

Current Regulatory Trends and Hot Topics Around the Globe - a European Regulatory Perspective

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WCBP 2020

28-30 January, Washington, D.C.

Steffen Gross,
Head Section monoclonal - and
polyclonal Antibodies
Paul-Ehrlich-Institut
Germany

Disclaimer

The view expressed in the following is the ones of the presenter and does not necessary express the view of either the CHMP, BWP, EDQM or the Paul-Ehrlich-Institut (including other sections)

Outline



Reduced activities due to Brexit; backstage activities

Device Regulation (MDR, IVDR)

Mutual recognition agreement (MRA)

Biosimilars/EP Monographs

Statistical evaluation

Continuous manufacturing (control strategy, RTRT, SUB)

EMA prepares for Brexit



Business continuity plan aims to preserve Agency's ability to protect public and animal health

Three layers of priority.

- **Category 3** activities (can be put on hold), e.g. web portal, staff reduced for organization of meeting etc., **working parties work backstage** on their own
- **Category 2**, consists of activities, such as the proactive publication of clinical data, and various initiatives aimed at promoting availability of medicines as well as some political priorities of the EU, for example, EMA's contribution to the fight against antimicrobial resistance or the Agency's interactions with Health Technology Assessment (HTA) bodies. These activities **will be maintained for as long as possible**, workload and staffing situation permitting, in order to maintain the development of new medicines
- **Category 1** highest priority activities that are either directly related to the assessment and safety monitoring of medicines or vital to maintaining the infrastructure of the European regulatory system for medicines, including for example the coordination of actions to protect the safety of patients in all EU Member States, inspections across the EU or maintenance of the functionality and security of critical IT applications used by all Member States.

Persons representing, appointed by, or nominated by the United Kingdom ('UK participants') can no longer participate in meetings of the Union. This includes meetings of Member State representatives in all settings (Union institutions, bodies, offices and agencies, standing committees, experts groups, etc.), including meetings of the CMDh and CMDv ('principle of non-participation'). Therefore, UK participants should no longer be invited to any meeting taking place after 31 January 2020.



Device legislation MDR and IVDR



- 1 29 May 2019
- 2 EMA/CHMP/QWP/BWP/259165/2019
- 3 Committee for Medicinal Products for Human Use (CHMP)
- 4

- 1 20 July 2017
- 2 EMA/CHMP/800914/2016
- 3 Committee for Medicinal Products for Human Use (CHMP)

- 5 Guideline on the quality requirements for drug-device combinations
- 6
- 7 Draft

- 4 Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle
- 5
- 6
- 7

Draft agreed by Quality Working Party	May 2019
Draft agreed by Biologics Working Party	May 2019
Draft agreed by Committee on Advanced Therapies	May 2019
Adopted by CHMP for release for consultation	29 May 2019
Start of public consultation	03 June 2019
End of consultation (deadline for comments)	31 August 2019

Agreed by Pharmacogenomics Working Party	7 April 2017
Adopted by CHMP for release for consultation	20 July 2017
Start of public consultation	28 July 2017
End of consultation (deadline for comments)	15 November 2017

clinical trials for medicinal products could also serve as Performance studies for CDx



Traceability: importance of identifying biological medicines by tradename and batch number

As required by EU law, every medicine will have an invented name (tradename or brand name) together with the active substance name (i.e. INN).

Interchangeability, switching and substitution: EMA and Member States' responsibilities

- **Switching**, the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.
- **Substitution (automatic)**, practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber.

Prescribing practices and advice to prescribers fall under the responsibility of Member States

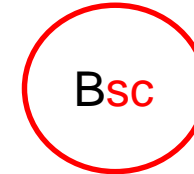
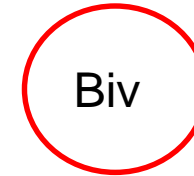
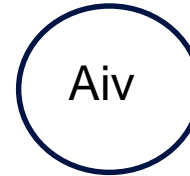




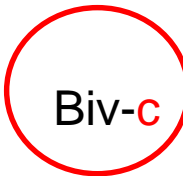
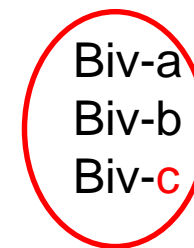
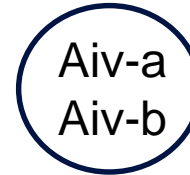
A, C
originator

B
Biosimilar

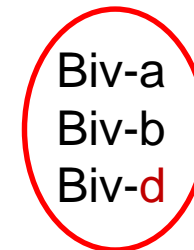
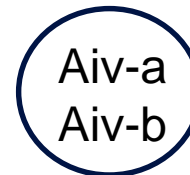
a) to introduce a subcutaneous version of originator which is not approved from the originator



b) biosimilar in an indication not approved for the originator



c) Biosimilar to originator A seeking extrapolation not approved for originator A but originator C



A, C originator
B, biosimilars
a, b, c, d, indications
iv, intravenous; sc, subcutaneous

MBU/bst

Working document, with no legally binding status, intended exclusively for the addressees and their associates, under the responsibility of the addressees (listed opposite). Level 4

English / Anglais

PA/PH/Exp. MAB/T (16) 5 ANP R1

Strasbourg, October 2017

GROUP MAB
(MONOCLONAL ANTIBODIES)

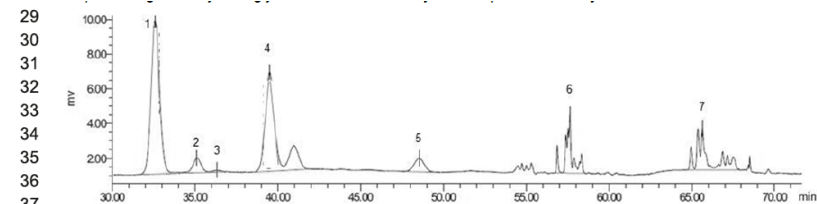
Infliximab concentrated solution

Infliximabum solutio concentrata

Monograph N°: 2928

- Product specific monographs (mAbs)
 - Block innovation
 - May inhibit product development
 - May not reflect approved dossier
 - Increase burden to industry and regulators

- International Standard?
 - Own in house standards (qualified)



Peak	Charged	Glycoform	Peak	Charged	Glycoform
1.	No	Fucosylated G0F (absence of terminal galactose)	5.	No	Fucosylated G2F (2 terminal galactoses)
2.	No	Afucosylated Man5 (addition of 2 mannoses instead of terminal N-acetylglucosamine)	6.	Yes	Sialylated SA1 (addition of 1 sialic acid)
3.	No	Afucosylated G0 (absence of fucose)	7.	Yes	Sialylated SA2 (addition of 2 sialic acids)
4.	No	Fucosylated G1F (1 terminal galactose)			

Figure 2928.-1. – Chromatogram for glycan analysis of infliximab



Questions regarding monograph compliance

1. Should the potency be expressed in international units relative to the infliximab CRS? **no**
2. Should the internal reference standard be calibrated to the infliximab CRS? **yes**
3. Should the analytical methods for glycan analysis (2.5.59), CEX (2.2.29), CE-SDS (2.2.47), SEC (2.2.30) and protein assay (2.5.33) be carried out according to the relevant monographs (indicated in brackets) **yes**
4. If yes to any of these questions are the MAHs for infliximab planning to submit variations? **most probably yes**

Other product-specific monographs (mAbs and derivatives): etanercept
Proposals for adalimumab, golimumab

Mutual recognition agreement (MRA) EU-US



Human medicines

The transition phase for human medicines covered by the agreement **ended on 11 July 2019:**

the [US Food and Drug Administration](#) (FDA) completed its assessment of all 28 EU GMP inspectorates for human medicines, confirming that they have the capability, capacity and procedures in place to carry out GMP inspections at a level equivalent to the US;

the [European Commission confirmed](#) in June 2017 that the US FDA has the capability, capacity and procedures in place to carry out GMP inspections for human medicines at a level equivalent to the EU.

As of 11 July 2019, qualified persons in the EU Member States **do not need to batch test** human medicines covered by the MRA, provided that they have verified that these controls have been carried out in the United States for products manufactured in and imported from the United States.

12 February 2019
EMA/866364/2018

11 July 2019
EMA/395913/2019
Committees and Inspections

[Q&A on impact of EU-USA Mutual Recognition Agreement on marketing authorisation applications and relevant variations](#)

[Questions & Answers on the impact of Mutual Recognition Agreement between the European Union and the United States as of 11 July 2019](#)



EUROPEAN
COMMISSION

EudraLex
The Rules Governing Medicinal Products in the European Union
Volume 4
Good Manufacturing Practice

**Guidelines on Good Manufacturing Practice specific to Advanced
Therapy Medicinal Products**

Document History	
Adoption by the European Commission	22 November 2017
Date for coming into operation	ATMP manufacturers should comply with these Guidelines no later than 22 May 2018.

Update: EMA's [CAT](#), together with the GMDP Inspectors Working Group and the [Biologics Working Party](#), have prepared the following questions-and answers-documents:

- [Questions and answers on the exemption from batch controls carried out on ATMPs imported into the European Union from a third country](#)
- [Questions and answers on the use of out-of-specification batches of authorised cell/tissue-based advanced therapy medicinal products](#)

Draft Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development - ongoing



Executive Summary

1. Introduction
2. Legal basis and relevant guidelines
3. Definitions and working assumptions
4. **Approaching the quality attributes comparison task from the inferential statistical perspective**
Understanding sources of variability in quality data and 'the unit of observation'
Random Sampling / Experimental Approach
Understanding a manufacturing process as a **data distribution**
Defining a similarity criterion based on the chosen distribution characteristics
Selecting a similarity criterion from a range of possible candidates
Defining an overall 'success criterion' to claim equivalence/similarity in presence of a large number of QAs
5. Implications for settings where the comparison on the quality level is of particular relevance in regulatory decision-making
Specific issues for the **pre/post-manufacturing** change setting
Specific issues for **Biosimilar** setting
Specific issues for **generic/hybrid** developments and dissolution comparisons
6. Quality Attributes data comparison protocol

Stangler and Schiestl <https://doi.org/10.1186/s41120-019-0033-9>

Similarity assessment of quality attributes of biological medicines: the calculation of operating characteristics to compare different statistical approaches



Real Time Release Testing



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 March 2012
EMA/CHMP/QWP/811210/2009-Rev1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Real Time Release Testing (formerly Guideline on Parametric Release)

Final



EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Medicinal Products – Quality, Safety and Efficacy

Draft Agreed by CHMP / CVMP Quality Working Party

Adopted by CHMP for release for consultation

End of consultation (deadline for comments)

Agreed by Quality Working Party

Adopted by CHMP

Date for coming into effect

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines for Good Manufacturing Practice
for Medicinal Products for Human and Veterinary Use

Annex 17: Real Time Release Testing and Parametric Release

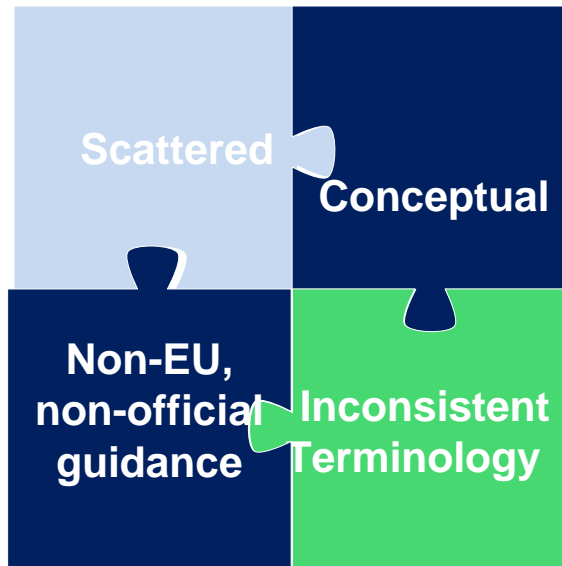
Deadline for coming into operation: 26 December 2018 (6 months after publication)



Background Issue Statement

Single use equipment extractables/leachables

Guidance exists however it is spread over numerous documents



Guidance is rather conceptual than practical in nature

Other Guidance exist however from professional organisations regulatory as or in other jurisdictions

A wide array of terms are used to describe parts or all of the related aspects and issues

Both biopharmaceutical manufacturers and regulators would benefit from a comprehensive and practical guide on E&L