suitability
- To be adopted together with monograph by EP Commission

Conclusions

- Bioassay in routine control: may provide missing link to ensure product activity and consistency for complex products
- Neccessity and selection requires careful consideration
- Several approaches for laying down bioactivity measurements in PhEur monographs
- Bioassay and its reference standards introduction and replacement require large efforts


C B G
M E B

EUROPEAN PHARMACOPOEIA:
TACKLING FUTURE CHALLENGES OF THE QUALITY OF MEDICINES TOGETHER
9th Edition of the Ph. Eur.; 27-28 September 2016, Tallinn, Estonia
Workshop: Setting Pharmacopoeial Standards for Biotherapeutic Products

Physico-chemical Ph. Eur. Reference Standards for Recombinant Proteins

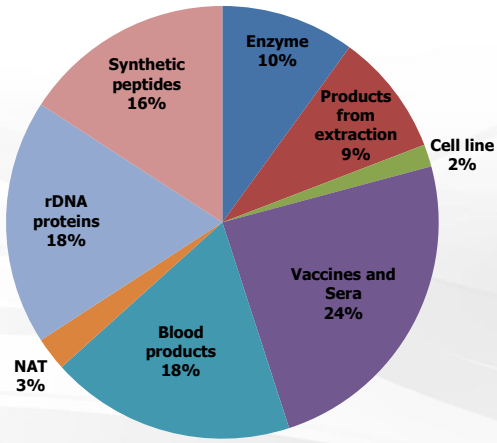
Dr Sylvie JORAJURIA
Head of the Biology Section – Laboratory Department
EDQM – Council of Europe

Outline

- Introduction
  - Ph. Eur. RS portfolio for biologicals and rDNA proteins
  - Type of CRS for rDNA proteins and use
- How CRS for rDNA substances may help address quality challenges – Case studies
- CRS for rDNA proteins: additional advantages
- Conclusion

Ph. Eur. RS portfolio for biologicals

About 130 Reference Standards for Biologicals (CRS and BRP): 4% of Ph. Eur. RS portfolio



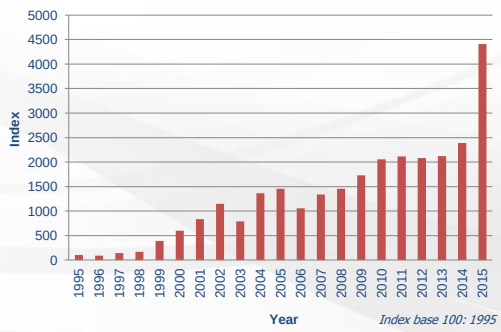
Ph. Eur. RS portfolio for rDNA proteins

First generation	
Human insulin	Coagulation factor VIII
Somatropin	Filgrastim
Interferon alfa-2	Interferon beta-1a
Erythropoietin	Follitropin
Interferon gamma-1b	Coagulation factor VIIa
Molgramostim	Coagulation factor IX
Human glucagon	Teriparatide

Second generation
Insulin lispro
Insulin aspart
Insulin glargine
PEG-Filgrastim
Etanercept
Darbepoeitin

Monoclonal antibodies
Infliximab

Distribution unit of RS for rDNA proteins



Increasing need

Type of reference standard for rDNA proteins

Bioassay

- **International Standard (WHO)**
  - Primary standard
  - Value assigned in International Units
- **BRP: Ph. Eur. Biological Reference Preparations**
  - Secondary standards calibrated in International Units

Physico-chemical tests

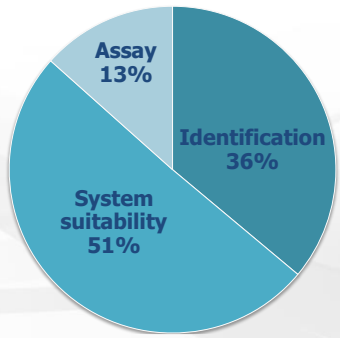
- **CRS: Ph. Eur. Chemical Reference Substances**
  - Primary standards

Ph. Eur. reference standards are to be used as stated in a text of the Ph. Eur. They are not intended to be used as reference (comparator) products in the context of applications for biosimilars

Ph. Eur. chapter 5.12. 04/2015

Types of CRS for rDNA proteins

- **System suitability**
  - to verify that a measurement system is operated within the boundaries of its validation scope
- **Qualitative purpose**
  - to test compliance of essential quality attributes, i.e. identification
- **Quantitative use**
  - quantitative determination of the substance subject of the monograph
  - assigned content



Remark: a CRS may serve both qualitative and quantitative purposes

How CRS for rDNA proteins may help address quality challenges?
Case studies

rDNA proteins: some quality challenges

- Derived from living cells
- Highly specific **three-dimensional structure**
- **Heterogeneous** mixtures of substances of similar molecular mass and charged isoforms
- May undergo complex **post-translational modifications**
- Complex pattern of product- and process-related **impurities**
- Potential for **aggregation**, adsorption and truncation

Challenge 1: Heterogeneity

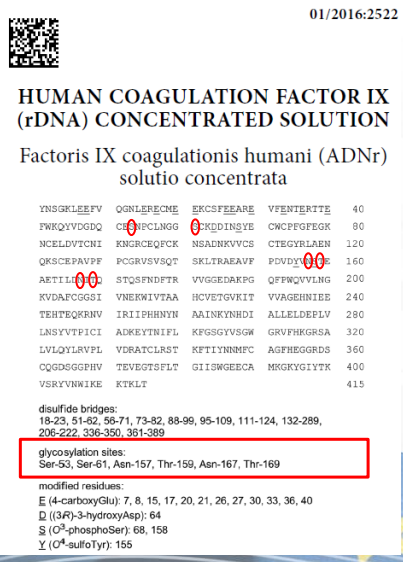
Changes in manufacturing processes can significantly affect quality attributes:

- **Glycosylation profile**
  Cell culture conditions may lead to glycan attachment and structure differences - *Case study: rFIX CRS*
- **Charge variants**
  Various modifications of the protein structure, such as deamidation, amino acid substitution/deletion, sialylation, glycation…, can constitute the sources of charge heterogeneity
  Case study: Infliximab CRS

Importance of testing the relevant quality attributes (QC, in-process control, stability) with a robust method
-> CRS for system suitability

Challenge 1 – Case studies

1) Human coagulation factor IX (rDNA) concentrated solution



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HUMAN COAGULATION FACTOR IX (rDNA) CONCENTRATED SOLUTION

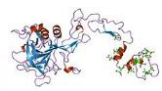
Factoris IX coagulationis humani (ADNr) solutio concentrata

```
YNSGKLEEFV  QGNLERECME  EKCSFEEARE  VFENTERTTE   40
FWKQYVDGDQ  CESNPCLNGG  SCKDDINSYE  CWCPFGFEGK   80
NCELDVTCNI  KNGRCEQFCK  NSADNKVVCS  CTEGYRLAEN  120
QKSCEPAVPF  PCGRVSVSQT  SKLTRAEAVF  PDVDYVNSTE  160
AETILDNITQ  STQSFNDFTR  VVGGEDAKPG  QFPWQVVLNG  200
KVDAFCGGSI  VNEKWIVTAA  HCVETGVKIT  VVAGEHNIEE  240
TEHTEQKRNV  IRIIPHHNYN  AAINKYNHDI  ALLELDEPLV  280
LNSYVTPICI  ADKEYTNIFL  KFGSGYVSGW  GRVFHKGRSA  320
LVLQYLRVPL  VDRATCLRST  KFTIYNNMFC  AGFHEGGRDS  360
CQGDSGGPHV  TEVEGTSFLT  GIISWGEECA  MKGKYGIYTK  400
VSRYVNWIKE  KTKLT                              415
```

disulfide bridges:
18-23, 51-62, 56-71, 73-82, 88-99, 95-109, 111-124, 132-289, 206-222, 336-350, 361-389

glycosylation sites:
Ser-53, Ser-61, Asn-157, Thr-159, Asn-167, Thr-169

modified residues:
E (4-carboxyGlu): 7, 8, 15, 17, 20, 21, 26, 27, 30, 33, 36, 40
D ((3*R*)-3-hydroxyAsp): 64
S (O^3-phosphoSer): 68, 158
Y (O^4-sulfoTyr): 155

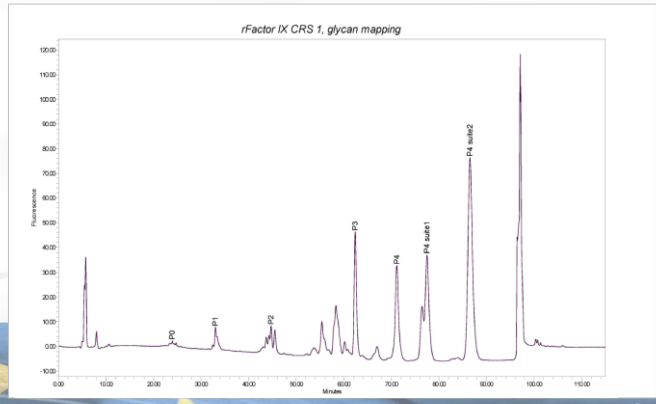


Glycosylation profiling:

- **General (mandatory):**
  - desalting
  - selective release of glycans
  - labelling of glycans
  - liquid chromatography with fluorimetric detection - ion exchange chromatography
- **Detailed instructions (given as an example): non-mandatory**
- **Limits approved by the competent authority**

Human coagulation factor IX (rDNA) concentrated solution (cont'd)

System suitability:
The chromatogram obtained with *human coagulation factor IX (rDNA) CRS* is **qualitatively similar** to the chromatogram supplied with *human coagulation factor IX (rDNA) CRS*



2) Infliximab concentrated solution (2928)

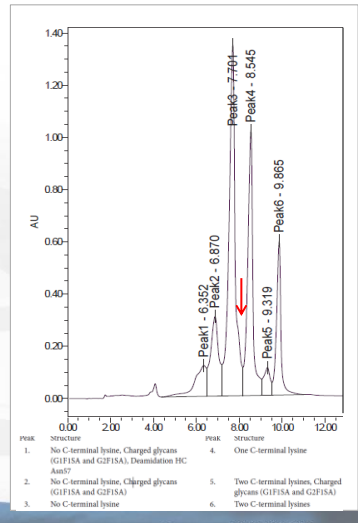
Charged variants

- **Isoelectric focusing**

System suitability:
- in the electropherogram obtained with *infliximab CRS*, 7 bands in the pI region 7.35-8.30 are clearly visible

- **Ion exchange chromatography**

System suitability:
- the chromatogram obtained with *infliximab CRS* is similar to the chromatogram supplied with *infliximab CRS*;
- resolution: minimum 1.5 between the peaks due to isoforms 3 and 4 in the chromatogram obtained with *infliximab CRS*



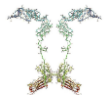
Challenge 2: Identification

Complexity of peptide map analysis

- **Mass spectrometric** characterisation (LC-MS, QTOF) is part of the regulatory filing as elucidation of structure, and not part of testing for a monograph
- **Ph. Eur. general notices**: the tests given in the Identification section are:
  - not designed to give full confirmation of the chemical structure or composition of the product
  - intended to give **confirmation**, with an acceptable degree of assurance, that the article conforms to the description on the label
- **Peptide mapping (LC-UV)**
  - fingerprint of a protein
  - compatibility of mobile phase with mass spectrometer detection is desirable
  - complexity of the resulting peptide map for mAb
  - **comparative procedure with CRS** - *Case study: Etanercept CRS*

Challenge 2 – Case study

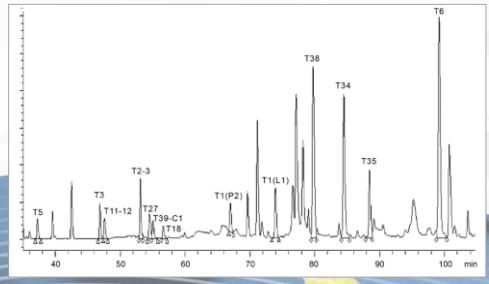
Etanercept (2895)



Peptide mapping

System suitability: the chromatogram obtained with *etanercept CRS* is qualitatively similar to the chromatogram supplied with *etanercept CRS*

Results:
- the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with *etanercept CRS*
- no additional peaks are observed in the chromatogram obtained with the test solution in comparison with the chromatogram obtained with *etanercept CRS*



CRS for system suitability and identification

Comparison of retention times, peak responses, number of peaks, overall elution pattern

Challenge 3: Multistep testing

Need for sample pretreatment for peptide/glycan mapping

- **Isolation and purification**
  rDNA proteins are usually included in complex matrixes specifically designed to improve their chemical and structural stability
  -> desalting
- **Unfolding the protein prior to digestion**
  The tertiary structure of proteins may hinder access to cleavage sites
  -> denaturation, reduction and alkylation of the disulfide bond

Challenge 3: Multistep testing (cont'd)

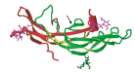
Consequences

- Residual interfering substances (excipients, denaturants, reducing or alkylation agents) may impact the enzymatic cleavage efficiency and chromatographic separation
- Peptide/Glycan mapping are comparative procedures:
  -> any pretreatment steps performed on the substance to be tested shall also be performed on the reference standard

Case study: Follitropin for peptide mapping and glycan analysis CRS

Challenge 3 – Case study

Follitropin concentrated solution (2286)



Peptide mapping

Separation of the α- and β-subunits → Reduction and modification of the purified subunits → Desalting of the purified subunits → Selective cleavage of the peptide bonds → Chromatographic separation

Glycan mapping

Protein denaturation → Selective release of ~~the~~ glycans → Chromatographic separation

Follitropin concentrated solution (2286) (cont'd)

Advantages of *Follitropin for peptide mapping and glycan analysis CRS:*

- CRS for system suitability and identification: qualitative comparison
- To be treated in the same way as sample to eliminate the bias due to pretreatment
- Allows verification of completion of the digestion
- Ensures that the glycan release was successful

-> Reference standard should be structurally related to the main substance

Challenge 4: Complex pattern of related proteins

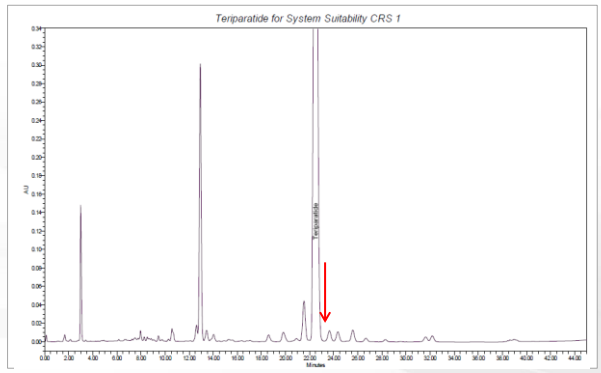
Solution for system suitability/peak identification

- Deamidation, oxidation, aggregation products:
  - can alter immunogenicity, potency, safety and efficacy of the substance
  - such impurities may be present at low levels in drug substance
- System suitability: need for stressed samples with increased amount of related proteins
- **Ready to use CRS for resolution solutions** are a more robust option than *in situ* degradation solutions prepared by users. The latters may be variable and not necessarily reproducible

Challenge 4 – Case studies

1) Oxidised and deamidated forms

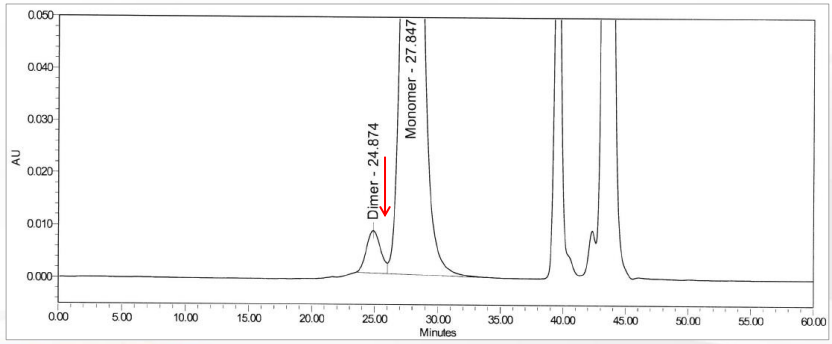
- Teriparatide (2829)
  Resolution solution: incubation of the substance to be examined at 50°C for 9 days
  -> replaced by *Teriparatide for system suitability CRS*



- Other examples: *Somatropin/desamidosomatropin resolution mixture CRS, Interferon gamma-1b for system suitability CRS* with increased deamidated and oxidised forms

2) Aggregates

- Erythropoietin concentrated solution (1316)
  Reference solution: 2% dilution of the test solution for system suitability purposes
  -> will be replaced by *Erythropoietin for system suitability CRS* with a defined dimer content



CRS for rDNA proteins: additional advantages

CRS material

- **CRS establishment**

- Characterisation of the CRS goes often beyond the boundaries of the monograph

- Orthogonal analytical methods based on other measurement principle
  -> reliability of the measurement result is enhanced

- Growing importance of mass spectrometry for rDNA proteins
  Ex: peak identification for peptide mapping, glycan mapping

Investment on LC-MS, QTOF

CRS material (cont'd)

- **CRS role**
  - Fit for purpose
  - Ensure sustainability of supply
  - Avoid drift between consecutive batches

- **Freeze-dried**
  - Preferred to liquid or powder filling
  - Better homogeneity
  - Enhanced stability
  - No risk of water uptake: reconstituted
  - User-friendly: no need to weigh

CRS material (cont'd)

Common reference standards

Collaboration to develop a common reference standard with the same assigned content

Conclusions

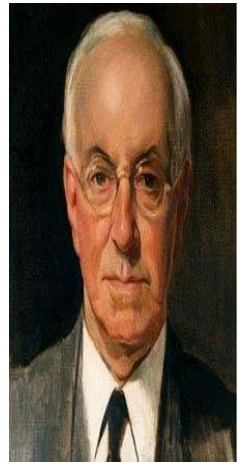
- Usefulness of CRS for rDNA proteins
- Relevance of different CRS types:
  - to control the performance of the method
  - to assess acceptance criteria (qualitative, quantitative)
  - to allow independent testing
- Need for an early CRS strategy carried out in sync with the monograph elaboration
- Value of experimental method verification and work of the Ph. Eur. Group of Experts
- **Importance of collaboration with all players**

THANK YOU

Bioassay Standards for Biologics (and Biotherapeutics) – an evolving role, but a continued need

Tina S. Morris, Ph.D.
Senior Vice President, Global Biologics

Insulin – First International Standard 1925



"Preparing insulin in a dry and stable form was the best way of defining and stabilizing the unit."

"The standard preparation would then serve as a convenient currency, by means of which the unit could be transmitted to every country concerned."

Sir Henry Dale

The Reality of Different Standardization Approaches

Pharmacopeial RS	CRM	WHO IS
		
Directly linked to use(s) and validated procedure(s)	Measurement uncertainties must be determined	Material determines the Unit of activity and is deemed

Important Dependencies

Calibration of National/regional standards for potency to an IS - established practice for global multi-manufacturer biologics

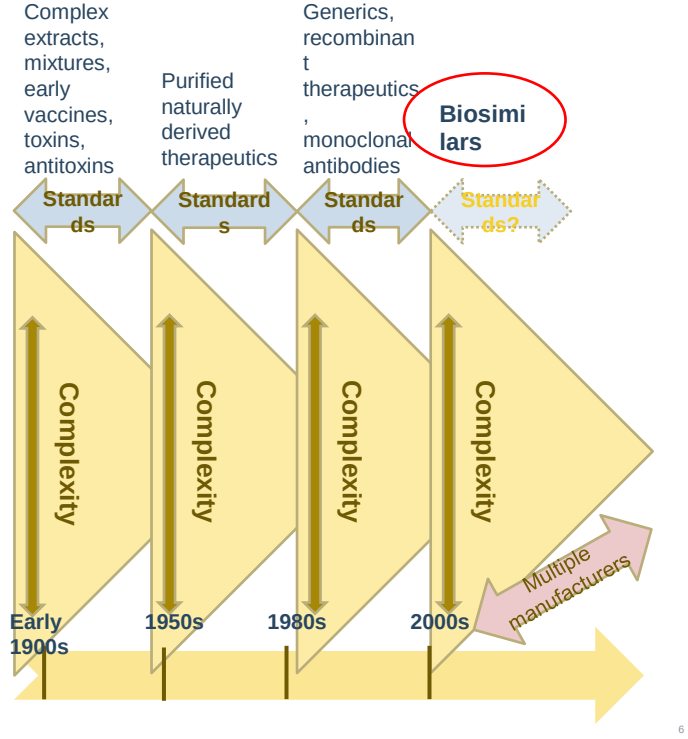
With highly characterized and more purified materials, the question of potency often evolves to a question of specific activity

Value assignment in SI and by mass balance has become common practice for biologics

Biosimilars – What Changed (and what didn't)?

Change	No Change
Many products have no naturally derived counterpart with known or described MOA	Functional assay(s) of activity are still important for characterization of molecules and clinical linkage
New regulatory paradigms for the determination of sameness and similarity based on reference product characterization	The measurement of "like vs like" materials against a suitable reference material should reduce the variability of independent assessments
Product manufacturing evolution and quality control are driven by product- and manufacturer-specific controls and standards	A global multi-manufacturer market of biologics exposes patients to a diverse set of products that may have unintended

Role of Standards in the Biologics Evolution



Reference Product vs. Biological Reference Standard

Key Characteristic	Reference Product	Reference Standard
Role	In biosimilarity paradigm – defines quality attributes for similarity	Measurement tool across laboratories, materials, methods, and time
Presentation	Dosage form formulated for Patient Dosing with defined shelf life (often 2 years for biologics), representative of single manufacturer product	Formulated for long term fitness for use, as inclusive/representative of as many relevant products as possible
Defined	Compliance	Potency/value

Impact of Reference Product Changes - Rituximab

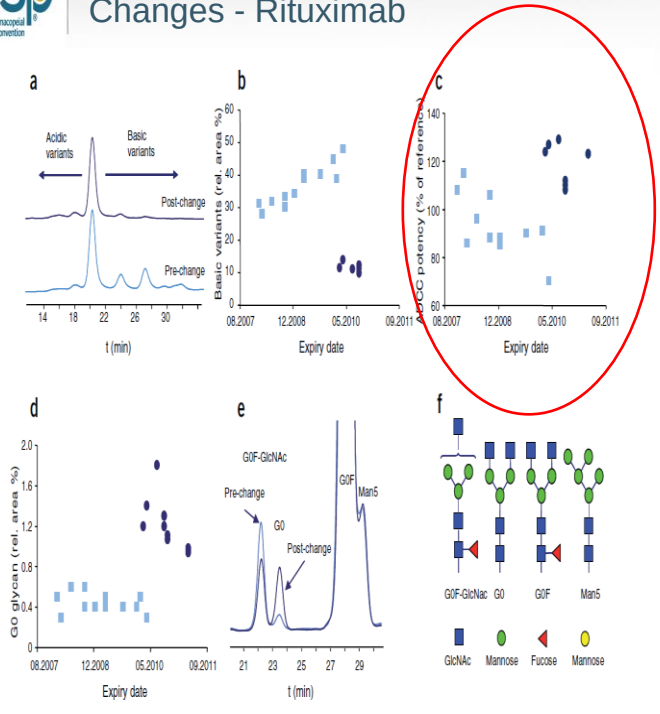
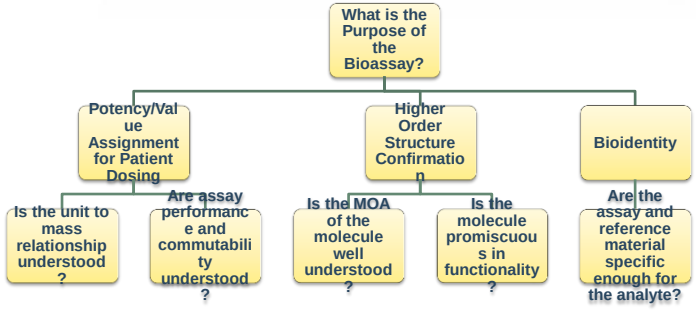


Figure 2 Comparison of the different pre- and post-change batches of Rituxan/Mabthera. (a) Exemplary CEX chromatograms. (b) Amount of basic variants of the pre-change ($n = 12$) and post-change ($n = 6$) batches as measured by CEX. (c) ADCC potency of the pre-change ($n = 11$) and post-change ($n = 8$) batches. (d) Relative amount of the G0 glycan of the pre-change ($n = 13$) and post-change ($n = 11$) batches. (e) Exemplary glycan mapping chromatograms. (f) Glycan legend.

From Schiestl et al. *Nature Biotechnology* Volume 29 Number 4 April

Suitability for Use as a Driver in the Bioassay

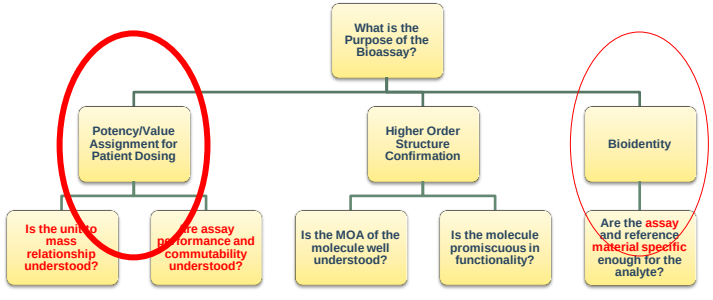


Utility of an associated reference material should be based on **fitness for purpose**

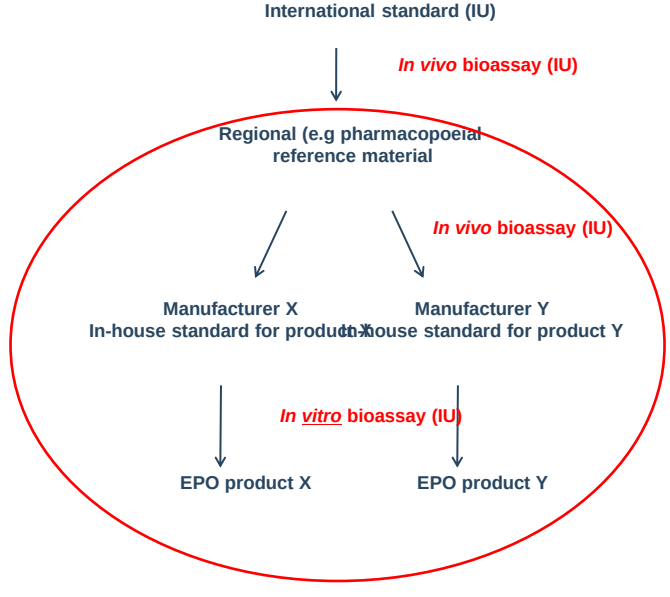
Units and Mass, specific activity – When and why is it still important?

Substance	Potency	Compendia	International Standard	Source	Harmonized Tests?	Labeling
Insulin Human	28.82 IU/mg 28.82 USP U/mg	USP and EP, USP unit =IU	yes	Recombinant	Mostly, EP: no bioassay	Units
Somatropin	3 IU/mg 3 USP U/mg	USP and EP USP unit = IU	Yes	Recombinant, mass assigned	Mostly, EP: no bioassay	mg
Glucagon	1 IU/mg NLT 0.8 USP U/mg	USP and EP USP and IU are assumed equivalent	Yes	Porcine	Mostly, EP: no bioassay	mg and U, assuming 1U/mg
Filgra	NLT	USP	Yes	Recom	Mostly	mg

When does Specific Activity Still Matter?



Understanding Commutability Remains a Key Issue – EPO



Introduction - commutability

- **<u>Traceability through a reference material</u>**. Routine measurement procedures which include a calibration step traceable to the same higher order reference material should produce numerical values for clinical samples that are comparable across time, place and laboratory method.

This concept requires the reference material to have inter-assay properties comparable to the properties demonstrated by authentic clinical samples when measured by more than one method.

Commutability – What is it?

- The WHO guidelines for preparation of International Standards state -
- *"The behaviour of the reference standard should resemble as closely as possible the behaviour of test samples in the assay systems used to test them"*
  - General Considerations
- *"The concept of commutability seeks to establish the extent to which the reference standard is suitable to serve as a standard for the variety of samples being assayed."*
  - Glossary

Important Dependencies

Calibration of National/regional standards for potency to an IS - established practice for global multi-manufacturer biologics

With highly characterized and more purified materials, the question of potency often evolves to a question of specific activity

Value assignment in SI and by mass balance has become common practice for biologics

Anti-Factor IIa assays by USP method: intra-laboratory variation (%GCV)

Lab	T	V	W	X	Y	Z
02	6.2	3.5	2.5	1.4	1.8	3.7
03	7.6	13.6	12.9	16.3	6.1	7.1
06	6.8	3.5	4.6	4.5	2.4	7.5
08	2.6	3.1	2.8	2.6	8.4	3.6
12	1.5	1.8	6.7	6.0	2.0	3.1
13	8.5	10.9	2.6	7.3	6.6	7.1
19	.	29.1	9.2	.	23.4	9.3
25	5.3	1.7	2.0	3.0	5.4	8.5
32	4.6	8.1	1.8	1.9	2.9	2.8

Range = 1.4 – 29.1 %; 27/52 < 5%; 44/52<7%; 46/52 <10%

Data from collaborative study to value assign 6th International Standard for Unfractionated Heparin

Elaine Gray, NI

What happens when you don't assay like against like…….lessons learned from the first B-domain deleted FVIII?

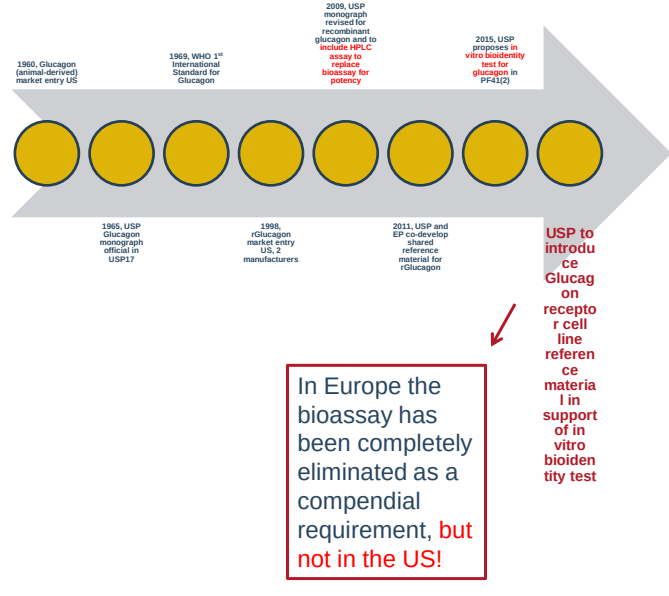
-licensed as "Xyntha" in USA (2008) - labelled by clotting assay
-licensed as "ReFacto AF" in Europe (2009) - labelled by chromogenic assay

"1 IU of the Xyntha product is approximately equivalent to 1.38 IU of the ReFacto AF product" (ReFacto AF product insert)

1000 IU vial of USA product contains approx 30% more Factor VIII protein than
1000 IU vial of European product

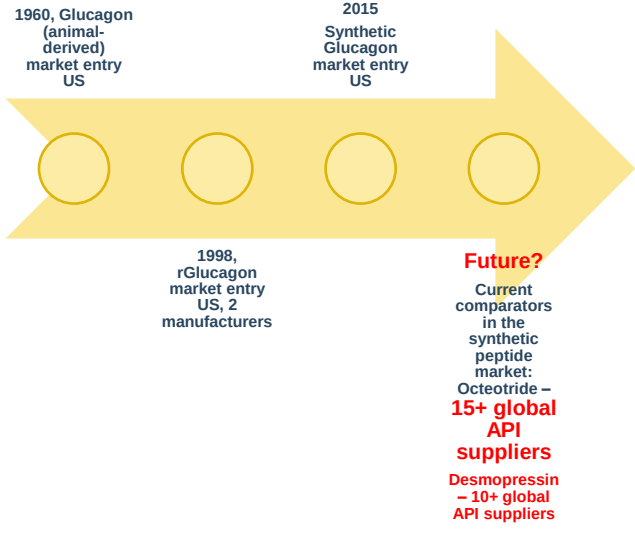
Elaine Gray, NIB

Looking back and ahead – the Glucagon Journey

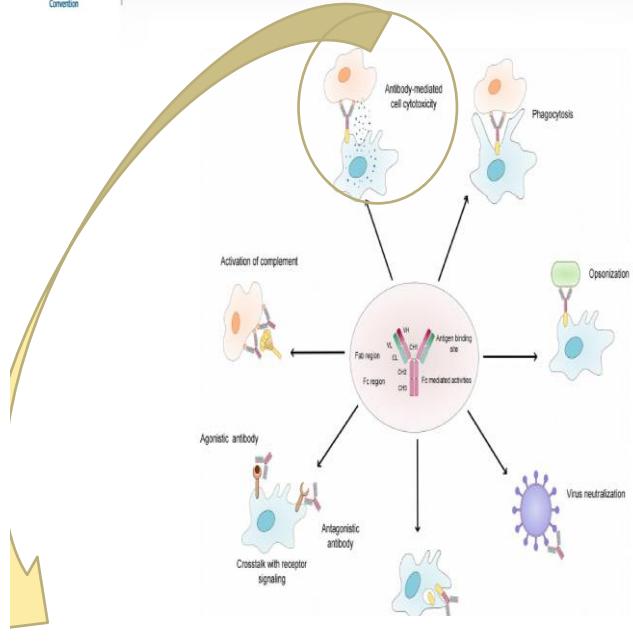


In Europe the bioassay has been completely eliminated as a compendial requirement, but not in the US!

Why this Continues to be Relevant in the US



Monoclonal Antibodies – What are We Measuring?



J Immunol Methods. 2014 May;407:63-75. doi: 10.1016/j.jim.2014.03.021. Epub 2014 Apr 3.

Characterization of in vitro antibody-dependent cell-mediated cytotoxicity activity of therapeutic antibodies - impact of effector cells.

Chung S[1], Lin YL[2], Reed C[2], Ng C[2], Cheng ZJ[3], Malavasi F[4], Yang J[2], Quarmby V[2], Song A[2].

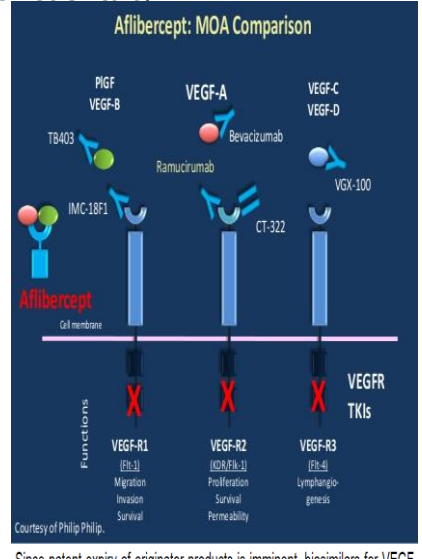
ECBS October 2014 – Rituximab International Reference Reagent Proposal

Proposed use

NIBSC

- Availability of Rituximab RR will allow manufacturers to use the same 'benchmark' for biological activity.
- Collaborative study will allow setting of recommended limits of deviation in specific activity from innovator product.
- Availability of Rituximab RR potentially allows assignment of IU, although it is unlikely that this would be acceptable in absence of regulatory requirements.

The Next Frontier – Standards for VEGF Antagonists: different molecules, Shared Functionality



Since patent expiry of originator products is imminent, biosimilars for VEGF antagonists (particularly bevacizumab and ranibizumab) are currently in development worldwide with some already licensed in BRIC countries. Therefore, there is an urgent need for bioactivity standards for these molecules.

Standards will be used by manufacturers and regulatory authorities to control the performance of assays for bioactivity evaluation of therapeutic products.

Considerations for International Standardization

Examining the key paradigms of assay independence of a standard:

- Where does this paradigm fail us – addressing commutability for key materials and measurements

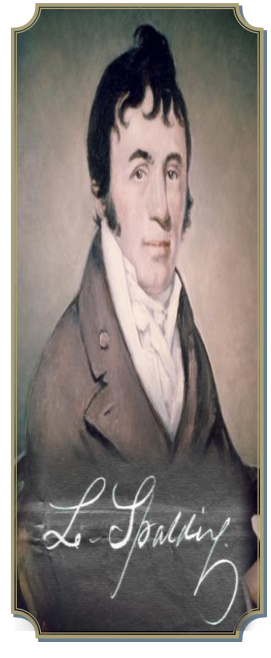
When is *like* not vs *like* anymore:

- Product and standard evolution – heparin and other "old" biologics teach us that "*like vs like*" is a moving target: standards have to stay in sync with and be relevant to the products in the global market place
- The market is expanding with products that have no equivalent in nature but share common functionality (e.g. VEGF antagonists)

We still need International Units

- Addressing specific activity and when that is meaningful and why
- Creating a common understanding regarding mass balance assignment of International Standards, especially the ones used in diagnostic contexts

A Word on Relevance…



The value of the pharmacopeia depends upon the fidelity with which it conforms to the best state of medical knowledge of the day.

Lyman Spalding, ca. 1820

USP
U.S. Pharmacopeial Convention

Global Expertise
Trusted Standards
Improved Health

Thank You

Perspective of the PMDA on Biotherapeutics

Takao Yamori
Executive Director / Director of Center for Product Evaluation
Pharmaceuticals and Medical Devices Agency (PMDA)

27-28 September 2016, Tallinn, Estonia

Today's Topic

1. What's Japanese Pharmacopoeia (JP) ?
2. Development of biotherapeutic products in Japan and JP
3. Challenge for biotherapeutic products in JP

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1. What's Japanese Pharmacopoeia (JP) ?
2. Development of biotherapeutic products in Japan and JP
3. Challenge for biotherapeutic products in JP

History and Legal Status of JP

- First published on June 25, 1886
  and implemented on July 1, 1887
  ⇒***JP has the history of 130 years***
- JP is published by the Japanese Government as a Ministerial Notification by the Ministry of Health, Labour and Welfare (MHLW)
- JP is published in accordance with the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices which is the most fundamental law for pharmaceutical regulation in Japan.
  - **Article 41-1** To standardize and control the properties and quality of drugs, the Minister shall establish and publish the JP, after hearing the opinion of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC).
  - **Article 41-2** The Minister shall consult the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) on the investigation and the revision of the whole of JP at least every 10 years.
- From 1991 New editions and its 2 supplements are published in 5 years and partial revisions are made as necessary.

Basic Principles for Preparation of JP17
(Five Primary Objectives)

Published in September 2011

1. Include all drugs which are important for health care and medical treatment
2. Make qualitative improvement by introducing the latest science and technology
3. Promote internationalization
4. Make prompt partial revision as necessary and facilitate smooth administrative operation
5. Ensure transparency regarding the revision, and disseminate the JP to the public

Composition of the JP17

JP17th Edition comprises the following items,

1. Notification of MHLW
2. Contents
3. Preface

Mandatory Part

4. General Notices
5. General Rules for Crude Drugs
6. General Rules for Preparations
7. General Tests **(78 General Tests)**
8. Official Monographs **(1962 Monographs)**
9. Ultraviolet-visible Reference Spectra
10. Infrared Reference Spectra
11. General Information (50 General Information)
12. Table of Atomic Mass as an appendix
13. Cumulative Index

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Official Monographs

<Scope>

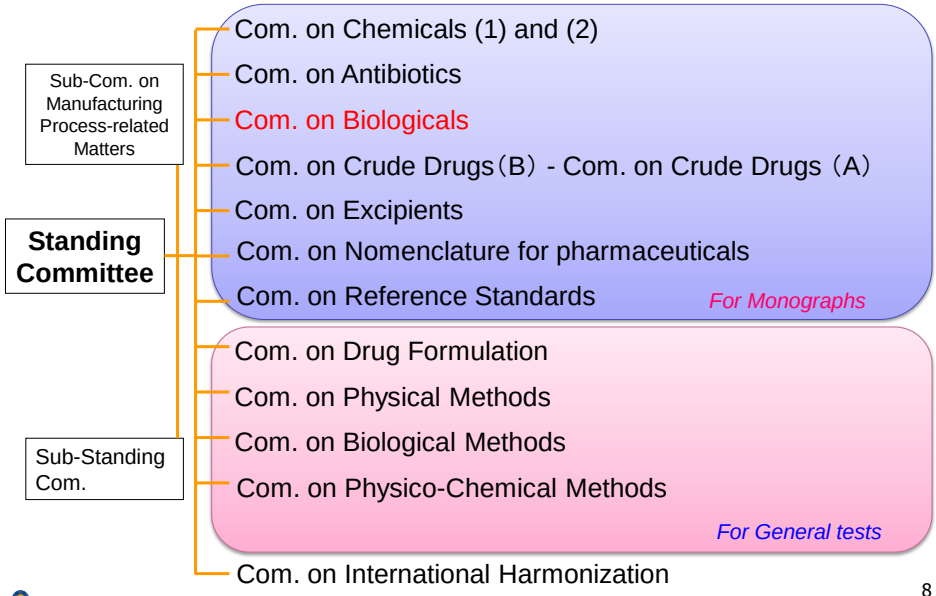
- Chemical Substances/Products
- Biological Substances/Products
- Vaccines and Blood Products, whose specifications are referred to another official standard: “Minimum requirement for biological products”
- Herbals

<Out of scope>

- Gene Therapy Products
- Cellular and Tissue-based Products

Organization of JP Expert Committees

Update; June 1, 2015



Today's Topic

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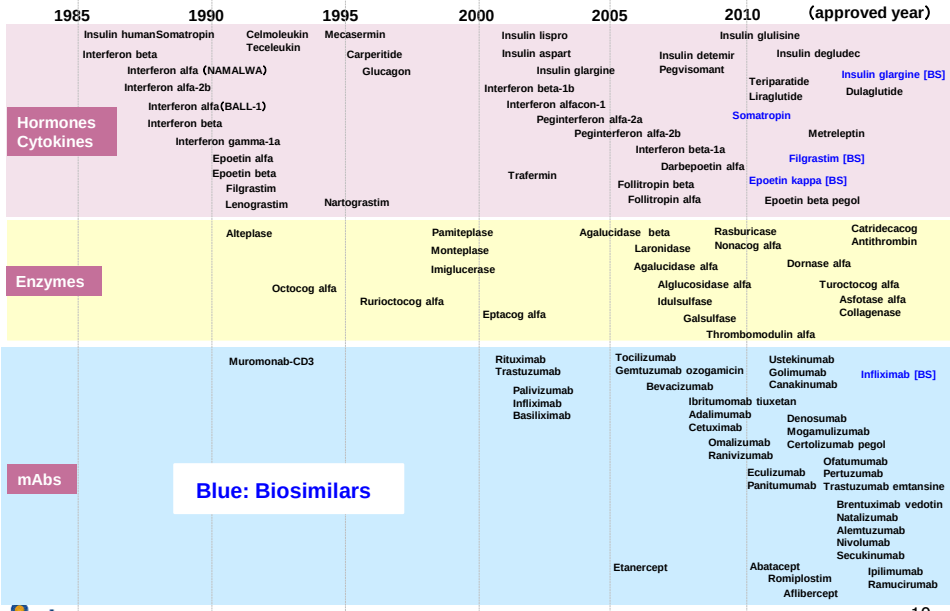
Trend of biotherapeutics approved in Japan

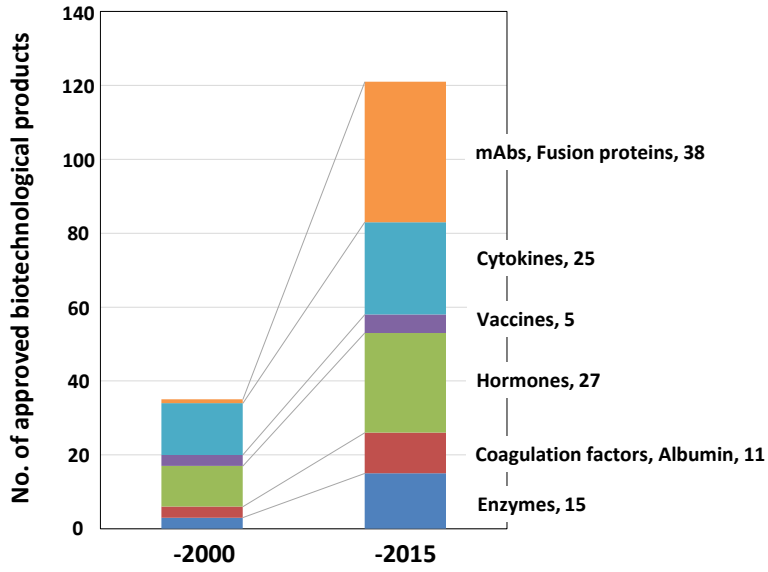
(Desired product base)



(Provided by Dr Akiko Ishii-Watabe of National Institute of Health Sciences)

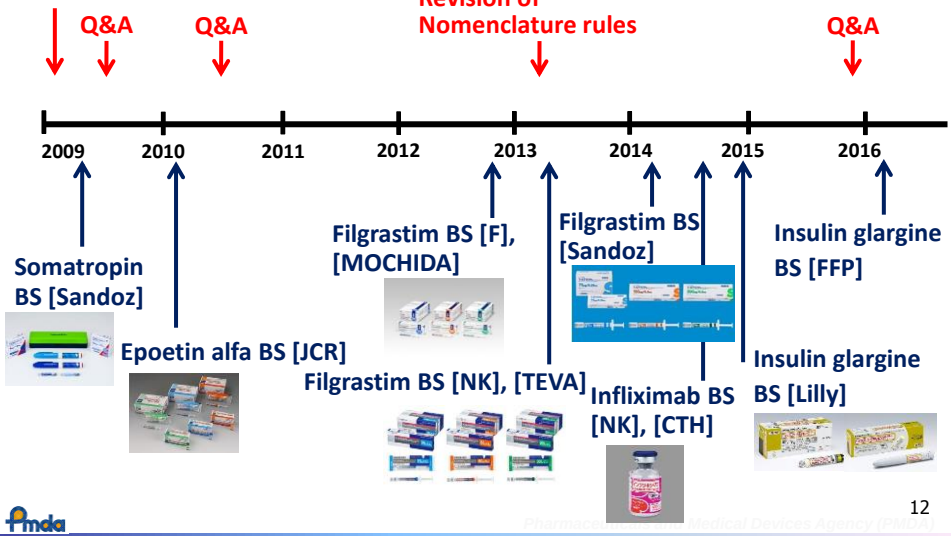
Trend of biotherapeutics approved in Japan

(Product base)



Regulatory History and Status of Biosimilars

- Application Category for biosimilars
- Guideline
- Nomenclature rules



Development of infrastructure for quality assurance to deal with expansion of biotherapeutics

- The significant drugs for health care and medical treatment have been shifted from chemical products to biotherapeutics.
- From now on, more and more biosimilars are expected to be marketed.
- Thus, it is necessary to develop the infrastructure to share information for the quality assurance of biotherapeutics among the regulatory agencies, the manufacturers and the academia.

Today's Topic

1. What's Japanese Pharmacopoeia (JP) ?
2. Development of biotherapeutic products in Japan and JP
3. **Challenge for biotherapeutic products in JP**

JP's approaches on biotherapeutics under discussion

1. Establishment of general rules regarding quality assurance of biotherapeutics
2. Listing test methods to be applied for biotherapeutics
3. Listing official monographs for biotherapeutics

JP's approaches on biotherapeutics under discussion

1. Establishment of general rules regarding quality assurance of biotherapeutics:
   - In response to recent increase in the drugs containing biotechnology-derived peptide and/or protein as their desired product, the basic principles on quality assurance of biotherapeutics including requirements for manufacturing methods will be developed.

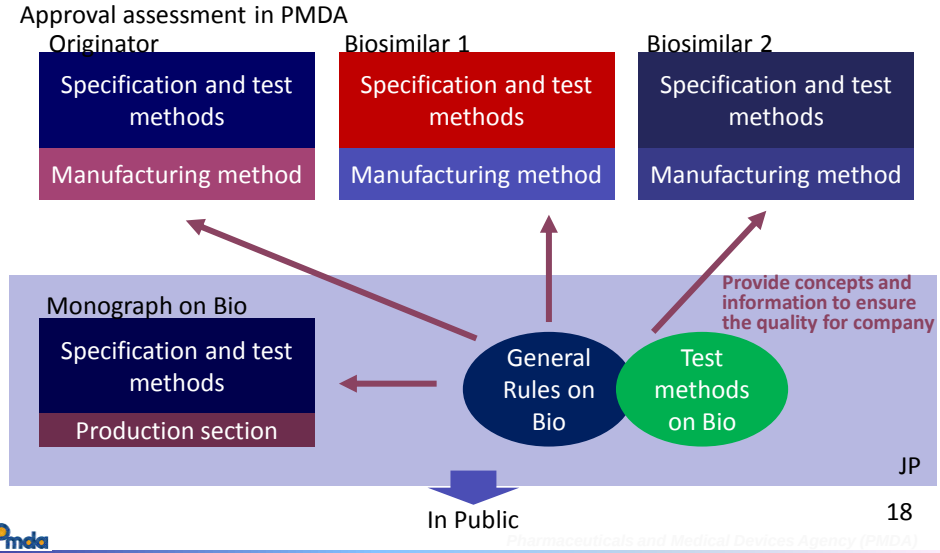
JP's approaches on biotherapeutics under discussion

2. Listing test methods to be applied to biotherapeutics:
   - The test methods for biotherapeutics will be included in JP as standard quality test methods. (The methods will be implemented without delay when internationally harmonized through the PDG activities (★) .

Test methods listed in JP 17

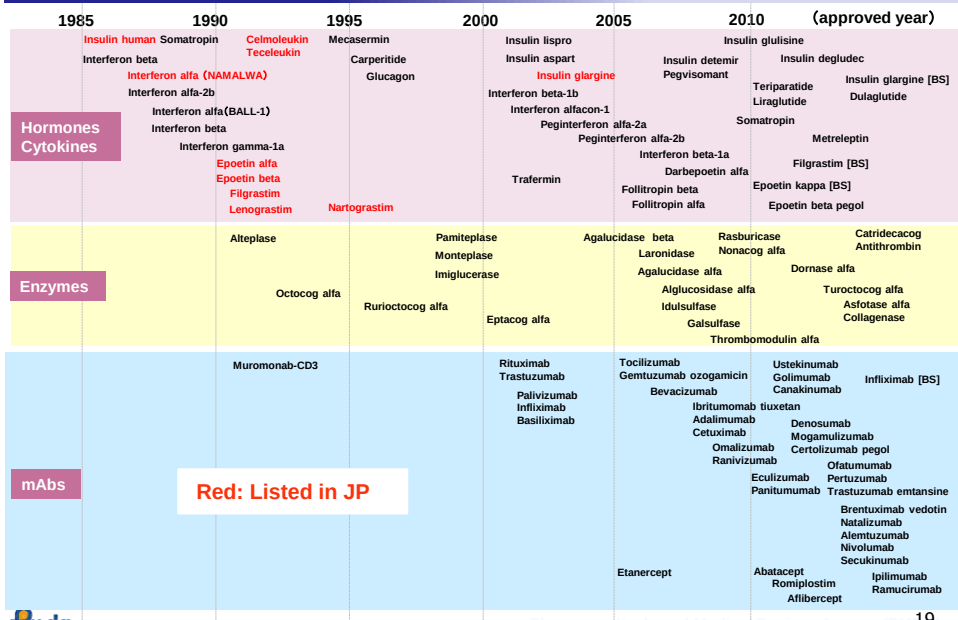
- ★ Amino Acid Analysis
- Basic Requirements for Viral Safety of Biotechnological/Biological Products listed in Japanese Pharmacopoeia
- ★ Capillary Electrophoresis
- ★ Isoelectric Focusing
- Mass Spectrometry of Peptides and Proteins
- Mycoplasma Testing for Cell Substrates used for the Production of Biotechnological/Biological Products
- ★ Peptide Mapping
- Qualification of Animals as Origin of Animal-derived Medicinal Products provided in the General Notices of Japanese Pharmacopoeia and Other Standards
- ★ SDS-Polyacrylamide Gel Electrophoresis
- ★ Total Protein Assay
- Monosaccharide analysis and oligosaccharide analysis

The expected role of JP to ensure the quality of Biotherapeutics



Biotherapeutics monographs listed in Japan

(Desired product base)



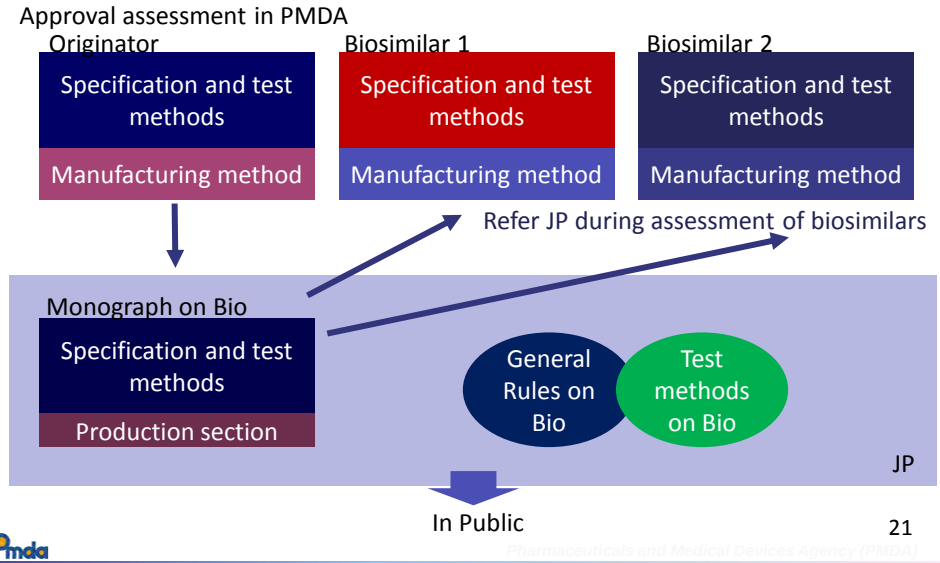
(Provided by Dr Akiko Ishii-Watabe of National Institute of Health Sciences)

JP's approach on biotherapeutics under discussion

3. Listing official monographs for biotherapeutics:
   - Current monographs on biotherapeutics is set based on the quality attributes of the originator.
   - It is difficult /usually impossible to present the specification covering all the biosimilars, because it is decided not by the specification but by the comparability exercise whether each biosimilar candidate is comparable to the originator or not.
   - However, JP monograph could present standard specifications for biosimilars, which will be submitted for the registration.

   - The new approach to set of JP monographs on biotherapeutics to control the biosimilars are under discussion.
     - General monograph, Family monograph, or typical one??

The expected role of JP to ensure the quality of Biotherapeutics



PMDA Web Site

http://www.pmda.go.jp/english/index.html

JP English Homepage

JP English electric version can be downloaded ***free of charge*** from the JP English website; http://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0010.html

Thank you for your attention !

Please visit to our website:
http://www.pmda.go.jp/english/pharmacopoeia/index.html