Euroopan farmakopean biologiset ja mikrobiologiset tekstit

Biologiset monografiat ja fleksibiliteetti

J Vesterinen,
FIMEA

8.11.2023

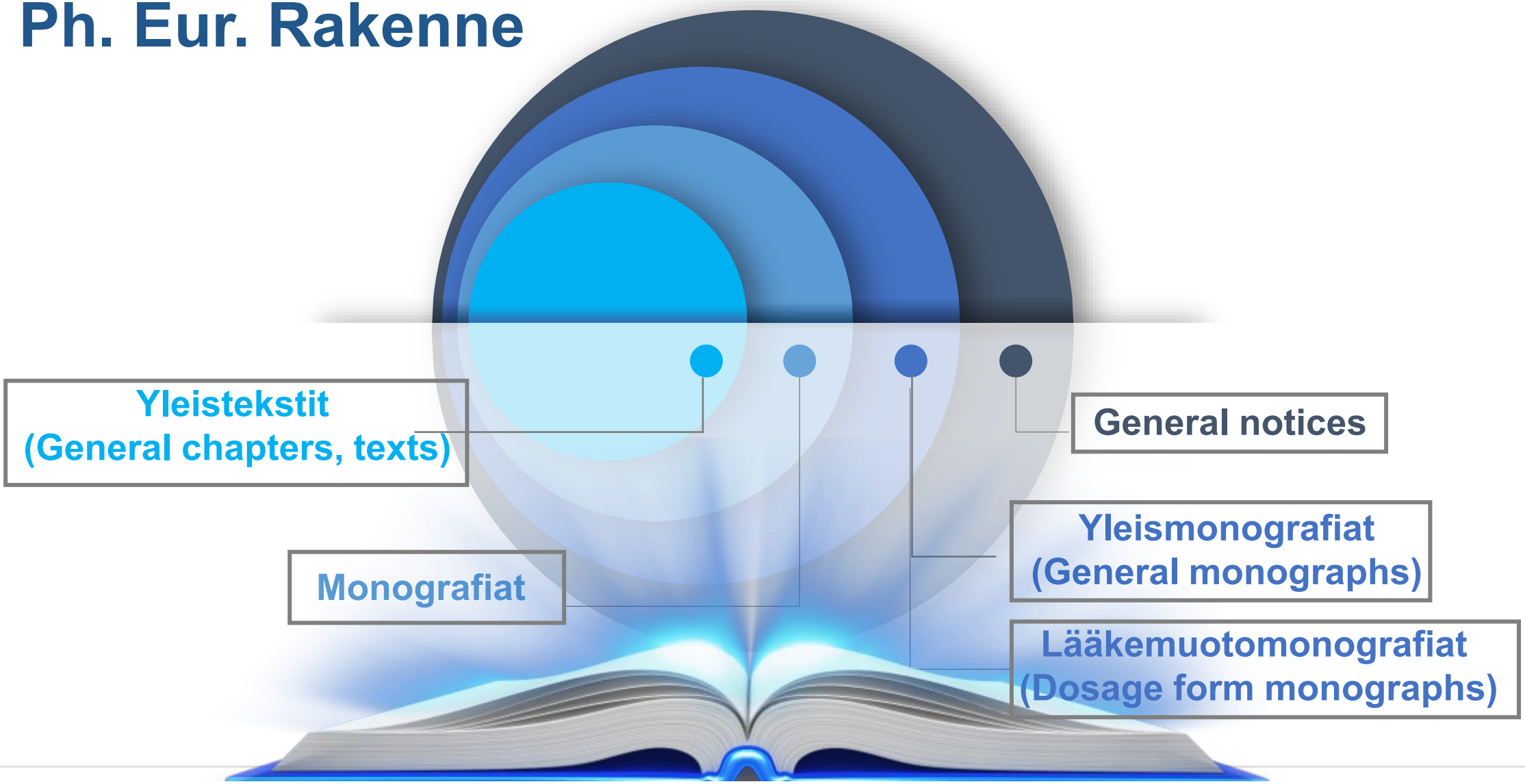
Esityksen runko

- Johdanto
- Tekstien soveltaminen
- Biologiset lääkevalmisteet
- Monografioiden rakenne
- Fleksibiliteetti ylätasolla ja monografioissa
    - *Vaihtoehtojen antaminen*
    - *Production-osio*
    - *Rajojen joustava ilmaisu*
    - *Kahden standardin käyttö*
- Knowledge database
- Yhteenveto

Euroopan Farmakopoeia, Ph. Eur.

- Euroopan Farmakopoeia kuuluu Euroopan Neuvoston (Council of Europe) vastuualueeseen. Valmistelusta ja päätäntävallasta vastaa Ph. Eur. Komissio
- Euroopan Neuvoston alainen EDQM (European Directorate for Quality of Medicines and Healthcare) organisoi ja tukee tekstien valmistelua kansallisista jäsenistä koostuvissa asiantuntijaryhmissä
- Ph. Eur. 11th Edition sisältää lähes 3000 monografiaa ja yleistekstiä
- Ph. Eur. on sitova 39 Euroopan Neuvoston jäsenmaassa sekä EU:ssa
- Biologisen puolen asiantuntijaryhmiä on runsaasti: rokotteille, verivalmisteille, ATMP valmisteille, mikrobiologisille menetelmille, menetelmille, *G6, P4Bio, MAB*

Ph. Eur. Rakenne



Slide: Courtesy of Mihaela Buda, EDQM

General notices

- Sovelletaan kaikkiin Ph Eur teksteihin
- Antavat yleisohjeita
- Tukevat monografioita

1.1.2 Compliance with the Ph. Eur.

1.1.2.1 Scope

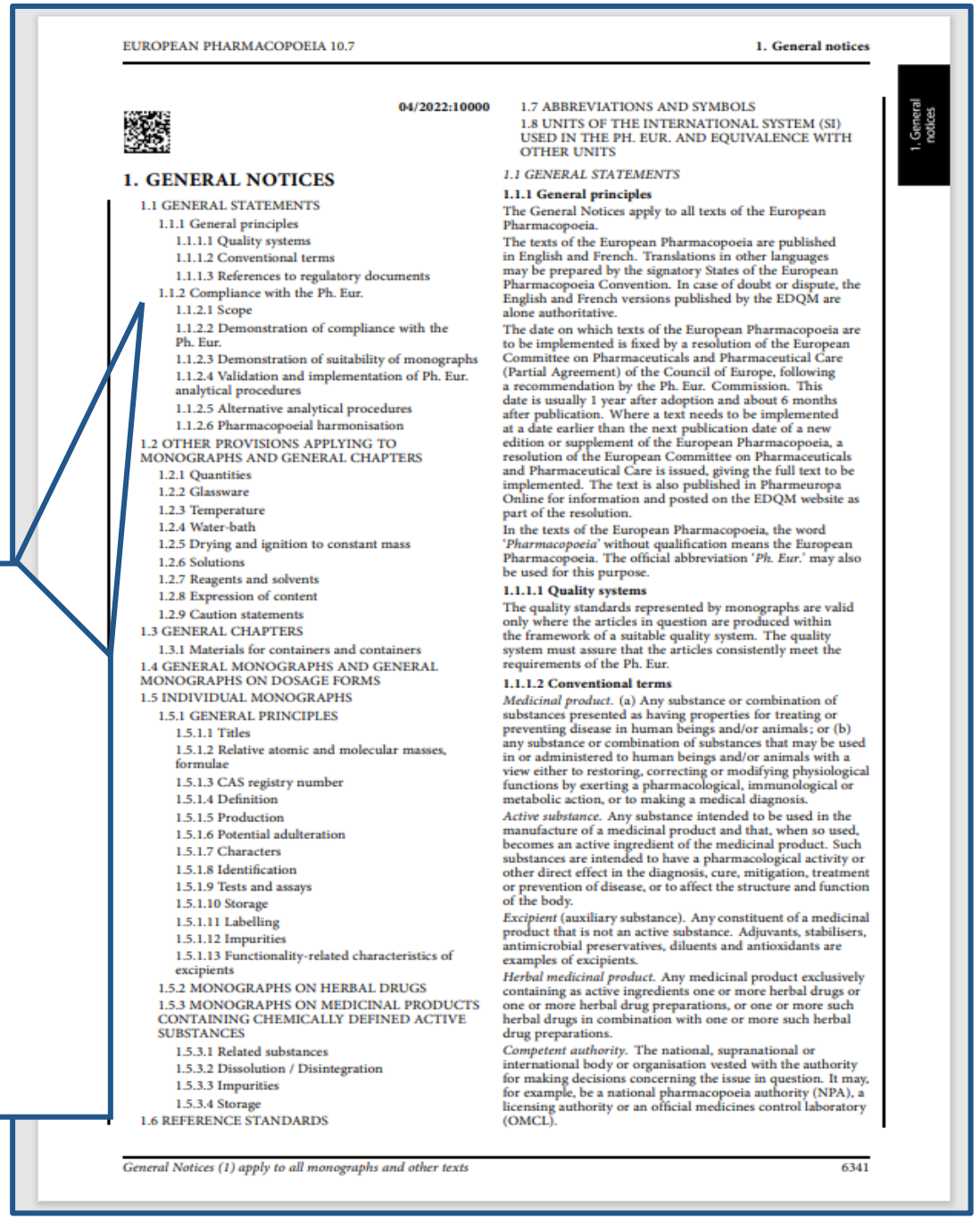
1.1.2.2 Demonstration of compliance with the Ph. Eur.

1.1.2.3 Demonstration of suitability of monographs

1.1.2.4 Validation and implementation of Ph. Eur. analytical procedures

1.1.2.5 Alternative analytical procedures

1.1.2.6 Pharmacopoeial harmonisation



EUROPEAN PHARMACOPOEIA 10.7 — 1. General notices

04/2022:10000

1. GENERAL NOTICES

1.1 GENERAL STATEMENTS
1.1.1 General principles
1.1.1.1 Quality systems
1.1.1.2 Conventional terms
1.1.1.3 References to regulatory documents
1.1.2 Compliance with the Ph. Eur.
1.1.2.1 Scope
1.1.2.2 Demonstration of compliance with the Ph. Eur.
1.1.2.3 Demonstration of suitability of monographs
1.1.2.4 Validation and implementation of Ph. Eur. analytical procedures
1.1.2.5 Alternative analytical procedures
1.1.2.6 Pharmacopoeial harmonisation
1.2 OTHER PROVISIONS APPLYING TO MONOGRAPHS AND GENERAL CHAPTERS
1.2.1 Quantities
1.2.2 Glassware
1.2.3 Temperature
1.2.4 Water-bath
1.2.5 Drying and ignition to constant mass
1.2.6 Solutions
1.2.7 Reagents and solvents
1.2.8 Expression of content
1.2.9 Caution statements
1.3 GENERAL CHAPTERS
1.3.1 Materials for containers and containers
1.4 GENERAL MONOGRAPHS AND GENERAL MONOGRAPHS ON DOSAGE FORMS
1.5 INDIVIDUAL MONOGRAPHS
1.5.1 GENERAL PRINCIPLES
1.5.1.1 Titles
1.5.1.2 Relative atomic and molecular masses, formulae
1.5.1.3 CAS registry number
1.5.1.4 Definition
1.5.1.5 Production
1.5.1.6 Potential adulteration
1.5.1.7 Characters
1.5.1.8 Identification
1.5.1.9 Tests and assays
1.5.1.10 Storage
1.5.1.11 Labelling
1.5.1.12 Impurities
1.5.1.13 Functionality-related characteristics of excipients
1.5.2 MONOGRAPHS ON HERBAL DRUGS
1.5.3 MONOGRAPHS ON MEDICINAL PRODUCTS CONTAINING CHEMICALLY DEFINED ACTIVE SUBSTANCES
1.5.3.1 Related substances
1.5.3.2 Dissolution / Disintegration
1.5.3.3 Impurities
1.5.3.4 Storage
1.6 REFERENCE STANDARDS
1.7 ABBREVIATIONS AND SYMBOLS
1.8 UNITS OF THE INTERNATIONAL SYSTEM (SI) USED IN THE PH. EUR. AND EQUIVALENCE WITH OTHER UNITS

1.1 GENERAL STATEMENTS

1.1.1 General principles

The General Notices apply to all texts of the European Pharmacopoeia.

The texts of the European Pharmacopoeia are published in English and French. Translations in other languages may be prepared by the signatory States of the European Pharmacopoeia Convention. In case of doubt or dispute, the English and French versions published by the EDQM are alone authoritative.

The date on which texts of the European Pharmacopoeia are to be implemented is fixed by a resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care (Partial Agreement) of the Council of Europe, following a recommendation by the Ph. Eur. Commission. This date is usually 1 year after adoption and about 6 months after publication. Where a text needs to be implemented at a date earlier than the next publication date of a new edition or supplement of the European Pharmacopoeia, a resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care is issued, giving the full text to be implemented. The text is also published in Pharmeuropa Online for information and posted on the EDQM website as part of the resolution.

In the texts of the European Pharmacopoeia, the word '*Pharmacopoeia*' without qualification means the European Pharmacopoeia. The official abbreviation '*Ph. Eur.*' may also be used for this purpose.

1.1.1.1 Quality systems

The quality standards represented by monographs are valid only where the articles in question are produced within the framework of a suitable quality system. The quality system must assure that the articles consistently meet the requirements of the Ph. Eur.

1.1.1.2 Conventional terms

Medicinal product. (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings and/or animals; or (b) any substance or combination of substances that may be used in or administered to human beings and/or animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Active substance. Any substance intended to be used in the manufacture of a medicinal product and that, when so used, becomes an active ingredient of the medicinal product. Such substances are intended to have a pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

Excipient (auxiliary substance). Any constituent of a medicinal product that is not an active substance. Adjuvants, stabilisers, antimicrobial preservatives, diluents and antioxidants are examples of excipients.

Herbal medicinal product. Any medicinal product exclusively containing as active ingredients one or more herbal drugs or one or more herbal drug preparations, or one or more such herbal drugs in combination with one or more such herbal drug preparations.

Competent authority. The national, supranational or international body or organisation vested with the authority for making decisions concerning the issue in question. It may, for example, be a national pharmacopoeia authority (NPA), a licensing authority or an official medicines control laboratory (OMCL).

General Notices (1) apply to all monographs and other texts — 6341

1. General notices

Miten tekstejä sovelletaan?

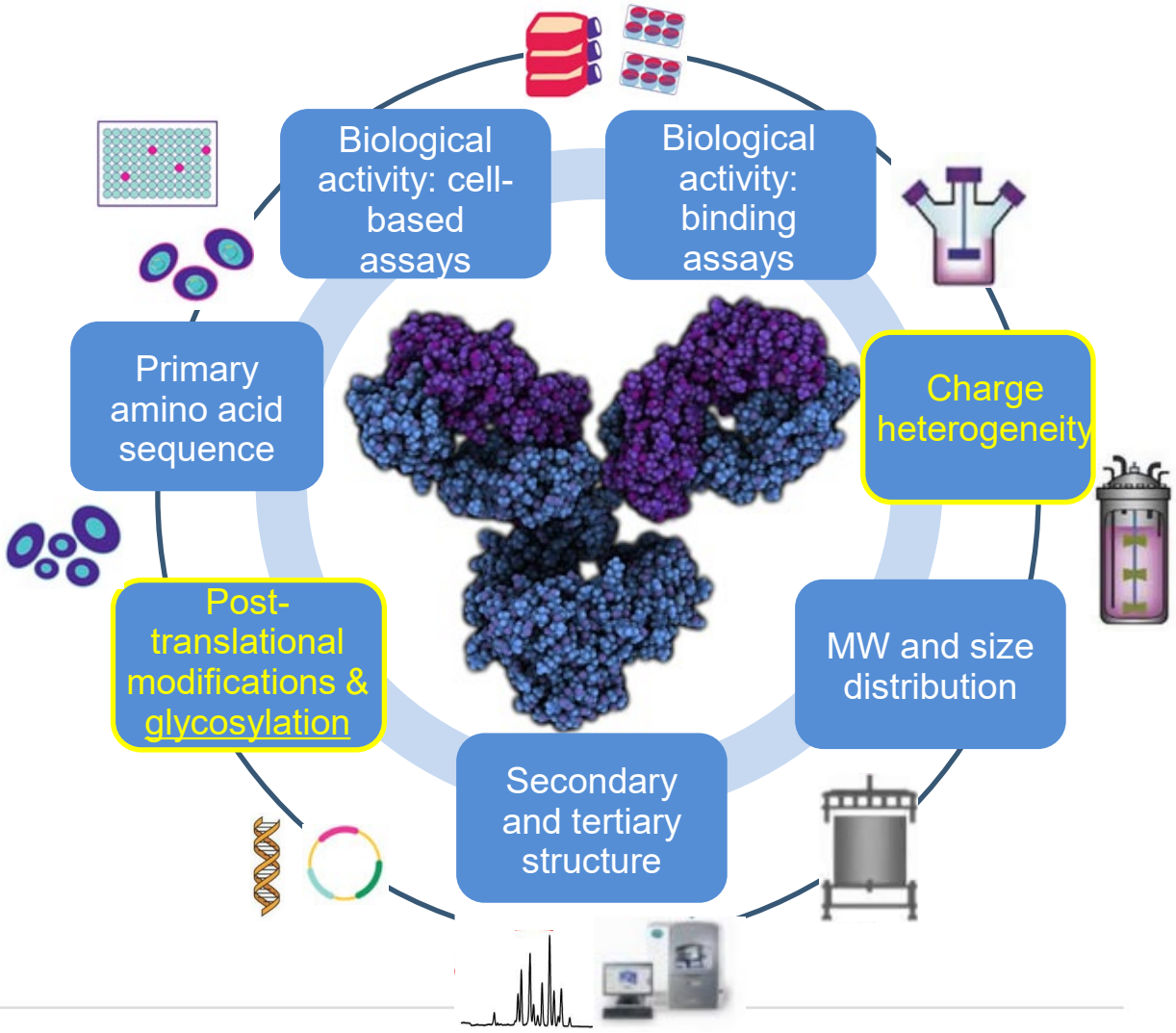
- General notices pätee kaikkiin teksteihin
- Monografiat ovat lainvoimaisia ja pakottavia
- Yleistekstit eivät ole pakottavia, jollei monografiassa viitata ko. yleistekstiin
- ***Biosimilaareille*** ei ole erillisiä tekstejä, vaan ainekohtaisten monografioiden vaatimukset koskevat kaikkia yhtälailla

  → Monografiat eivät sovellu komparabiliteetin osoittamiseen, komparabiliteetin osoittaminen on paljon laajempi kokonaisuus
- Farmakopeateksteissä esitetään myös yleisiä periaatteita, joita voi soveltaa usein laajemminkin (eg. Raaka-aine teksti, **5.2.12. *Raw* materials of biological origin for the production of cell-based and gene therapy medicinal products**)

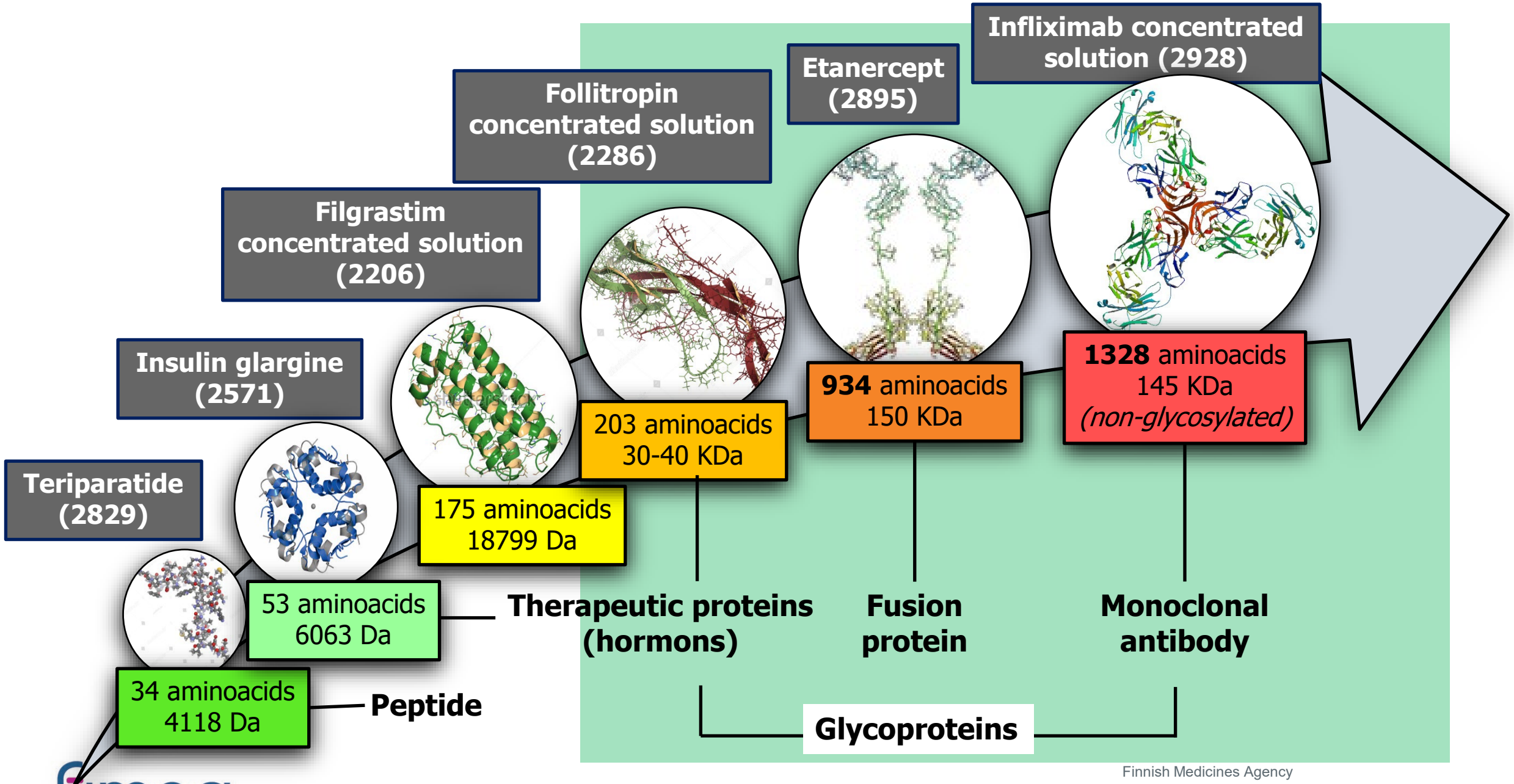
Biologiset lääkevalmisteet ja farmakopea

- *Biologiset lääkeaineet ovat rakenteeltaan monimutkaisia*
  - ✓ post-translationaaliset modifikaatiot
  - ✓ glykosylaatio
  - ✓ varausheterogenia

- *Farmakopeaan on luotu joustavuutta,* jotta monografiat kattavat eri tavoin tuotetut API:t (DS)
  - erythropoietin
  - infliksimabi



Picture: Courtesy of Mihaela Buda, EDQM



Slide: Courtesy of Mihaela Buda, EDQM

Flexibiliteetti General notices -osiossa - milloin valmiste on monografian mukainen (complies)?

Valmisteen tulee täyttää monografiassa kuvattujen testien vaatimukset.

- *Kaikkia testejä ei välttämättä tarvitse sisällyttää eräkohtaiseen testaukseen*
- Vaatimusten mukaisuuden voi osoittaa myös valmisteen ominaisuuksien avulla tai kontrollistrategian avulla saatavan tiedon perusteella
- *Vaihtoehtoisia menetelmiä* voi käyttää, mikäli ne kiistatta osoittavat valmisteen täyttävän monografian vaatimukset. Kiistatapauksissa vain monografiamenetelmät ovat päteviä.
- *"Enhanced approach"* voidaan toteuttaa mm. PAT teknologian (process analytical technology) tai real-time release testauksen avulla

Monografian rakenne
Infliximab concentrated solution, 2928

- Definition
- Production
- Characters
- Identification
- Tests
- Assay
- …

DEFINITION

Solution of a monoclonal antibody consisting of a bisdisulfide dimer of 1328 amino acid residues with a molecular weight of approximately 145 kDa, which binds with high affinity to both soluble and transmembrane forms of TNF-α.

Infliximab is a chimeric human-murine IgG1 kappa …

Content (milligrams of protein per millilitre): as approved by the competent authority.

Potency: 8×10^3 to 12×10^3 IU per milligram of protein.

PRODUCTION …

Host-cell-derived proteins (*2.6.34*).

Host-cell- and vector-derived DNA.

Residual Protein A.

Glycan analysis.

Charged variants

fimea

IDENTIFICATION

A. It complies with the limits of the assay (potency).

B. Peptide mapping (*2.2.55*). …

TESTS

pH (*2.2.3*). As approved by the competent authority.

Related proteins. Capillary electrophoresis (*2.2.47*) under both reducing and non-reducing conditions. …

Impurities with molecular masses differing from that of infliximab. Size-exclusion chromatography (*2.2.30*): use the normalisation procedure. …

ASSAY

Protein (*2.5.33, Method 1*).

Test solution. Dilute the preparation to be examined with a suitable buffer to obtain a concentration of about 1 mg/mL. Prepare and analyse each preparation in duplicate.

Record the UV spectrum between 280 nm and 350 nm. Measure the value at the absorbance maximum of 280 nm, after correction for any light scattering measured up to 350 nm. Calculate the protein content, taking the specific absorbance to be 14.5.

Potency. The potency of infliximab is determined by comparison of dilutions of the test preparation with dilutions of *infliximab BRP* using a suitable cell-based assay based on the inhibitory action of infliximab on the biological activity of TNF-α with a ~~suitable readout for assessing~~ this inhibitory effect.

The following procedure is given as an example.

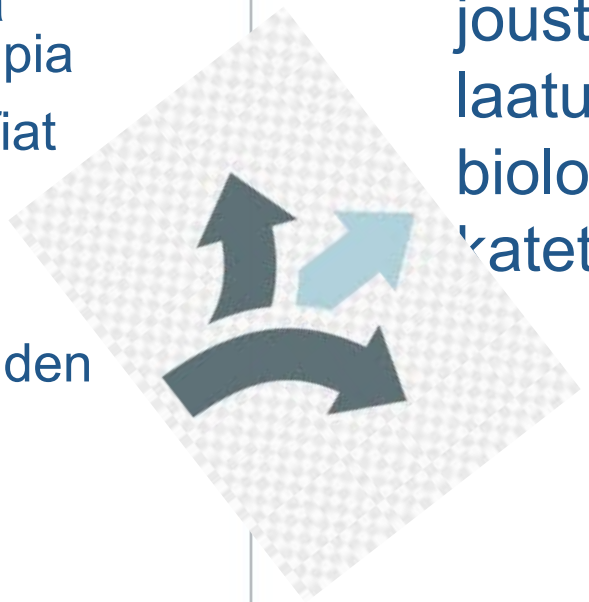
WEHI-164 cytotoxicity assay (*2.7.26, Procedure B*). Carry

…

Flexibiliteetti monografioissa - mitä se tarkoittaa?

Ennakkoluulot

- Biologisella puolella farmakopea käytänteet ovat firmoille vieraampia
- On turhia pelkoja, että monografiat haittaavat myyntiluvan saaneita valmisteita
- Monografiat perustuvat aina myyntiluvan saaneiden valmisteiden spesifikaatioihin



On tärkeää osallistua työhön ja kommentoida Pharmeuropa julkaisuja

- Monografioihin on rakennettu joustoa eri tavoin, jotta tärkeät laatuominaisuudet saadaan biologisissa monografioissa katettua

Production-osio

Rajojen joustava ilmaisu

Kahden standardin käyttö

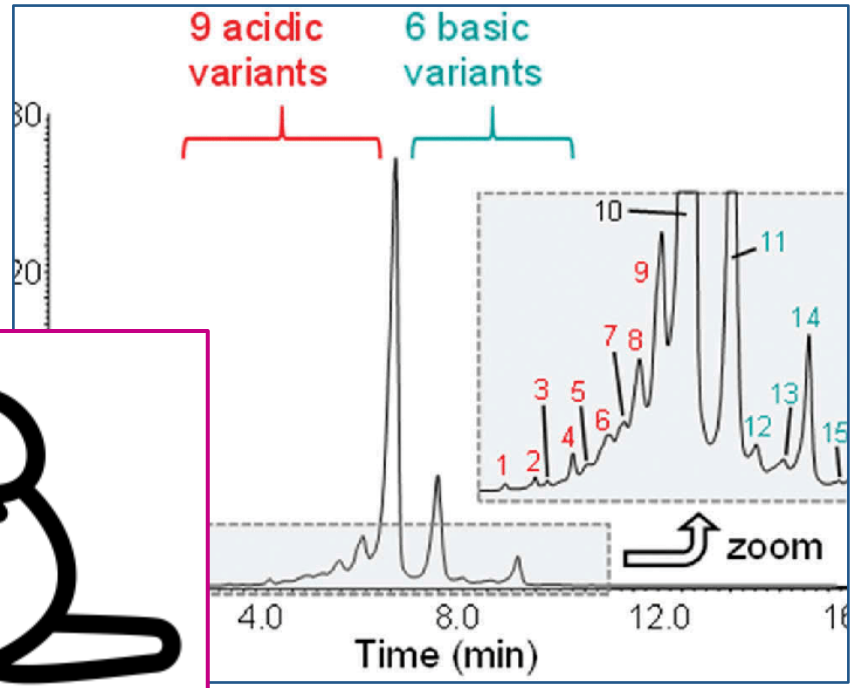
Vaihtoehtojen antaminen

Fleksibiliteetti monografioissa

Tyypillisiä analyyseja
HCP, HCD
glycan analysis
charged variants determination

'Production' kappale

- Ne testit, jotka mittaavat tuotantoprosessille tyypillistä heterogeniaa ja konsistenssia, luetellaan *'Production'* kappaleessa
- Näitä testejä ei voida sisällyttää farmakopean *'Tests'* osaan, eikä ne yleensä ole mukana spesifikaatioissa
- Testit ovat kuitenkin oleellisia
- Testeille tarvitaan numeeriset rajat, joita ei monografiassa kuvata, koska rajat riippuvat valmistusprosessista, eikä kaikille valmisteille sopivaa yhteistä numeerista raja ole
- Testeissä käytetään in-house standardeja, joten niitä ei voi itsenäisesti tehdä



Production -osio

Infliximab concentrated solution, 2928

PRODUCTION

Infliximab is produced in a suitable mammalian cell expression system by a method based on recombinant DNA (rDNA) technology. In the course of product development, it must be demonstrated that the manufacturing process consistently produces a product with the expected *N*-glycan occupancy and Fc-effector functions (antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC)) using suitably qualified assay(s).

Prior to release, the following tests are carried out on each batch of infliximab concentrated solution, unless an exemption has been granted by the competent authority.

Host-cell-derived proteins (*2.6.34*). The limit is approved by the competent authority.

Host-cell- and vector-derived DNA. The limit is approved by the competent authority.

Residual Protein A. Use a suitable immunochemical method (*2.7.1*) based on an ELISA. To determine residual Protein A,

Erythropoietin concentrated solution, 1316

PRODUCTION

Erythropoietin is produced in rodent cells *in vitro* by a method based on recombinant DNA (rDNA) technology. During the course of product development, it must be demonstrated that the manufacturing process consistently produces a product with the expected glycosylation pattern using suitably qualified assay(s).

Prior to batch release, the following tests are carried out on each batch of the erythropoietin concentrated solution, unless exemption has been granted by the competent authority.

Host cell-derived proteins: the limit is approved by the competent authority.

Host cell- and vector-derived DNA: the limit is approved by the competent authority.

Glycan analysis. Use a suitable method developed according to general chapter *2.2.59. Glycan analysis of glycoproteins*, section 2-3:

- after desalting, release the *N*–glycans using 1 of the agents described in Table 2.2.59.-1, for example peptide *N*-glycosidase F (PNGase F);
- if needed, label the released *N*–glycans with 1 of the fluorescent labelling agents described in Table 2.2.59.-2;
- analyse the labelled or unlabelled *N*-glycans using a suitable technique.

The following procedure is given as an example.

fimea

”The following procedure is given as an example”

- Esimerkki antaa tarkan ohjeen, jotta riippumaton taho voi suorittaa analyysin
- Esimerkkiproseduurit perustuvat valmistajien menetelmiin ja ovat valmistajien validoimia
- Kansalliset valvontalaboratoriot käyttävät usein näitä proseduureja laaduntarkastuksessa
- Käytettäessä systeemin toimivuus varmistetaan SST kriteerien avulla, implementoimalla menetelmä Ph. Eur. sääntöjen mukaan
- Tarvittaessa menetelmän soveltuus voidaan/tulee osoittaa lisäverifioimalla

Kahden standardin käyttö (dual standards)

Ph. Eur. Referenssistandardi

- Referenssistandardi luodaan aina yhdessä monografian kanssa
- CRS tai BRP
- Käytetään monografian osoittamalla tavalla toteamaan systeemin toimivuus

In-house referenssistandardi

- Valmistajan oma referenssistandardi (primary / working)
- Käytetään osoittamaan tuotannon konsistenssia ja erän kelpoisuus
- Ulkopuolisilla ei käytössä

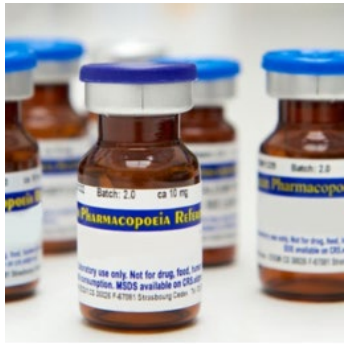
→ Eri standardeja käytetään eri tarkoituksiin

Kahden standardin käyttö, glykaanianalyysi

Infliximab concentrated solution, 2928

Reference solution (a). Dissolve the contents of a vial of *infliximab CRS* in *water R*. Desalt a volume of this preparation and carry out the glycan release at the same time and in the same manner as for the test solution.

Reference solution (b). Use a suitable infliximab in-house reference preparation shown to be representative of batches tested clinically and batches used to demonstrate consistency of production. Desalt a volume of this preparation and carry out the glycan release at the same time and in the same manner as for the test solution.



System suitability:

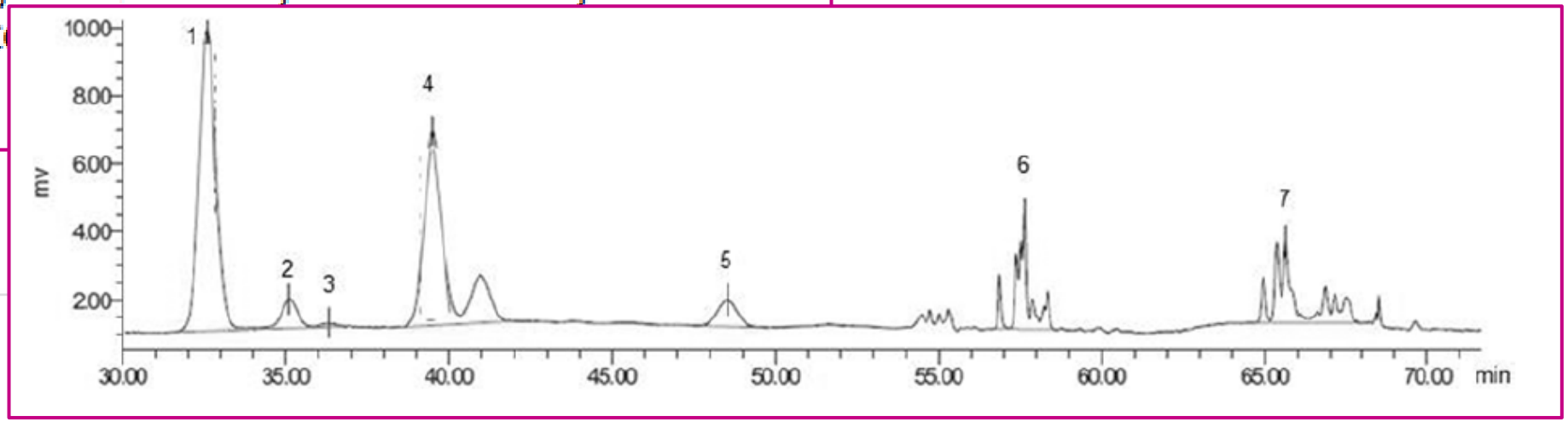
- the chromatogram obtained with reference solution (a) is qualitatively similar to the chromatogram supplied with *infliximab CRS* and peaks 1 to 7 are clearly visible;

Results:

- the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with reference solution (b);
- the retention times of the peaks in the chromatogram obtained with the test solution correspond to those in the chromatogram obtained with reference solution (b);
- no additional peaks are observed in the chromatogram obtained with the test solution in comparison with the chromatogram obtained with reference solution (b).

Calculate the relative peak areas of the individual peaks corresponding to fucosylated, afucosylated and sialylated glycans with reference t
glycan peaks.

In house standardi



fimea

Hyväksymisrajat

- Yleensä *Production* – osiossa oleville testeille ei anneta numeerisia arvoja
- Testejä ei voi riippumattomasti toistaa, koska määrityksissä tarvittava tieto ja standardit ovat liikesalaisuuden alaisia

  → *”as authorised by the competent authority”*
- *Tests*-osiossa annettaville testeille on hyvä antaa numeeriset rajat, jotta monografialla on merkitystä
- Numeeriset rajat pohjaavat aina jo hyväksyttyjen valmisteiden spesifikaatioihin
  → valmistajien on tärkeää osallistua kommentointiin
- Joskus sopivia rajoja on vaikea määrittää, koska eri dossiereissa laskuperuste eroaa

  Esim. glykaanimäärityksissä ja charge variant määrityksissä eri piikkiryhmät lasketaan yhteen

Calculate the percentage contents of fucosylated, afucosylated and sialylated glycans, using the following expressions:

Limits:
Rajojen joustavuus

$$\frac{A}{A+B+C} \times 100$$

$$\frac{B}{A+B+C} \times 100$$

$$\frac{C}{A+B+C} \times 100$$

A = sum of the areas of the peaks due to fucosylated glycans;

B = sum of the areas of the peaks due to afucosylated glycans;

C = sum of the areas of the peaks due to sialylated glycans.

NOTE: sialylated glycans elute as peak clusters and are integrated as such.

Limits:

- *percentage of fucosylated glycans*: as authorised by the competent authority;
- *percentage of afucosylated glycans*: as authorised by the competent authority;
- *percentage of sialylated glycans*: as authorised by the competent authority.

Knowledge database

Hyödyllinen, sisältää lisätietoja

- ✓ Tekstin tilanteen (onko revisiossa ym.)
- ✓ Kromatogrammeja
- ✓ Reagenssien ja kolonnien valmistajien tietoja
- ✓ Tekstiin liittyvien referenssistandardien tiedot

Detailed view of Infliximab concentrated solution.

Status	In Use
Monograph Number	02928
English Name	Infliximab concentrated solution
French Name	Infliximab (solution concentrée d')
Latin Name	Infliximabum solutio concentrata
Pinyin Name	
Chinese Name	
Pharmeuropa	33.2
Published in English Supplement	11.3
Published in French Supplement	11.1
On-going	Revision
State of work	0
Pharmeuropa	
Description	Production (charged variants test A): replacement of isoelectric focusing procedure with capillary isoelectric procedure
Chromatogram	Available
Additional information	Not available
History	View history
Interchangeable (ICH_Q4B)	NO
Pharmacopoeial harmonisation	NO

Reference standards

Available since	Cat. No.	Name	Batch No.	Unit Quantity	Price	SDS Product Code
	Y0002047	Infliximab CRS	1	100 mg	79 EUR	
	Y0002110	Infliximab BRP	1	25 mg	150 EUR	

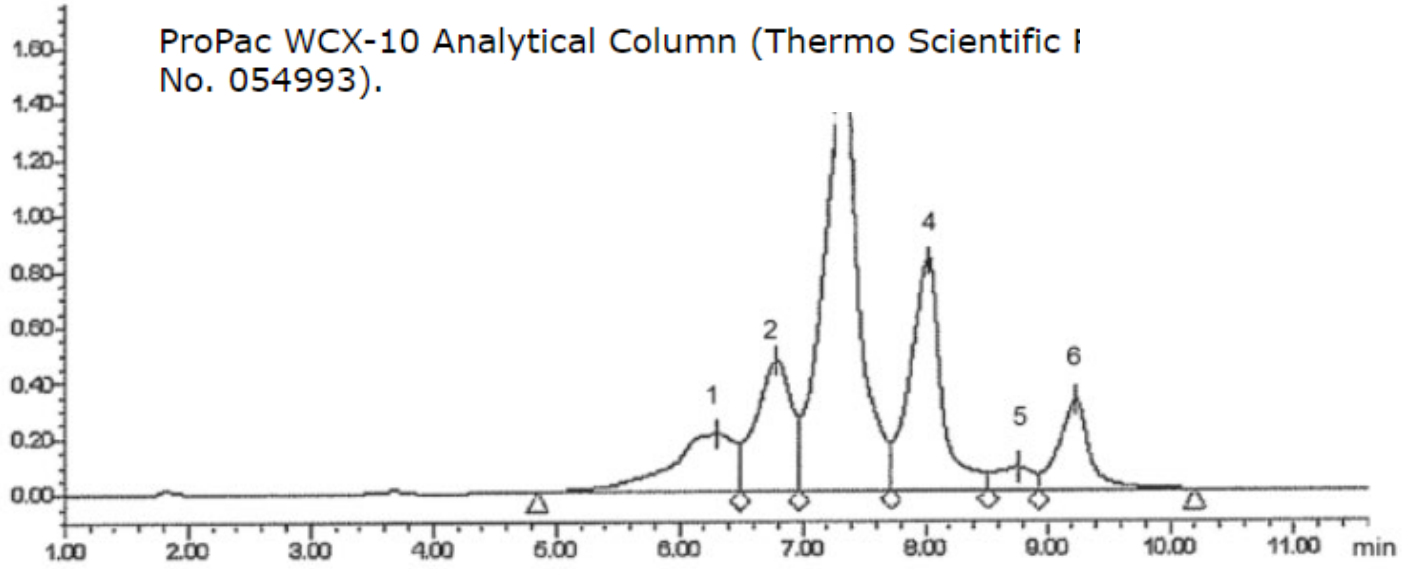
Practical Information

Test(s)	Brand Name/Information
Glycan analysis	Dionex CarboPac PA200 guard column (Thermo Scientific Cat. No. 062895).
Glycan analysis	Dionex CarboPac PA200 column (Thermo Scientific Cat. No. 062896).
Glycan analysis	Dionex ED40.
Charged variants. B. Liquid chromatography	ProPac WCX-10G guard column (Thermo Scientific Part No. 054994).
Charged variants. B. Liquid chromatography	ProPac WCX-10 Analytical Column (Thermo Scientific Part No. 054993).
Peptide mapping	Vydac Protein C18 (Cat. No. 218TP54).
Impurities with molecular masses differing from that of infliximab	TSKgel G3000SWXL (Tosoh, Cat. No. 08541).
Potency	Cell Counting Kit-8 by Dojindo (Cat. No. CK04).
Glycan analysis	Peptide N-glycosidase F (PNGaseF) from New England Biolabs (Cat. No. P0705S).

CEP

Infliximab concentrated solution, knowledge database

On-going	Revision
State of work	0
Pharmeuropa	
Description	Production (charged variants test A): replacement of isoelectric focusing procedure with capillary isoelectric procedure



Peak	Structure	Peak	Structure
1.	No C-terminal lysine, Charged glycans (G1F1SA and G2F1SA), Deamidation HC Asn57	4.	1 C-terminal lysine
2.	No C-terminal lysine, Charged glycans (G1F1SA and G2F1SA)	5.	2 C-terminal lysines, Charged glycans (G1F1SA and G2F1SA)
3.	No C-terminal lysine	6.	2 C-terminal lysines

fimea

Reference standards	Available since	Cat. No.	Name	Batch No.	Unit Quantity	Price	SDS Product Code
		Y0002047	Infliximab CRS	1	100 mg	79 EUR	
		Y0002110	Infliximab BRP	1	25 mg	150 EUR	

BRP standardien aktiivisuus on IU/mL

↓

spesifistä aktiviteettia ei anneta (IU/mg)

Information Leaflet Ph. Eur. Reference Standard

Infliximab BRP batch 1

Identification

Catalogue code: Y0002110

Scientific Information

2.1 Intended use

Infliximab BRP batch 1 is intended for use in the potency assay according to the Ph. Eur. monograph on Infliximab concentrated solution (2928). The BRP consists of freeze-dried Infliximab. The BRP is presented in an ampoule with an assigned potency of 500 IU/ampoule.

2.2 Instructions for use

Allow the ampoule and content to equilibrate at ambient temperature before opening to avoid uptake of moisture. Reconstitute with 1.0 mL of sterilised water for injections. This solution will contain Infliximab at a concentration of 500 IU/mL. Use as soon as possible after reconstitution or aliquot and store at -40°C or below. Avoid repeated thawing/freezing.

2.3 Uncertainty of the assigned value, when applicable

The uncertainty of the assigned value is not stated since it is considered to be negligible in relation to the defined limits of the method-specific assays for which the reference standard is used. Please also refer to Ph. Eur. chapter 5.12.

fimea

Tietoja valmistajista:

Test(s)	Brand Name/Information
Glycan analysis	Dionex CarboPac PA200 guard colu Cat. No. 062895).
Glycan analysis	Dionex CarboPac PA200 column (Thermo Scientific Cat. No. 062896).
Glycan analysis	Dionex ED40.
Charged variants. B. Liquid chromatography	ProPac WCX-10G guard column (Thermo Scientific Part No. 054994).
Charged variants. B. Liquid chromatography	ProPac WCX-10 Analytical Column (Thermo Scientific Part No. 054993).
Peptide mapping	Vydac Protein C18 (Cat. No. 218TP54).
Impurities with molecular masses differing from that of infliximab	TSKgel G3000SWXL (Tosoh, Cat. No. 08541).
Potency	Cell Counting Kit-8 by Dojindo (Cat. No. CK04).
Glycan analysis	Peptide N-glycosidase F (PNGaseF) from New England Biolabs (Cat. No. P0705S).

The following chromatogram is shown for information but will not be published in the European Pharmacopoeia.

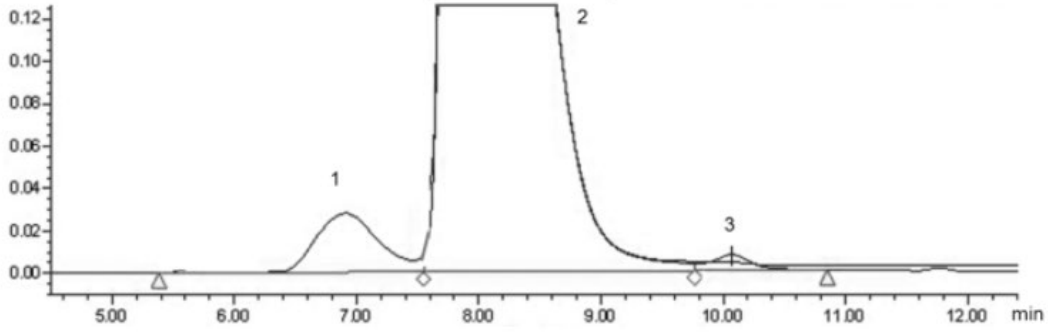


Figure 2928.-6. – *Chromatogram for the test for impurities with molecular masses differing from that of infliximab*

Yhteenveto

- Biologisten valmisteiden monografiat valmistellaan asiantuntijaryhmissä, ryhmä valikoituu valmisteesta riippuen
- General notices kappaleen suoman jouston lisäksi biologisiin monografioihin on luotu lisää joustoa (flexibility) monin tavoin
- Biologisten lääkeaineiden valmistajien on tärkeätä seurata farmakopean tapahtumia ja kommentoida Pharmeuropan kappaleita

➢ Biologiselle puolelle on tulossa useita menetelmiin keskittyviä yleistekstejä (horizontal metohod, performance based texts)

➢ Uudet tekstit pyritään luomaan siten, että ne huomioivat ICH guideline-muokkausten uudet tuulet (platform methods, ATP…)

Kiitokset!!

Mihaela Buda
Fimean laboratorio
MAB ryhmä