Biologicals of the twenty PhEurst century

Emmanuelle Charton, Ph. D.

Head of Division, European Pharmacopoeia Department

European Directorate for the Quality of Medicines

Council of Europe, Strasbourg

Topics covered by the talk

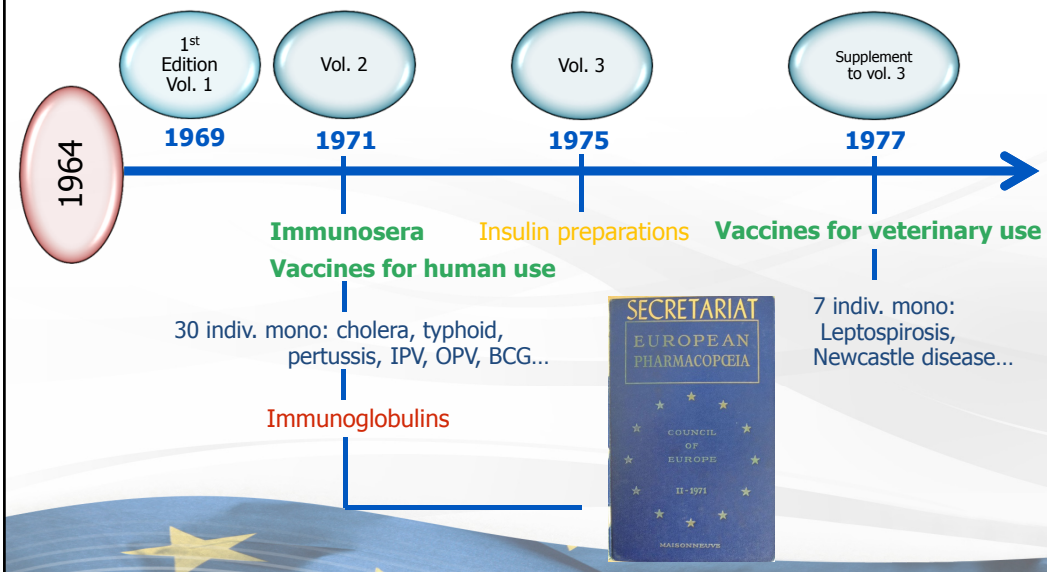
- Brief introduction to the Ph. Eur.
- How monographs and general chapters are elaborated
- Overview of the main texts dealing with biologicals, with a specific focus on biotech products (role of general chapters, general monographs and specific monographs)
- The flexibility provided by the Ph. Eur., including examples of QbD approaches for biologicals
- The Ph. Eur. and biosimilars, with examples of how their development is being fostered
- Update on the current work programme and hot topics in the field of biotech product monographs

Place of the Ph. Eur. within EU regulatory network

- Lays down common, compulsory quality standards for all medicinal products in Europe.
- Mandatory on the same date in 37 states (CoE) and the EU (European Union Directives **2001/82/EC**, **2001/83/EC**, and **2003/63/EC**, as amended, on medicines for human and veterinary use).
- The Ph. Eur. is legally binding. The legislation also includes a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market;
- The European Pharmacopoeia needs to keep pace
  - with the regulatory needs of licensing, control and inspection authorities in the public health area,
  - with technological and scientific advances, and with industrial constraints.

BIOLOGICALS OF THE 20TH CENTURY

The seventies: Vaccines for human and veterinary use



Policy concerning monographs for vaccines for veterinary use (PA/PH/SG (82) 13)

- *"…the function of any pharmacopoeial monograph is to provide standards by which the quality of a given sample of the finished product in question can be judged by an independent analyst;…*
- *"…It is therefore maintained that the body of a monograph, that is the section under the heading TESTS, should comprise those tests which can be performed on the final product and which are considered to be essential in cases of doubt or dispute in order to ascertain whether a particular product is satisfactory or not…"*

Policy concerning monographs for vaccines for veterinary use (PA/PH/SG (82) 13)

- *"…It is recognised however that for many biological products especially vaccines, other aspects of control play a major role in ensuring the safety and efficacy of the final product…"*
- *"…In addition it is appreciated that, in order to facilitate free exchange of such products throughout the countries party to the convention on the Elaboration of a European Pharmacopoeia,* ***a common approach to control*** *is desirable."*

Policy concerning monographs for vaccines for veterinary use (PA/PH/SG (82) 13)

- *"…Recognising the* ***need for flexibility*** *with respect to statements relating to facets of control such as the choice of vaccine strains, the Group has proposed that such details be included in the* ***introductory section*** *of the monograph."*

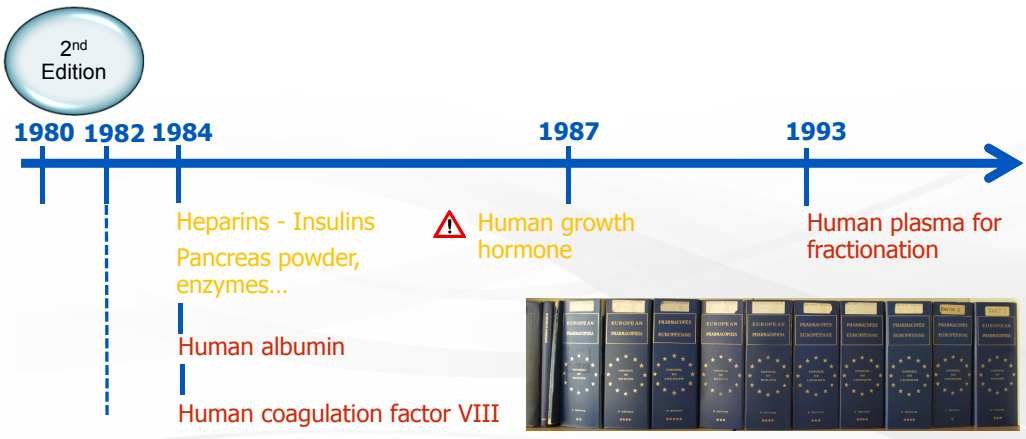
These discussions led to the creation of the **Production section** in **1991** in:

- General monograph *Vaccines for veterinary use* (0062)
- **General Notices**

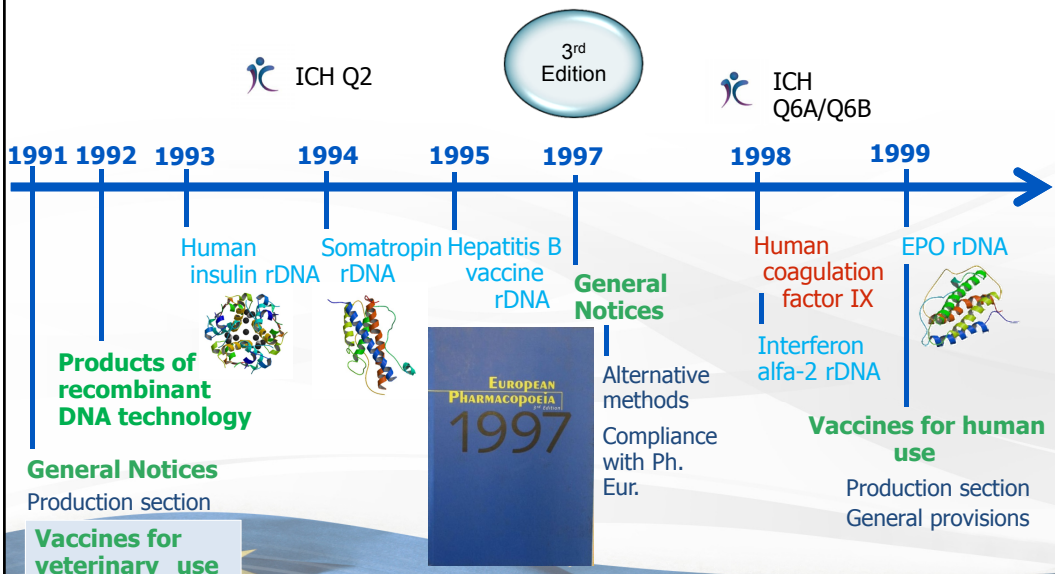
Production section

General Notices: "*Statements under the heading Production draw attention to particular aspects of the manufacturing process but are not necessarily comprehensive. They constitute* ***mandatory requirements for manufacturers****, unless otherwise stated. These statements cannot necessarily be verified on a sample of the final article by an independent analyst. The* ***competent authority*** *may establish that the instructions have been followed, for example, by examination of data received from the manufacturer, by inspection of manufacture or by testing appropriate samples.*"

The eighties: Blood products, substances extracted from animal tissues



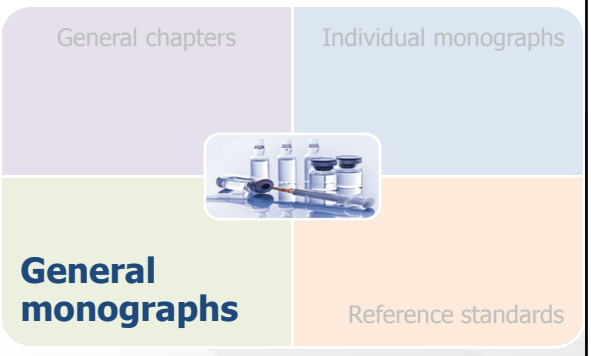
The nineties: rDNA products



Ph. Eur. texts

classes of substances, dosage forms

- *Recombinant DNA technology, products of* (784)



- Quality aspects that cannot be dealt with in each individual monograph
- Quality aspects that are common to a class of products
- Classes defined by different criteria: production method, origin, risk factors (*e.g.* fermentation, TSE risk)
- General monographs apply to all substances and preparations within the scope of the **Definition section of the general** monograph, except where a preamble limits its application

Ph. Eur. texts (cont'd)

- based on approved specification(s) backed up by batch data
- specifications for drug substance or finished products
- analytical procedures and acceptance criteria to demonstrate that the substance meets required quality standards

General chapters

Individual monographs

General monographs

Reference standards

DEFINITION (amino acid sequence, glycosylation site, assay limits)

PRODUCTION: instructions for manufacturers (*expression systems, parameters that cannot be verified by independent analysts: e.g. HCP)*

IDENTIFICATION peptide mapping, glycan analysis, bioassay…

TESTS physico-chemical and/or chromatographic methods to assess the level of process- and product-related impurities such as oxidated, deamidated forms, aggregates,…

ASSAY physico-chemical assay methods, bio/immuno-assays

Ph. Eur. texts (cont'd)

standard analytical methods general requirements for equipment

- *Peptide mapping* (2.2.55)
- *Amino acid analysis* (2.2.56)
- *Glycan analysis of glycoproteins* (2.2.59)
- *Isoelectric focusing* (2.2.54)
- *Size-exclusion chromatography* (2.2.30)
- *Capillary electrophoresis* (2.2.47)

General chapters

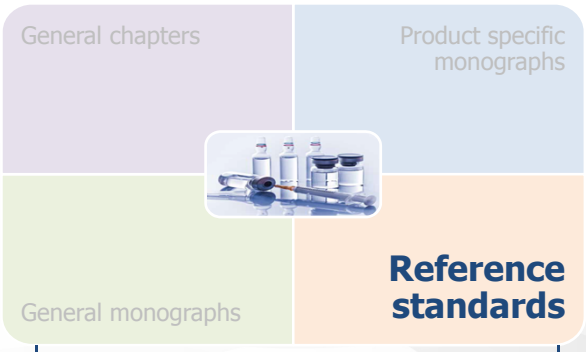
Individual monographs

General monographs

Reference standards

- Editorial convenience: avoid repeating standard methods in each monograph
- Provide standard methods that can be used where there is no monograph
- Give general requirements for equipment, equipment verification
- Not mandatory ***per se***
- When referred to in a monograph, they become part of the standard

Ph. Eur. reference standards



Ph. Eur. Chapter 5.12 *Reference standards*

- Established specifically for use in monographs or general chapters of the Ph. Eur., as prescribed in the methods given
- **Chemical Reference Standards** (CRSs) and **Biological Reference Preparations (BRPs**)
- Assay of biologicals: always refer to **WHO International Standards**
- BRPs are established by the **Biological Standardisation Programme** (BSP) of the EDQM

The Biological Standardisation Programme

- A contract signed in 1991 between the **Commission of the European Communities** and the **Council of Europe** to allow for the provision of logistical and scientific assistance for activities related to the testing of biologicals, in particular vaccines and blood products.
- The BSP makes available BRPs calibrated against the I.S. but using only methods of the Ph. Eur., *e.g.* coagulation factors VII, VIII.
- The BSP establishes **BRPs** and **BRRs** that allow alternative methods to be carried out instead of *in vivo* assays, *e.g.* Clostridia antisera; Bordetella pertussis antiserum; swine erysipelas vaccine; ELISA reagents.

Flexibility in the Ph. Eur. – Alternative methods

- **Ph. Eur. tests are reference methods**, essential in cases of dispute.
- Compliance is required, but **alternative methods** may be used as long as they lead to the **same pass/fail result**.
- It is the responsibility of the user to demonstrate their suitability. **Approval of the competent authority** is necessary in many cases.

Flexibility in the Ph. Eur. – Waiving of tests

"An article is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. ***This does not imply that performance of all the tests*** *in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality from data derived, for example, from validation of the process and from validation studies of the manufacturing process and from in-process control".*

General Notices (3rd Edition to Supplement 8.1)

Vaccines for human use (0153) – General provisions

- **Consistency of production process**: batches must be comparable to batches of proven safety and efficacy
- **Omission of tests** is possible when consistency is demonstrated:
  - by **validation;**
  - in **agreement by the competent authority.**

Vaccines for human use (0153) – General provisions (cont'd)

- **Consistency** of production: an **important feature**.
- **Compliance with the Tests** described in monographs (during production or on the final lot) **is not sufficient** to ensure consistency of production.
- The manufacturer must define **suitable additional tools** (statistical process control).

The nineties: rDNA products

ICH Q2

3rd Edition

ICH Q6A/Q6B

1991 1992 1993 1994 1995 1997 1998 1999

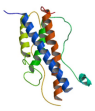
General Notices
Production section

Vaccines for veterinary use
Production section

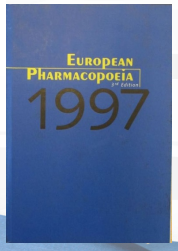
Products of recombinant DNA technology

Human insulin rDNA

Somatropin rDNA



Hepatitis B vaccine rDNA



General Notices

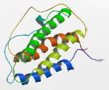
Alternative methods

Compliance with Ph. Eur.

Human coagulation factor IX

Interferon alfa-2 rDNA

EPO rDNA



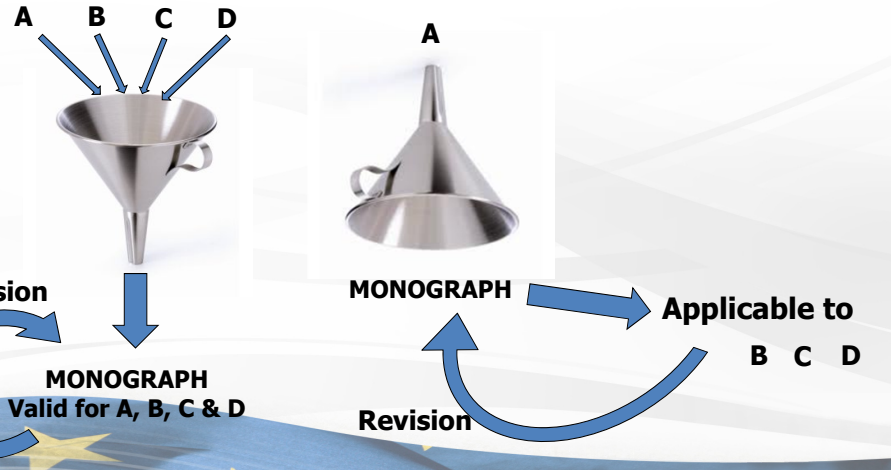
Vaccines for human use

Production section
General provisions

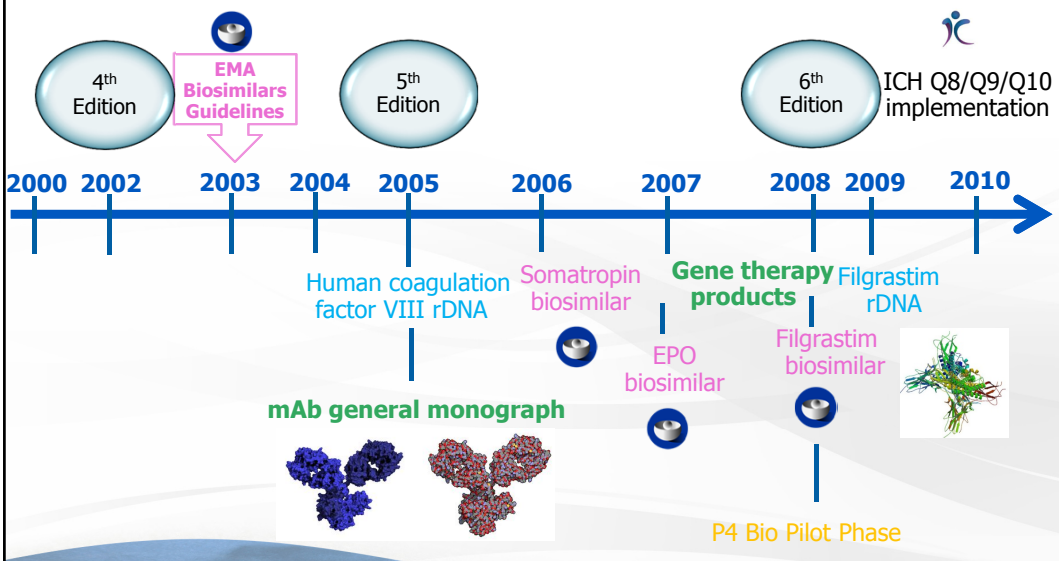
BIOLOGICALS OF THE 21ST CENTURY

P4 Bio Procedure: Pilot Phase

Procedure 1 Procedure 4



The 21st century: 1st decade



PURIFIED BULK FACTOR VIII (rDNA)

The purified bulk complies with a suitable combination of the following tests for characterisation of integrity of the factor VIII (rDNA). Where any substance added during preparation of the purified bulk interferes with a test, the test is carried out before addition of that substance. Where applicable, the characterisation tests may alternatively be carried out on the finished product.

Specific biological activity or ratio of factor VIII activity to factor VIII antigen. Carry out the assay of human coagulation factor VIII (*2.7.4*). The protein content, or where a protein stabiliser is present, the factor VIII antigen content, is determined by a suitable method and the specific biological activity or the ratio of factor VIII activity to factor VIII antigen is calculated.

Protein composition. The protein composition is determined by a selection of appropriate characterisation techniques which may include peptide mapping, Western blots, HPLC, gel electrophoresis, capillary electrophoresis, mass spectrometry or other techniques to monitor integrity and purity. The protein composition is comparable to that of the manufacturer's reference preparation.

Molecular size distribution. Using size-exclusion chromatography (*2.2.30*), the molecular size distribution is comparable to that of the manufacturer's reference preparation.

Peptide mapping (*2.2.55*). There is no significant difference between the test protein and the manufacturer's reference preparation.

Carbohydrates/sialic acid. To monitor batch-to-batch consistency, the monosaccharide content and the degree of sialylation or the oligosaccharide profile are monitored and correspond to those of the manufacturer's reference preparation.

***Human coagulation factor VIII (rDNA)* (1643)**

- Reference to Ph. Eur. general chapters
- No details of the exact procedure to be followed
- Carbohydrates/sialic acid to monitor batch to batch consistency

General monograph: *Monoclonal antibodies for human use* (2031)

- Applies to all monoclonal antibodies products
- **General requirements** for the production and testing of monoclonal antibodies:
  - Production based on seed lot system using master cell banks
  - **Tests**: reference to general chapters: degree of opalescence (2.2.1) and degree of coloration (2.2.2), pH (2.2.3), Osmolality (2.2.35), Extractable volume (2.9.17), Total protein (2.5.33), Molecular-size distribution by size-exclusion chromatography (2.2.30), Water (2.5.12), Sterility (2.6.1), Bacterial endotoxins (2.6.14)
  - **Purity**: Tests for process- and product-related impurities are carried out by suitable validated methods
  - **Assay**: Carry out a suitable biological assay compared to the reference preparation

Gene transfer medicinal products for human use (5.14)

- Chapter is informative
- Framework of requirements
- Use of alternatives
- Applicable for approved products
- Can also be applied during clinical trials
- Approval by competent authority
- Reference to EU guidelines

Human haematopoietic stem cells (2323)

"This monograph provides a standard for the preparation and control of human haematopoietic stem cells for use in therapy. It does not exclude the use of alternative preparation and control methods that are acceptable to the competent authority."

QbD APPROACHES IN THE PH. EUR.

"The European Pharmacopoeia blocks the implementation of QbD."

"Specifications set in European Pharmacopoeia monographs are against the principle of QbD."

"Monographs block the development of innovative testing strategies."

We do not agree with these statements!

Process Analytical Technologies (PAT)

EDQM International Symposium, Cannes, 3-4 May 2004

- Concurrent with ICH Q8 finalisation
- Recognition of the fact that the European Pharmacopoeia:

  - has to provide legal requirements for the quality of medicinal products and their components: methodologies and acceptance criteria;
  - …while at the same time… has to provide flexibility, to keep pace with current thinking and concepts, to allow for the use of modern technologies.

- **Ph. Eur. chapters**:
  - 2.9.47 Demonstration of Uniformity of Dosage Units Using Large Sample Sizes (Supplement 7.7, 04/2013); 2.2.40 Near Infrared Spectroscopy (Revised: 8th Edition, 01/2014);

Close collaboration with EMA PAT team

  - **JUST ADOPTED: Raman spectrometry (2.2.48), Chemometric methods applied to analytical data (5.21)**

Ph. Eur. texts on biologicals
Flexibility / Alternative methods – Overview

- ✓ **Production section** (since 1991)
- ✓ **Alternative methods** and possibility to omit tests in General Notices (since 1997)
- ✓ General provisions in the general monograph on vaccines for human use: **need for control strategy and suitable in-process testing** (since 1998)
- ✓ Clear statements on the **non-mandatory character of many texts** (especially in the field of advanced therapies)

These were solutions that the experts found at the time to cope with the complexity of biologicals (there was no other way).

Flexibility in the Ph. Eur. – Waiving of tests

"***Demonstration of compliance with the Pharmacopoeia***

(1) *An article is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality* ***on the basis of its design, together with its control strategy and data derived****, for example, from validation studies of the manufacturing process."*

General Notices – New (Supplement 8.2.)

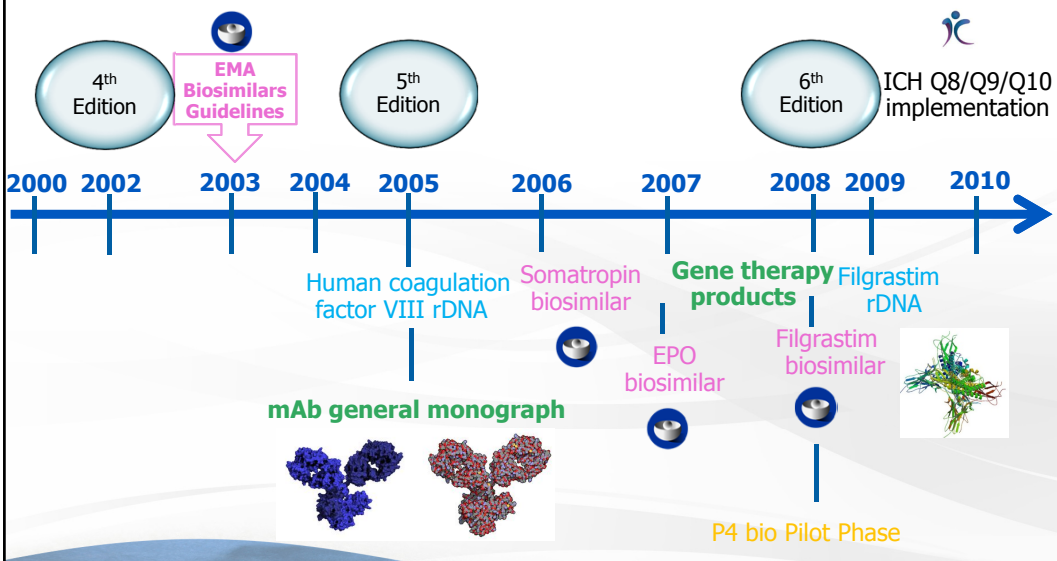
Flexibility in the Ph. Eur. PAT/Real Time Release Testing (RTRT)

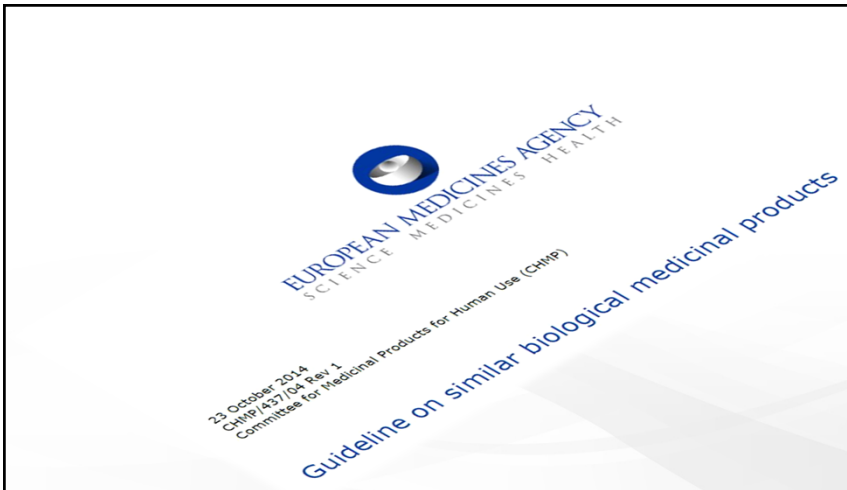
- As a consequence of the publication of the EMA Guideline on Real Time Release Testing (formerly Guideline on Parametric Release) EMA/CHMP/QWP/811210/2009-Rev1
- The Ph. Eur. provides a framework for the use of PAT/Real Time Release Testing

Acceptance criteria/specifications in Ph. Eur.

- **Conventional specifications** are needed!
- Correlation to be made between the prediction (RTRT) and the conventional specifications
- Conventional expression of specifications will always be needed for:
  - ✓ Product development
  - ✓ Independent controls (*e.g.* Official Medicines Control Laboratories)
  - ✓ Stability studies
  - ✓ Applicants that decide to apply the "conventional approach"
- **Need for a tiered system**, providing "conventional" specifications, but enabling the implementation of new approaches, *e.g.* PAT
- **PAT and public standards are compatible** with each other

The 21st century: 1st decade





CONSIDERATIONS ON BIOSIMILARS

Biosimilars and Ph. Eur.

- **Directive 2001/83/EC:**

"*The provisions of Article 10(1)(a) (iii) may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided*."

- **Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1)**:

*"The **similar biological medicinal product** shall, with regard to the quality data, fulfil all requirements for Module 3 as defined in Annex I to Directive 2001/83/EC and satisfy the technical requirements of the monographs of the European Pharmacopoeia and any additional requirements, such as defined in relevant CHMP and ICH guidelines."*

Biosimilars and Ph. Eur. (cont'd)

- **Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)** EMA/CHMP/BWP/247713/2012

"A comparison of the biosimilar to a publicly available standard, e.g. a pharmacopoeial monograph, is not sufficient for the purpose of comparability.
(…)
Extensive state-of-the-art characterisation studies should be applied to the biosimilar and reference medicinal products in parallel, to demonstrate with a high level of assurance that the quality of the biosimilar is comparable to the reference medicinal product.
It is the responsibility of the applicant to demonstrate that the selected methods used in the biosimilar comparability exercise would be able to detect slight differences in all aspects pertinent to the evaluation of quality (e.g. ability to detect relevant variants with high sensitivity). Methods used in the characterisation studies form an integral part of the quality data package and should be appropriately qualified for the purpose of comparability. If applicable, standards and reference materials (e.g. from Ph. Eur., WHO) should be used for method qualification and standardisation."

WHO GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs), 2009

8.3 Specifications

"Specifications are employed to verify the routine quality of the drug substance and drug product rather than to fully characterize them. As for any biotherapeutic product, specifications for a SBP should be set as described in established guidelines and monographs, where these exist.
It should be noted that pharmacopoeial monographs may only provide a minimum set of requirements for a particular product and additional test parameters may be required."

WHO GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs), 2009 (cont'd)

Reference biotherapeutic product (RBP)

"A reference biotherapeutic product is used as the comparator for head-to-head comparability studies with the similar biotherapeutic product in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as a RBP. It does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards."

Ph. Eur. reference standards

Ph. Eur. Reference standards are not intended to be used as reference (comparator) products in the context of applications for biosimilars!

Ph. Eur. Reference standards can be used during the development of biosimilars for method qualification and standardisation

Ph. Eur. Chapter 5.12 *Reference standards*

- Established specifically for use in monographs or general chapters of the Ph. Eur., as prescribed in the methods given
- **Chemical Reference Standards** (CRSs) and **Biological Reference Preparations (BRPs)**
- Assay of biologicals: always refer to **WHO International Standards**
- BRPs are established by the **Biological Standardisation Programme** (BSP) of the EDQM

"Monographs are not sufficient to demonstrate comparability"

"Monographs are not necessary to demonstrate comparability"

"Monographs are not relevant to demonstrate comparability"

✓ ***EDQM agrees with all these statements!***

➡ ***Monographs*** *– provide* ***framework requirements*** *for the* ***quality of biosimilars***

"*While we appreciate that monographs provide public standards for the quality of medicinal products and their constituents, these monographs are not sufficient to assess identity and similarity of medicinal products that are required to establish comparability of a biosimilar with an original biological product in the context of a marketing authorisation application.*"

Dr. Susanne Keitel, Director of EDQM,

Comments on the Draft Decree establishing requirements and procedures for the "Pharmacological and Pharmaceutical Evaluations of Biological Medicines in the Health Registration Process", published on the website of the Ministry of Health of Republic of Colombia. Letter sent to the Ministry on 14 August 2014.

Need for monographs to remain up to date

Annex 1 of Directive 2001/83/EC: "*In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder. The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.*"

Feedback on the ability of the Ph. Eur. monograph to support the quality part in the comparability exercise is essential for the monograph to remain useful.

20 Biosimilars approved in Europe

- ✓ …within the product classes of **human growth hormone**, **granulocyte colony-stimulating factor**, **erythropoietin**, **insulin** and **TNF-inhibitor**, for use in the EU.
- ✓ Corresponding **Ph. Eur. monographs**:
  - *Somatropin* (0950, 0951, 0952, 2370)
  - *Erythropoietin* (1316)
  - *Filgrastim* (2206)
  - *Follitropin* (2285, 2286)
  - *Insulin glargine* (2571)

Corresponding Ph. Eur. monographs

- **EPO: limits for isoforms 3 and 7** have been modified in light of batch data for approved products (Supplement 5.3)
  - ➢ Current work to strengthen the **carbohydrate analysis**
  - ➢ **3R strategy** for the ***in vivo*** **assay**
- **Filgrastim:** adopted by Commission Nov. 2014, to be published in Supplement 8.6
  - ✓ **Definition**: minimum potency limit lowered, based on recent batch data.
  - ✓ **Impurities with molecular masses higher than that of filgrastim**:

    separate limit for the sum of aggregates and oligomers, in addition to that for tota impurities with molecular masses higher than that of filgrastim.
  - ✓ **Related proteins**: new method which is simpler and allows better resolution of impurities
- **Somatropin**: request for revision (March 2015)
- **Follitropin, insuline glargine:** only recently published

Human coagulation factor IX (rDNA) concentrated solution (2522)

Glycan Analysis: Problem statement

- ➢ On the one hand, generic methods of analysis that are already described in the Ph. Eur. should be referred to if applicable.
- ➢ On the other hand, all details should be given for a user to be able to carry out the test.
- ➢ One specification might not be suitable for all registered products.

Human coagulation factor IX (rDNA) concentrated solution (2522) (cont'd)

Production Section

- The **glycan analysis** test is described in the **Production section** of the monograph, according to the provisions given in the General Notices, as the test cannot be performed by an independent analyst for the following reasons:
  - the glycan profile depends on the manufacturing process;
  - the test prescribes the use of an in-house reference standard shown to be representative of batches tested clinically and batches used to demonstrate consistency of production;
  - no specifications are given: they have to be set by the manufacturer in agreement with the competent authority.

- **This approach is compatible with the development of biosimilars!**

Biosimilars and Ph. Eur.

European Pharmacopoeia

Biosimilarity/ Comparability

European Pharmacopoeia: a public standard providing harmonised **quality requirements for medicinal products** throughout Europe: used by all. Monographs **are established, whether or not the products** are to be submitted/approved as **generics/biosimilars**.

Biosimilars and Ph. Eur. (cont'd)

European Pharmacopoeia

Biosimilarity/ Comparability

Biosimilars: a class of products that was established to avoid unnecessary pre-clinical and clinical trials. The regulatory pathway to be followed is given in appropriate **guidelines. Biosimilars** are developed by companies and evaluated by licensing **authorities, whether or not a compendial** standard exists.

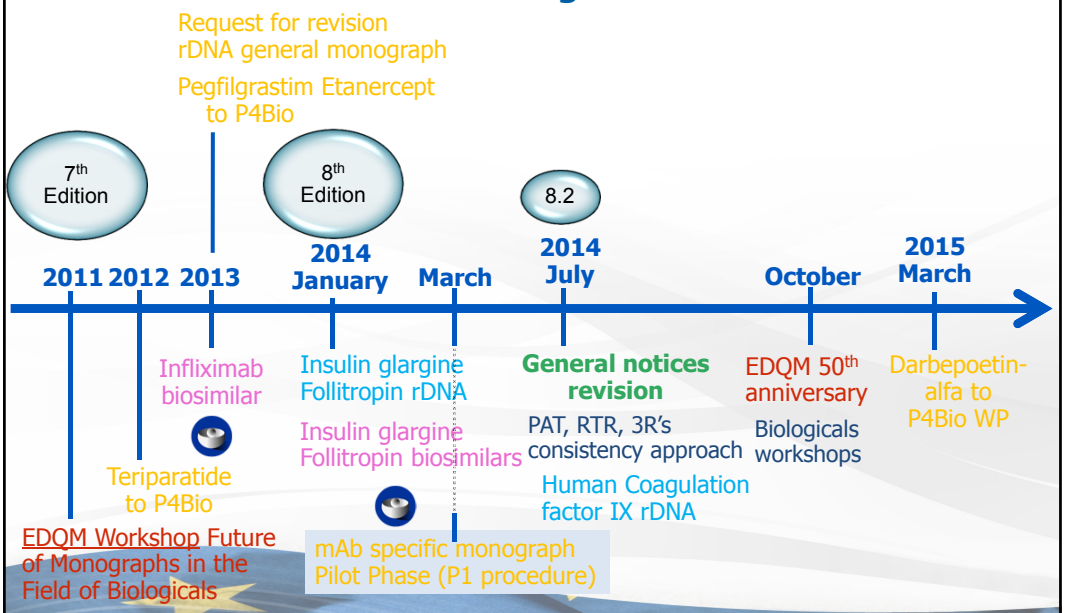
Biosimilars and Ph. Eur. (cont'd)

European Pharmacopoeia

Biosimilarity/ Comparability

These are <u>complementary instruments</u> that have different purposes but with the same goal: to <u>ensure quality of medicinal products</u>.

The 21st century: present activities and future challenges



EDQM Workshop on the Future of Monographs in the field of Biologicals

(Strasbourg, February 2011)

- ✓ Praise of **general chapters**
- ✓ **Specific monographs**: time of elaboration; **need for flexibility**
- ✓ What route to follow for **mAbs**? Individual monographs *vs.* subclasses / general monographs
- ✓ Individual monographs for **modified proteins** (*i.e.* pegylated)?
- ✓ **Host Cell Proteins**: need for guidance
- ✓ **Raw materials for the production of cell and gene therapy products**: need for harmonised quality criteria
- ✓ **Need for strong communication channels between the main players in Europe: EMA, National Authorities and EDQM**

Raw materials for the production of cell and gene therapy products

- ✓ EDQM International Workshop: April 2013
- ✓ Publication of draft chapter ***Raw materials for the production of cell and gene therapy products*** **(5.2.12)** in **Pharmeuropa 26.4** (October 2014)

© Pharmeuropa 26.4 | October 2014 61

Reference: PA/PH/Exp. RCG/T (14) 5 ANP

XXXX:50212

5.2.12. RAW MATERIALS FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

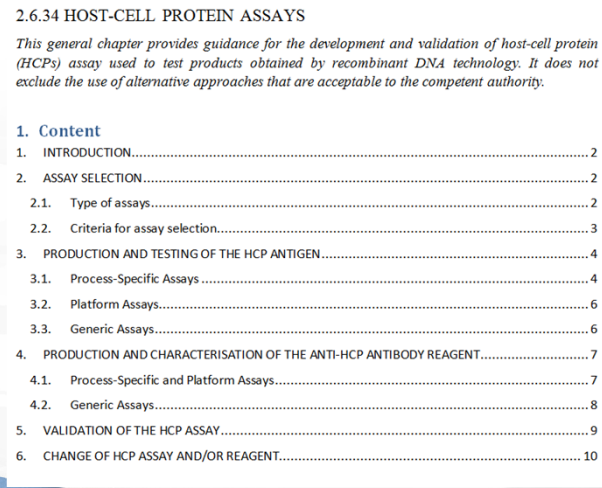
This general chapter is published for information.

It contains sections on the quality requirements of raw materials used for the production of cell-based and gene therapy medicinal products for human use. The provisions of the chapter do not exclude the use of different production and control methods. It is ultimately the responsibility of the user of a raw material to ensure it is of suitable quality for the intended use.

- ✓ **Work performed in close collaboration with EMA CAT and BWP (EMA Observer in the RCG Working Party)**

Host Cell Proteins

- ✓ **New Chapter 2.6.34**: Host-Cell Protein Assays
- ✓ Publication of draft chapter in **Pharmeuropa 27.2** (April 2015) → *comments until end of June 2015*

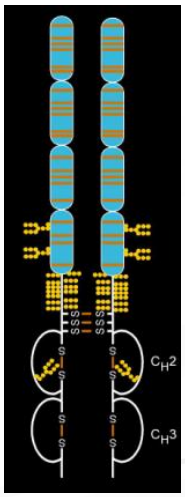


2.6.34 HOST-CELL PROTEIN ASSAYS

This general chapter provides guidance for the development and validation of host-cell protein (HCPs) assay used to test products obtained by recombinant DNA technology. It does not exclude the use of alternative approaches that are acceptable to the competent authority.

1. Content

Etanercept monograph (P4Bio)
considerations for monograph development



Protein (primary) structure:
- amino acid sequence (Definition)
- peptide mapping

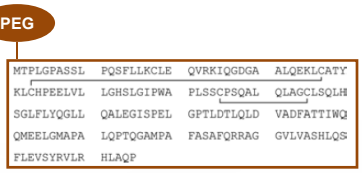
Glyco-variants:
- glycan profile -- manufacturing process dependent (→ PRODUCTION section of the monograph)

Aggregates / size variants:
- comparative procedure (against a defined reference standard)
- system suitability criteria and acceptance criteria

Potency determination:
- TNF-alpha neutralisation assay (cell-based apoptosis assay)
- reference preparation being established by BSP and calibrated in International Units against WHO standard

Pegfilgrastim monograph (P4Bio)
considerations for monograph development

Protein (primary) structure:
- amino acid sequence, disulfide bridges, *N*-terminal pegylation
- peptide mapping (consideration of testing at the level of intermediate protein)



PEG reagent:
- molecular mass, structure, polydispersity (DEFINITION section)
- quality requirements (PRODUCTION section)
- determination of residual PEG (TESTS section)

Charge variants / minor forms (oxidised species)
Aggregates / size variants

Assay:
- **Protein content**: UV determination *vs.* LC method
- **Potency determination:** cell proliferation assay using M-NFS-60 cells (responsive to filgrastim); reference standard strategy under discussion.

P4Bio challenges, novel molecules

- How to translate release specifications into a public standard
- Specifications for comparability are not release specifications!
- **Assay**:
  - proprietary cell lines or reagents are not an option
  - concurrent establishment of International Standard
- ***Collaboration with World Health Organisation***

MAB Working Party: mAb P1 pilot phase using infliximab as case study

- **Specific** monographs versus **general** monograph
- Define the **quality attributes** that are **common** to all mAbs or to all biosimilars of the same specific mAb
- **Assay** standardisation
- **MAB Working Party**: P1 Procedure – manufacturers of biosimilar/follow-on biologicals can participate in the discussions
- **Link with P4Bio** on the approaches to be followed

Introducing new technologies to Ph. Eur. texts on biologicals (1/2)

Replacement of current Ph. Eur. methods

Validation of alternative methods is a challenge:

- The results may not be expressed in the same way
- Practical implementation of equipment, knowledge of analytical software, automation
- Higher sensitivity: if more impurities are seen, what to do with the new information:
  - Should new specifications be added?
  - or rather, use the methods to verify the consistency of the production process
- The current methods were validated before ICH Q2: this is particularly the case for vaccine monographs: need for guidance on substituting methods with others when one-to-one comparison is not possible.

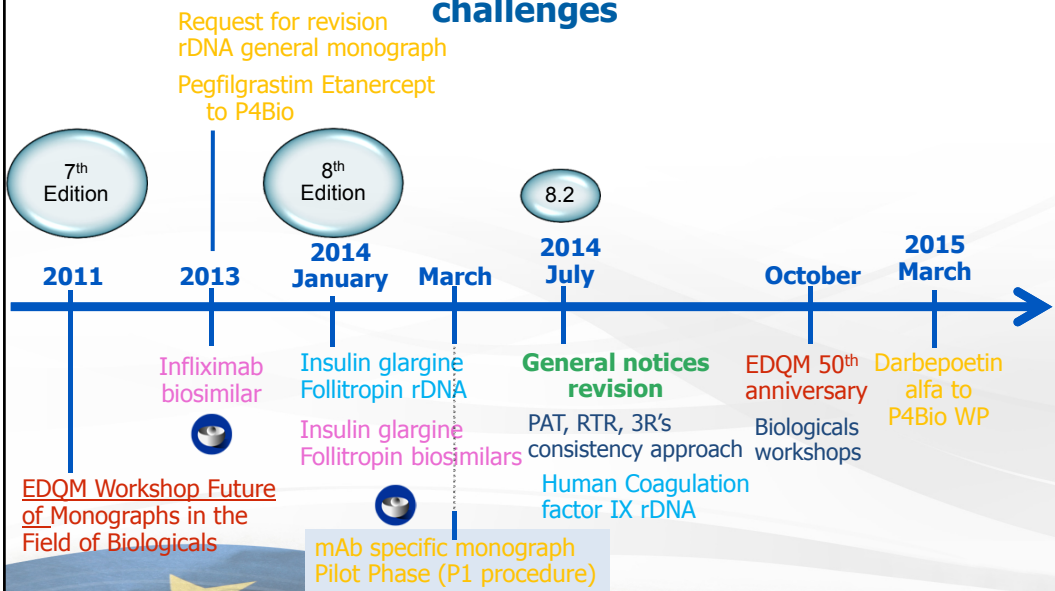
Introducing new technologies to Ph. Eur. texts on biologicals (2/2)

- **Use of alternative methods** could be facilitated by provision of **additional tools** for verification of method performance;
- The reflection has to take place between **all partners**: regulators (at EMA and in all member states), industry, Official Medicines Control Laboratories and Ph. Eur.

Example: *Influenza vaccine (surface antigen, inactivated, prepared in cell cultures)* (2149)

- Acknowledgement of time constraint
- **Alternative to 2.6.16 is possible** (e.g. PCR)
  - risk assessment
  - validation
  - agreement by the competent authority

The 21st century: present activities and future challenges



European Pharmacopoeia Convention (1964)

Objectives:

to harmonise specifications for medicinal substances which, in their original state or in the form of pharmaceutical preparations, are of general interest and importance to the peoples of Europe;

to hasten the drawing up of specifications for the growing number of new medicinal substances appearing on the market.

This aim can best be achieved by the progressive establishment of a common pharmacopoeia for the European countries concerned.

Acknowledgements

All the experts and specialists of the European Pharmacopoeia!

Acknowledgements

EDQM colleagues:

Rachel Hegenhauser, Eva Vitkova, Mihaela Buda

Biologicals of the twenty PhEurst century

Emmanuelle Charton, Ph. D.

Head of Division, European Pharmacopoeia Department

European Directorate for the Quality of Medicines