The status of challenge material within the EU regulatory framework

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Disclaimer

- Alan Fauconnier is Quality/CMC assessor at the Federal Agency for Medicines and Health Products (FAMHP), the Belgian regulatory authority competent for Medicinal Products.
- Alan Fauconnier is also one of the Belgian delegates at the Biologics Working Party (BWP) of the CHMP (EMA/London).
- However, this presentation represents a personnal view, which may not necessarily reflect the view of the FAMHP, the BWP, the CHMP, the EMA and/or other regulatory bodies.

Phamaceutical legislation

In the European Union (EU), the pharmaceutical legislation is essentially laid down in the Community code…

…available on the Eudralex website of the European Commission (EC)

http://ec.europa.eu/health/documents/eudralex/index_en.htm

Acts of the Community code

The Community code includes 3 types of acts:

1. Regulations
2. Directives
3. Decisions

Acts of the Community code

A “Regulation" is a binding legislative act. It must be applied in its entirety across the EU.

A “Directive" is a legislative act that sets out a goal that all EU countries must achieve. However, it is up to the individual countries to devise their own laws on how to reach these goals.

Thus, each Member State must transpose the Directive provisions in its national legislation.

Directive 2001/83/EC

Directive 2001/83/EC on the Community code relating to medicinal products for human use

→ applies to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.

Directive 2001/83/EC

Directive 2001/83/EC does not apply to

- Magistral formulas and officinal formulas
- …
- Medicinal products intended for research and development trials.

Directive 2001/20/EC

Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

'investigational medicinal product' (IMP): a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial.

Clinical trial applications (CTA) are within the remit of Member States (and not of the EU, the EMA or the CHMP)

In between medicinal products

‘Industrial medicinal products intended to be placed on the market’ (2001/83/EC)

‘IMP being tested or used as a reference in a clinical trial’ (2001/20/EC)

What about medicinal products which are used in clinical trial (CT) and as such out of the scope of Directive 2001/83/EC…

but which are not themselves under evaluation, thus not to be considered as IMPs and, accordingly, not within the scope of Directive 2001/20/EC ?

e.g. rescue medication, medicinal products used to assess end-points

non-Investigational Medical Products (NIMPs)

Concept of NIMP

NIMPs are medicinal products intended for research and development trials, while not falling within the definition of IMP of Directive 2001/20/EC (i.e. tested or used as reference).

non-Investigational Medical Products (NIMPs)

Guidance document of the European Commission on IMPs and non-IMPs

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/imp_03-2011.pdf

However:

- this is only a guidance document
- the NIMP definition left room for different interpretation among European Union (EU) Member States

New Regulation

Regulation 536/2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Brings important changes to CT regulation.
Among these, the former terminology NIMPs is now replaced by “auxiliary medicinal product” (AMP).

Inclusion of AMP definition in the Regulation provides a firmer legal basis.

Auxiliary medicinal product (AMP)

‘Auxiliary medicinal product’ means a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product.

AMP should be authorised (i.e. MA granted) unless an EU authorised AMP is not available.

AMPs include, for instance, medicinal products used for background treatment, challenge agents, rescue medication, or used to assess end-points in a clinical trial,
but not concomitant medications (unrelated to the CT)

Auxiliary medicinal product (AMP)

Expert group consultation document on the

Definition of Investigational Medicinal Products (IMPs) and use of Auxiliary Medicinal Products (AMPs)

available at

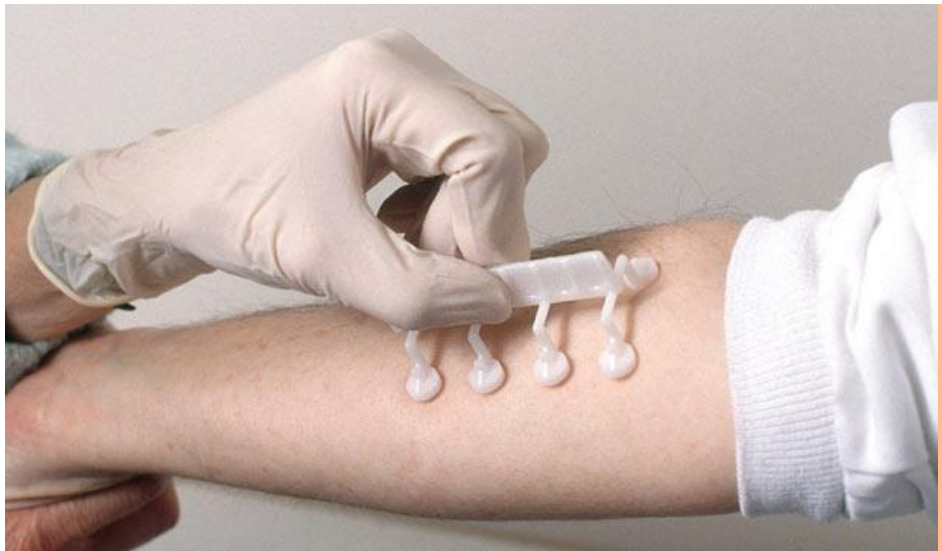
https://ec.europa.eu/health//sites/health/files/files/clinicaltrials/2016_06_pc_guidelines/gl_2_consult.pdf

Challenge agents

Challenge agents may be, for example:

Skin prick test: dilute solutions of allergens (pollens, house dust…) used to identify subjects with allergic responses. This test may be used as part of the inclusion criteria for a clinical trial of a new medicine to control or prevent symptoms from allergic reactions.

Blood pressure: open-label sensitivity test of blood pressure response to oral tyramine following treatment new monoamine oxydase inhibitor in healthy volunteers.



Auxiliary medicinal product (AMP)

By definition, an AMP must first be a medicinal product. Consequently, not all products used for the needs of a clinical trial are AMPs, e.g. some challenge agents are not defined as AMPs because they are not medicinal products.

Thus, may a challenge pathogen (viruses, bacteria, parasites) preparation be considered as a medicinal product ?

Definition of a medicinal product

Directive 2001/83/EC

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Challenge material as AMP

Whereas the definitions and basic principles are set up in the Community code, the management of CTA is in the remit of Member States.

No definitive position taken at national level yet

Considering that challenge material consisting of pathogens meets the definition of medicinal product would allow to recognise it as an auxiliary medicinal product.

Challenge material as AMP

- application dossier: quality/CMC data as well as data from non-clinical studies and, where relevant, from its clinical use should be submitted in CTD format.
- assessment of CTA by RA includes AMP for properties, labelling, manufacturing and control
- information regarding the traceability, storage, return and destruction of AMP (as for the IMP) should be contained in the application dossier.
- pharmacovigilance tasks (same requirements as authorised medicinal products)
- modification (variations) should be subject to an authorisation procedure.

Challenge material as AMP

Manufacturing and import of AMP (as it is the case for IMP)

- subject to the holding of an authorisation
- suitable and sufficient premises, technical equipment and control facilities
- manufactured according to GMP or to at least an equivalent standard, in order to ensure appropriate quality.
- a qualified person (QP) ensuring that each batch complies with the above requirements.

Thanks for your attention

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