The European Pharmacopoeia

Part 3

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Agenda

- Latest news on Water for Injections monograph
- New General chapters in the field of biologicals (Host Cell Proteins, Raw materials for the production of cell and gene therapy products)
- The place of the Ph. Eur. within the context of biosimilars
- Monographs for new generation biotherapeutics
- The 3R's

LATEST NEWS ON THE WATER FOR INJECTIONS MONOGRAPH

Water, purified (Ph. Eur. 0008) PW	Water for Injections (Ph. Eur. 0169) WFI	Water, highly purified (Ph. Eur. 1927) HPW
DEFINITION		
➢ for preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised	➢ for preparation of medicines for parenteral administration (bulk WFI) and for dissolving or diluting substances / preparations for parenteral administration (SWFI)	➢ intended for use where water of high biological quality is needed, except where WFI is required
PRODUCTION		
• distillation • ion exchange • reverse osmosis • any other suitable method	• distillation only	• double-pass reverse osmosis coupled with other suitable techniques such as ultrafiltration and deionisation

Reflection Paper on WFI

- ✓ elaborated by the **Ph. Eur. WAT Working Party** (2013)
- ✓ summarises **current status of alternative methods for producing water of WFI quality,** based on scientific data received from the enquiry on non-distillation technologies
- ✓ reviews all **evidence to support a revision** of the WFI monograph to **allow non-distillation technologies** for producing WFI to be included in addition to distillation
- ✓ recognises concerns about **microbiological safety**

→ not necessarily an issue, provided that microorganisms are suitably controlled and final quality of water is appropriate:

Revised WFI monograph (0169)

Ph. Eur. WFI monograph

- **Quality standard**
- Defines quality of WFI in terms of **microbiological** and **physico-chemical** requirements

PRODUCTION section

The revised monograph allows WFI to be produced either
- by distillation
- by a purification process that is equivalent to distillation

System design, operation, maintenance (validation and monitoring)

GMP requirements

NEW GENERAL CHAPTERS IN THE FIELD OF BIOLOGICALS

Raw materials for the production of cell-based and gene therapy medicinal products

- Identified needs
  - ✓ Requirements identified
  - ✓ lack of harmonisation in the quality standards for raw materials
  - ✓ variability in approaches (grades / quality / stage of use)
  - ✓ raw materials considered to be most critical are sera, media, growth factors and enzymes.
- New General Chapter 5.2.12
- Close collaboration with EMA

Chapter aims

Chapter 5.2.12 is a general chapter – it gives quality requirements for raw materials of biological origin used for the production of cell-based and gene therapy products. The chapter :

- ✓ is non-mandatory
- ✓ harmonises current practices
- ✓ helps users identify the critical quality attributes of raw materials
- ✓ encourages raw material manufacturers to record and share information on the origin and quality of the raw material

General Chapter 5.2.12 Overview

1. Scope
2. Risk Assessment
3. General requirements

   Origin, Production, General quality requirements (ID / Tests / Ref. mat/batch), Storage, Labelling
4. Sera and serum replacements

   4.1 *Definition / 4.2 Production / 4.3 Identification / 4.4 Tests / 4.5 Assay*
5. Proteins produced by recombinant DNA technology

   5.1 *Definition / 5.2 Production / 5.3 Identification / 5.4 Tests / 5.5 Assay*
6. Proteins extracted from biological material

   6.1 *Definition / 6.2 Production / 6.3 Identification / 6.4 Tests / 6.5 Assay*
7. Vectors

Adopted 153rd Ph. Eur COM → 9th Edition July 2016 → Implementation 1 January 2017

Host Cell Proteins

- ✓ **New Chapter 2.6.34**: Host-Cell Protein Assays
- ✓ **Host-cell proteins in individual monographs**

PRODUCTION

***Host-cell proteins**. The limit approved by the competent authority*

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

THE PLACE OF THE PH. EUR. WITHIN THE CONTEXT OF BIOSIMILARS

Biosimilars and the Ph. Eur. - *a disambiguation*

"Some biologicals have been rejected as biosimilars by licensing authorities although they met all requirements of monographs"

- A comparison of the biosimilar to a publicly available standard, e.g. a pharmacopoeial monograph, is not sufficient for the purpose of comparability (EMA/CHMP/BWP/247713/2012)
- The role of the monograph is to set the quality requirements

"Ph. Eur. reference preparations used in individual monographs are inappropriate [for the biosimilarity exercise] since they do not reflect the quality of the approved innovator product"

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

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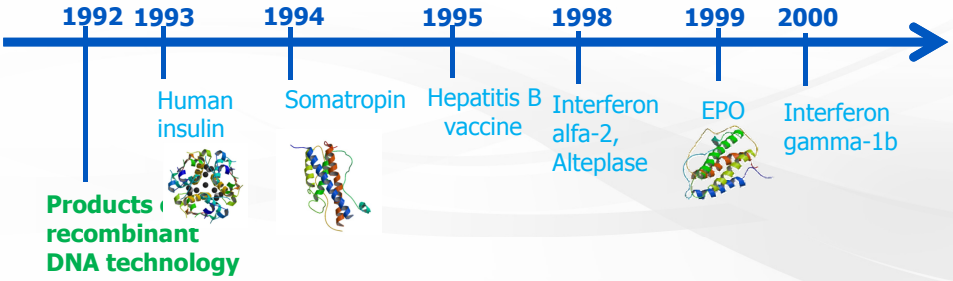
rDNA products in the Ph. Eur. (1992-2000)



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rDNA products in the Ph. Eur. (2003-2010)

EMA Biosimilars Guidelines

2003 2004 2005 2006 2007 2008 2009 2010

Human coagulation factor VIII
Insulin lispro
Insulin aspart

Molgramostim

Somatropin biosimilar

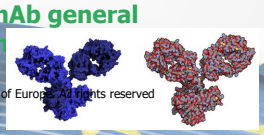
EPO biosimilar

Filgrastim biosimilar

Filgrastim

Interferon beta-1a

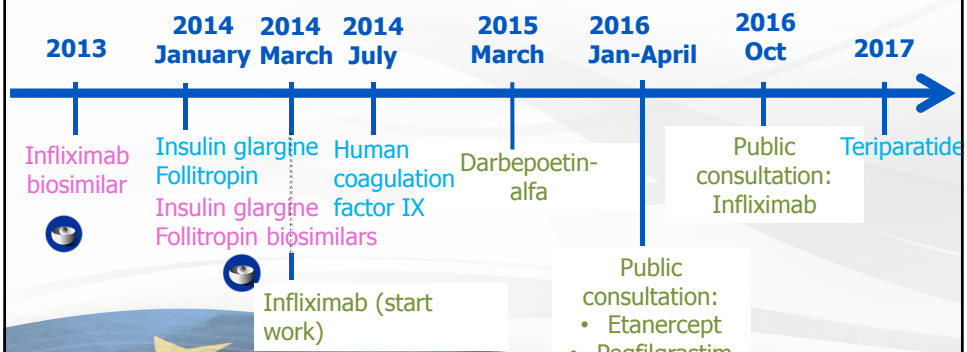
mAb general



MONOGRAPHS FOR NEW GENERATION BIOTHERAPEUTICS

Future challenges rDNA products in the Ph. Eur. (2013-2017)

From single to multisource



From single source to multisource: Flexibility is needed!

PRODUCTION: Glycan analysis (2.2.59)

Example: Human coagulation factor VIIa (rDNA) (2534

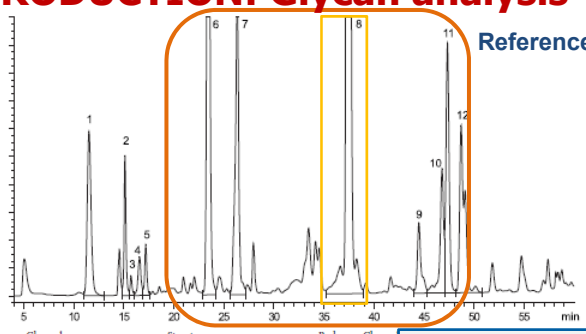
✓ **General (mandatory):**

- desalting
- selective release of glycans
- labelling of glycans
- liquid chromatography (2.2.29) with fluorometric detection - ion exchange chromatography

✓ **Detailed SOP-like instructions (given as an example): non-mandatory**

Example: Human coagulation factor VIIa (rDNA) (2534)

PRODUCTION: Glycan analysis



Reference chromatogram

Peak	Charged	Structure	Peak	Charged
1.	No	Core fucosylated biantennary – non sialylated (2 *N*-acetylgalactosamine terminals)	7.	Yes
2.	No	Core fucosylated biantennary – non sialylated (*N*-acetylgalactosamine and galactose terminals)	8.	Yes
3.	No	Structure not determined	9.	Yes
4.	No	Core fucosylated biantennary – non sialylated (galactose and *N*-acetylglucosamine terminals)	10.	Yes
5.	No	Core fucosylated biantennary – non sialylated (2 galactose terminals)	11.	Yes
6.	Yes	Core fucosylated biantennary – monosialylated (and 1 *N*-acetylgalactosamine terminal)	12.	Yes

Figure 2534.-2. – *Chromatogram for the test for glycan analysis of human coagula*

System suitability (reference):
- peaks 1-12
- peak width at half-height

Limit: *percentage of charged glycans as authorised by the competent authority*

THE 3R'S

Animal Welfare

- **Use of animals**. In accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (European Treaty Series No. 123) elaborated under the auspices of the Council of Europe, the Ph. Eur. Commission is committed to the reduction of animal usage wherever possible in pharmacopoeial testing
- Reference to the European Convention in General monographs (e.g. Vaccines for human use, Vaccines for veterinary use and individual monographs

Animal Welfare

General Notices

Demonstration of compliance with the Pharmacopoeia (Supplement 8.2)

(3) Reduction of animal testing: the European Pharmacopoeia is dedicated to phasing out the use of animals for test purposes, in accordance with the 3Rs (Replacement, Reduction, Refinement) set out in the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes. In demonstrating compliance with the Pharmacopoeia as indicated above (1), manufacturers may consider establishing additional systems to monitor consistency of production. With the agreement of the competent authority, the choice of tests performed to assess compliance with the Pharmacopoeia when animal tests are prescribed is established in such a way that animal usage is minimised as much as possible.

Animal Welfare

- Achievements are advertised on the EDQM website: Alternatives to animal testing
  http://www.edqm.eu/en/Alternatives-to-animal-testing-1483.html
- Impact evaluation of EU Directive 2010/63/EU on the texts of the European Pharmacopoeia