EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Considerations on regulatory aspects

Regulatory framework for medicinal products in the context of therapeutic use of bacteriophages

EMA Workshop on 8 June

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Medicinal product

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

Article 1(2) of Directive 2001/83/EC

General requirements for medicinal products

Routes for marketing authorisation

- National, mutual recognition, decentralised routes
- Centralised procedure
  - Mandatory scope, inter alia:
    - Recombinant DNA technology
    - Controlled gene expression
    - Advanced therapy medicinal products
  - Optional scope, inter alia:
    - New active substance(s) (as of 20 November 2005)
    - Significant therapeutic, scientific or technical innovation
    - Interests of patients at EU level

Main requirements for obtaining a marketing authorisation

Detailed pharmaceutical, non-clinical and clinical data provided:

- Data complies with requirements of Directive 2001/83/EC
- Data properly and sufficiently demonstrates the quality, safety and efficacy, and establishes a positive benefit-risk balance of the product

Manufacturing process defined and controlled, performed by authorised manufacturers

Pharmacovigilance system

Agreed product information

Etc.

Exemptions from the requirements of Directive 2001/83/EC

- Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula)
- Any medicinal product prepared in a pharmacy in accordance with prescriptions of a pharmacopoeia and supplied directly to patients (commonly known as the officinal formula)
- Medicinal products intended for research and development trials […]
- Intermediate products intended for further processing by an authorized manufacturer
- [..]

Art. 3 of Directive 2001/83/EC

Possible exemptions from the requirements of Directive 2001/83/EC

- Member state may exclude products supplied in response to bona fide unsolicited order, formulated in accordance with the specifications of a health-care professional and for use by an individual patient under his direct personal responsibility
- Member state may temporarily authorise distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents [..]

Art. 5 of Directive 2001/83/EC

Biological medicinal products

A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

Biological active substances have inherent variability, but they must be appropriately characterised, their critical parameters identified, specifications and their acceptability justified, manufacturing process described, validated and controlled. The required level of details in characterisation can be discussed on a case by case basis.

Changes to the Marketing authorisation

Changes to the MA dossier require notification and/or authorisation. In particular, major changes require submission (and approval) of:

- Extension of a marketing authorisation – changes that are listed in Annex I of Regulation 1234/2008 and fulfil the conditions laid down there
- Major variation of type II – a variation which is not an extension and which may have a significant impact on the quality, safety or efficacy of the medicinal product concerned

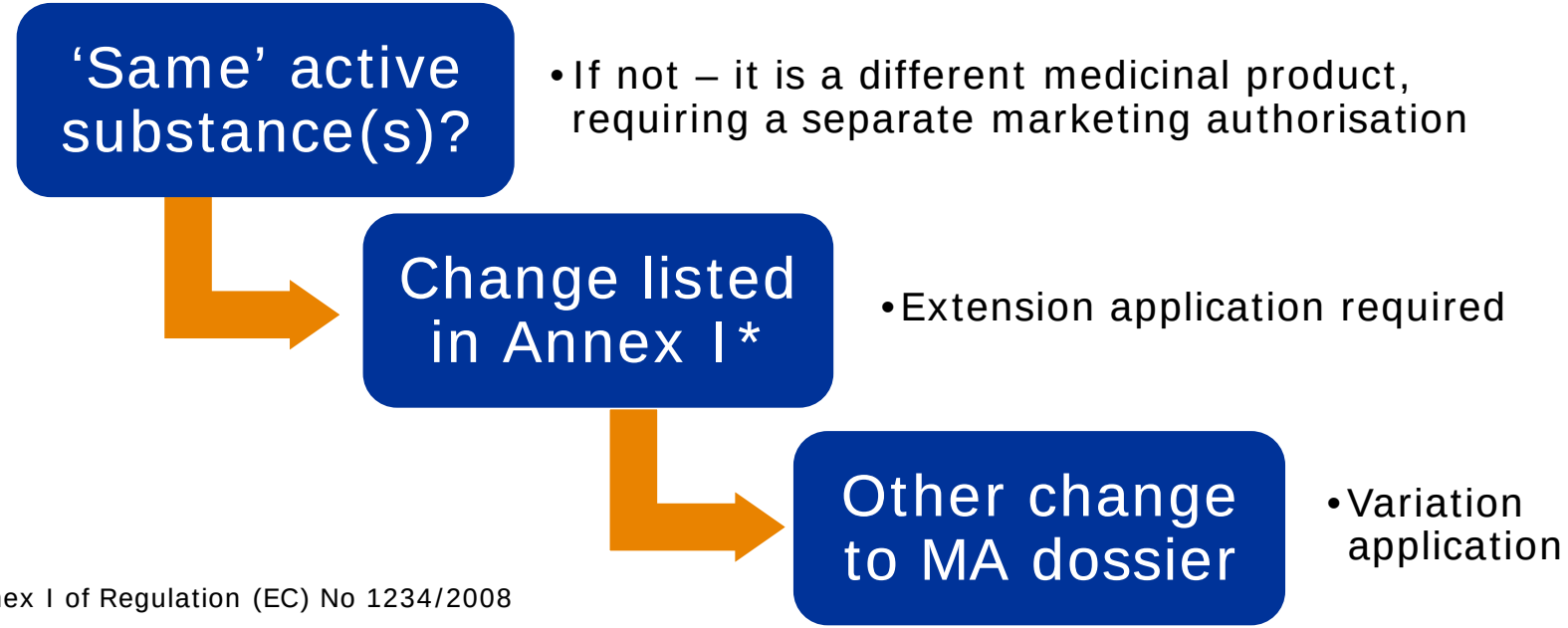
Changes to the active substance (I)

Extension of Marketing authorisation required for, inter alia:

- Changes to the active substance(s) – replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different [..]

Annex I of Regulation (EC) No 1234/2008

Changes to the active substance (II)



* Annex I of Regulation (EC) No 1234/2008

Advanced therapy medicinal products (ATMPs)

- a somatic cell therapy medicinal product
- a tissue engineered product
- a gene therapy medicinal product:
  - contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence
  - its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence
  - excludes vaccines against infectious diseases

ATMP classification

Wild-type bacteriophages are clearly not gene-therapy products. For products with a recombinant nucleic acid sequence and potentially considered as gene therapy product, applicants are encouraged to ask for an ATMP classification:

- Committee for Advanced Therapies (CAT) delivers scientific recommendations on ATMP classification after consultation with the European Commission within 60 days after receipt of the request
- EMA publishes the outcome of the assessment of the classification of ATMPs as summary reports
- The procedure does not have a fee

Specific provisions for ATMPs

Risk based approach may be applied to determine the extent of quality, non-clinical and clinical data to be provided

Part IV of Annex I of Directive 2001/83/EC

Hospital exemption: ATMPs prepared on a non- routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient are exempt from requirements of Directive 2001/83/EC, but shall be authorised by the Competent authority of the Member State

Art. 3(7) of Directive 2001/83/EC

Other regulatory aspects to consider

- Products consisting of or containing genetically modified organisms have additional requirements
- Manufacture authorisation required for total or partial manufacture of the medicinal product

Examples of exceptions for other types of products

Exceptions introduced for other types of products with extensive experience:

- MA not required for radiopharmaceuticals prepared at the time of use by a person or establishment authorised exclusively from authorised radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions

  Art. 7 of Directive 2001/83/EC

- Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza do not require extension application (but rather a special case of a type II variation)

  Annex I of Regulation (EC) No 1234/2008

References

Eurdalex, a compilation of EU legislation in the pharmaceutical sector and related guidelines, published by the European Commission – http://ec.europa.eu/health/documents/eudralex/index_en.htm

EMA website – http://www.ema.europa.eu, in particular the section 'Human Regulatory' and:

- SME office page (for small and medium enterprises)
- Innovation Task Force page
- Scientific advice and Protocol assistance page

Thank you for your attention

Further information

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