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

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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)
EMI 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.
Guideline on the quality requirements for drug-device combinations

- 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

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

- Agreement 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
Biosimilars in the EU
Information guide for healthcare professionals last updated 29 October 2019

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) 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 Biosimilar

Aiv
Biv

Aiv-a Aiv-b

Biv-a Biv-b Biv-c

Civ-a Civ-d

A, C originator
B biosimilars
a, b, c, d indications
iv, intravenous; sc, subcutaneous
- 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)
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
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.
GMP for ATMPs

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

<table>
<thead>
<tr>
<th>Adoption by the European Commission</th>
<th>22 November 2017</th>
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<td>Date for coming into operation</td>
<td>ATMP manufacturers should comply with these Guidelines no later than 22 May 2018.</td>
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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

Stangl 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

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

Final

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

Guidance exists however it is spread over numerous documents.

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

Guidance is rather conceptual than practical in nature.

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.