European Commission

Enterprise and Industry
Directorate-General

Pharmaceutical Acquis

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Marketing authorisation legislation in the EU

- Human code - Directive 2001/83/EC (last amended Directive 2004/27/EC)
- Veterinary code - Directive 2001/82/EC (last amended Directive 2004/28/EC)
- Centralised procedure – Regulation (EC) No 726/2004
- Regulation (EC) No 1085/2003 (Variations – human)
- Regulation (EC) No 1084/2003 (Variations – veterinary)

Further legal framework for medicinal products

- Orphan medicinal products - Regulation (EC) No 141/2001
- Clinical trials - Directive 2001/20/EC
- Commission Directive 2003/94/EC (Good manufacturing Practice)
- Regulation (EEC) No 2377/90 (maximum residue limits for veterinary medicinal products in foodstuffs of animal origin)

Marketing authorisations for medicinal products for human use (Article 6 of Directive 2001/83/EC)

- A medicinal product may only be placed on the market in the European Union when a marketing authorisation has been issued by the competent authority of a Member State for its own territory (a national authorisation) or when an authorisation has been granted for the entire Community (a Community authorisation)
- Authorisations are granted on the basis of the criteria of QUALITY, SAFETY and EFFICACY

Types of applications

Applications must include a standard dossier described in the legislation

- Application types:
  - Independent full dossier (all tests and trials), Article 8 of Directive 2001/83/EC
    - “data exclusivity” for the data submitted
  - Generic, Article 10
  - Well established medicinal use, Article 10a
  - Fixed combinations, Article 10b
  - Informed consent, Article 10c

Renewal and ”Sunset clause”

- Validity of 5 years / possible renewal, Article 24(1-3)
  - Once renewed – valid unlimited
  - Exception on grounds of pharmacovigilance
- “sunset clause”, Article 24(4-6)
  - Not on the market for 3 years

The procedures available

Centralised procedure

- Applications made directly to the European Agency for the Evaluation of Medicinal Products (EMEA) leading to the grant of a Europe-wide marketing authorisation issued by the Commission

Mutual Recognition and Decentralised procedures

- Applications made to the MS selected by the applicant and the procedure is based on mutual recognition of national marketing authorisations; where this is not possible, a Community arbitration procedure is triggered

The centralised procedure – Scope

Mandatory for medicinal products:

- developed by means of biotechnological processes (recombinant DNA, controlled expression of genes coding, hybridoma and monoclonal antibody methods)
- containing new actives substances indicated for the treatment of AIDS, cancer, diabetes and neuro-degenerative diseases
- orphan designated medicinal products
- 4 years after entry into force, also: autoimmune diseases and other immune disfunctions, viral diseases

The centralised procedure - Scope Optional:

- New active substances
- MP with a significant therapeutic benefit, scientific or technical innovation, or answering the interest of patients or animal health at Community level
- Generics of centralised products

The centralised procedure - operation

- Application to the EMEA
- Scientific assessment by the CPMP/CVMP → Opinion
- Possible appeal (re-examination) of the Opinion
- Opinion forwarded to the Commission
- Draft Commission decision
- Standing Committee (comitology procedure)
- Adoption of Commission decision – valid throughout the EU

Mutual recognition procedure – Scope

- Compulsory for all medicinal products to be marketed in a member State other than that in which they were first authorised
- May be used for all products except those which fall within the mandatory scope of the centralised procedure

The mutual recognition procedure, Chapter 4 of Directive 2001/83/EC - Operation

- Applications submitted in one or more MS
- Identification of Reference and Concerned Member States
- Assessment by RMS (90 days) and suspension of evaluation in CMS
- Recognition of the assessment by RMS by CMS (90 days), Article 28(4)
- Refusal to recognise – Arbitration EMEA →Commission decision

Community rules on authorisations – Impact in Turkey and Croatia

Centralised marketing authorisations:

- Valid in the entire EU, also Turkey and Croatia
- Conflicting national authorisations become inapplicable

National marketing authorisations:

- Upgrading of old dossiers
- Mutual recognition procedure
- Maintenance of achieved harmonisation

Timelines

- The procedure for granting a marketing authorisation for medicinal products shall be completed within a maximum of 210 days, Article 17 of Directive 2001/83/EC

Data protection/exclusivity, Article 10

- 10 years of protection (8+2)
- +1 year for new therapeutic indications bringing a significant clinical benefit
- 1 year for new indication of a well established substance (significant pre-clinical or clinical studies)
- 1 year for OTC switch (significant pre-clinical or clinical studies) Article 74a

10 years of protection (8+2)

- **Data exclusivity**: a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.
- **Marketing protection**: shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.

+1 new therapeutic indication

The ten-year period of marketing protection shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.

New indication of a well established substance

Where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.

OTC switch, Article 74a

Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised.

Definitions and data requirements

- Generic product: same qualitative and quantitative composition, same pharmaceutical form, bioequivalence. Data requirements where changes in active substance or where product does not fall fully under definition
- Reference product
- Similar biological product: supplementary data to be provided in accordance with the Annex

Facilitating generic access through the rules protecting research

- Data protection period broken into data exclusivity and marketing protection, allowing immediate market access after 10 years
- Global marketing authorisation: data protection for the initial authorisation only of a reference product
- Preparation of a generic application and patent law: Bolar clause

Flexibility in the authorisation status of the reference product

- Reference product which is or has been authorised
- "Euro-reference product" if the reference medicinal product was not authorised in the Member State in which the application for the generic medicinal product is submitted

Manufacture and …, Title 4 of Directive 2001/83/EC

– Article 40(1):

”Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. This manufacturing authorization shall be required notwithstanding that the medicinal products manufactured are intended for export.”

…and Importation

– Article 40(3):

”Authorization referred to in paragraph 1 shall also be required for imports coming from third countries into a Member State..”

Time frames and qualified person

- The authorities have a maximum og 90 days for the handling of an application for manufacturing authorisation, Article 43.
- The holder of the manufacturing authorisation shall have a qualified person at his disposal, Article 48.

GMP Directive

- Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

Labelling and package leaflet, Chapter V of Directive 2001/83/EC

Wholesale distribution / Pharmacovigilance, Title VII and IX

- Member States shall ensure that only medicinal products with a marketing authorization in accordance with Community law are distributed on their territory
- Pharmacovigilance, Title IX

Supervision

Article 111(1):
“The competent authority of the Member State concerned shall ensure, by means of repeated inspections, and if necessary unannounced inspections, and, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory designated for that purpose to carry out tests on samples, that the legal requirements governing medicinal products are complied with.”

Human Blood and Plasma

- Special provisions on medicinal products derived from human blood and plasma are included in Title X of Directive 2001/83/EC

Refusal of application for MA

- Article 26 of Directive 2001/83/EC establishes when an application for MA shall be refused
- An authorization to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in the Directive, Article 126

Decisions of Directive 2001/83/EC, Article 125

- Every decision shall state the reasons on which it is based
- Such decision shall be notified to the party concerned
- Information as to the redress available to him under the laws in force and of the time-limit allowed for access to such redress shall be given
- Decisions to grant or revoke a marketing authorisation shall be made publicly available

Clinical trials, Directive 2001/20/EC - Scope

- The Directive establishes specific provisions regarding conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products, in particular relating to the implementation of good clinical practice

Definitions

Clinical trial:

- Investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of investigational medicinal products,
- identify any adverse reactions to investigational medicinal products
- study absorption, distribution, metabolism and excretion of investigational medicinal products

- with the object of ascertaining their safety and/or efficacy

Definitions

- Sponsor:
  - an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial

The sponsor

- Each trial shall have one sponsor
- Responsible for the trial
- Can not start the trial until favourable opinion of the Ethics Committee
- Shall submit application for the trial to the authorities

Timelines

- For the consideration by the competent authority of a request for authorisation – 60 days, Article 9(4)
- At the end of the trial the sponsor shall notify the competent authorities and the Ethics Committee within 90 days (15 if the trial had to be terminated early)

Directive 2005/28/EC

- Implementing Commission Directive
- laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

Colouring matters – Directive 1978/25/EEC

- Colouring matters shall be authorised for medicinal products if included in Annex I of Directive 94/36/EC or Annex to Directive 95/45/EC relating to foodstuffs

Conclusions

- This was not the full picture, but some parts of the legislation which shall be in implemented

- More information can be found on http://pharmacos.eudra.org/

- Further details of the legislation are explained in the Notice to applicants

Thank you