Regulatory approval routes in the European System for Medicinal Products

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Background

EU law requires all medicinal products to obtain a Marketing Authorisation (MA) before they can be put on the market.

Permission (Authorisation) must be granted by one or more Member States or the European Commission for centrally authorised products (i.e. via the EMA).

Product needs to satisfy criteria of quality, safety and efficacy and to be submitted in a Marketing Authorisation Application dossier.
EU pharmaceutical legislation - Hierarchy

- **Regulation** – Binding to all Member States (MS), no national changes allowed (e.g. Paediatric Regulation)
- **Directive** – Results binding but method up to MS, local interpretation (e.g. Clinical Trials Directive)
- **Guidelines** – Interpretation of requirements, recommended but not binding (e.g. “Guideline on the readability of the labelling and package leaflet of medicinal products for human use”)

Current Pharmaceutical Legislation

• **Directive 2001/83/EC** (replacing old Directives) - the core legislation governing the regulation of drugs in EU, provides the framework for regulation of medicines at national level

• **Regulation (EC) No 726/2004** (replacing (EC) No 2309/93) – Sets out the centralised procedure
Legal basis for applications in the EU

- Article 8(3) Full application
- Article 10a Well-established use application
- Article 10b Fixed dose combination application
- Article 10c Informed consent application
- Article 10(1) Generic application
- Article 10(3) Hybrid application
- Article 10(4) Similar biological application

Directive 2001/83/EC (as amended)
Since 2003 CTD structure in EU, harmonised format for applications in EU, Japan & US

User friendly review, worldwide submission & exchange easier
Post Nov 2005 European Systems

Centralised Procedure (via EMA)

Mutual Recognition procedure

Decentralised Procedure

National Procedure

Better Resource Utilisation
Harmonised Scientific Opinions
Harmonised Information to Doctors / Patients

Still possible for authorisation in a single MS
Mutual Recognition Procedure (MRP)

1. Authorisation in one Member State, the Reference Member State (RMS) (210 days)

2. Submission to chosen Concerned Member States (CMS) for recognition of Authorisation (90 days)

   - Authorisation in CMS (within 30 days)
   - In case of disagreement referral to CMD(h)/CHMP (60 + 60 days)

   - Serious risk to public health

   - Referral to CMD(h)
Decentralised Procedure (DCP)

No MA existing in EEA
Application to RMS & CMS
Initial assessment by RMS and comments by CMS (120 days including)

Second phase of assessment and position by Member States (90 days)

Authorisation in all MS if agreement (within 30 days)

In case of disagreement referral to CDM(h)/CHMP (60 + 60 days)

Serious risk to public health

Referral to CMD(h)

210 days
MRP + DCP Evaluation

- Referral to CMD(h)
- 60 days CMS to approve
- Referral to CHMP Art. 29.4
- 60 days to adopt opinion
- OPINION

Commission Decision

Binding in RMS + CMS and across EU

67 days
MRP & DCP

- 2013 finalised:
  - MRP = 207 (7 referrals CMD(h));
  - DCP = 1052 (15))

- 100,000’s National Marketing Authorisations across EU

- Risk flooding Centralised Procedure if free access granted

- Resource limitation starting slot rationing
Decentralised Procedure
Pros / Cons

- Choice of RMS
- Multiple licenses – multiple (invented) names possible
- Choice of MS possible
- Reduced follow-up commitments
- Reduced transparency of outcome
- Predictable timelines

- Slot rationing
- Consensus vote or referral to CHMP
- Lack of 2nd primary review
- Valuable international recognition
- Lack of product team leader
Centralised Procedure

• **1 Marketing Authorisation** valid through EU

• **1 (invented) name**

• **1 Common Product Information** (identical in 25 languages, including Icelandic and Norwegian)
  – Summary of Product Characteristics (SmPC)
  – User Package Leaflet & Labelling

• **Maximum time limit**
  – 210 days Evaluation ---> Opinion
Centralised Procedure

- Reserved procedure: dedicated to innovative products

- May be open to ‘old’ substances in a new delivery system, or in a new indication

- Products eligible are defined in the legislation
Eligibility in CP - Mandatory Scope

- Auto-immune disease and Other immune dysfunctions
  - AIDS
  - Cancer
  - Neurodegenerative disorder
    - Recombinant DNA technology controlled gene expression Monoclonal AB [Reg. 2309/93]
    - Diabetes
    - Orphan NAS/“known” AS [Reg. 726/2004]

- Viral diseases

NAS

NAS/“known” AS?
Eligibility in CP - Optional Scope

Art. 3(2) of Regulation (EC) No 726/2004

Art. 3(2)(a)
New Active Substances

Art. 3(2)(b)

Significant Innovation:
Therapeutic &/or
Scientific &/or
Technical

OR

Interest of Patients at Community Level

“known” AS

Art. 3(3) of Regulation (EC) No 726/2004 – generics of CAPs
Overview of Centralised Procedure Timetable

Pre-submission
- Orphan Paediatrics
- Filing strategy

Primary Evaluation
- Pre-submission
  - 7/6m Pre-submission meeting
  - 7m rapporteurs appoint.
  - 18 to -7m
  - 12 to -36m
- Day 80 AR
- Rap/Co-Rap

Secondary Evaluation
- Clock Stop
- LoQ
- Responses
- Day 150 AR on responses

Final Evaluation
- Clock Stop
- LoOI
- Responses
- SmPC, PL, labelling, Risk min. measures, conditions to MA

Opinion
- Post Authorisation
- Pharmacovigilance
- Variations
- Extensions
- Renewal

Decision
First steps prior to MAA

✓ Applicant must be duly established in the EEA i.e. must have a permanent legal structure that is formed in accordance with the law of an EEA Member State and allows the concerned holder to assume the duties and responsibilities as well as to perform the tasks laid down by Union law.

✓ Submission of an eligibility request/Receipt of confirmation.

✓ Letter of Intention to submit an MAA and request for Rapporteur appointment.

✓ Request for pre-submission meeting: typically address product-specific legal, regulatory and scientific issues in order to facilitate subsequent validation and assessment of the application.
Re-examination of Opinion

Re-examination = “appeal”

15 days to request re-examination

60 days to submit grounds

CHMP 60 days to consider revision of initial opinion:

- No new data

- Scientific advisory group may be consulted
Decision making process

- **Commission Decision phase**
- EMA ~15 days to transmit Opinion to the Commission
- Commission ~15 days to prepare draft decision for circulation to Standing Committee (Member State representatives)
- Standing Committee ~22 days to review
- Commission ~15 days to implement changes and issue final Decision legally binding throughout the EU
Centralised Procedure

Pros / Cons

Pros:
- Pan-EU license – single (invented) name
- Majority vote
- Transparency
- Predictable timelines
- Two independent Primary Reviews
- Dedicated EMA Product Team

Cons:
- Restricted access to CP
- No control over CHMP Rapp appointment
- All or nothing outcome
- Transparency to third parties
- Single (invented) name – single MAH
- No independent “appeal” body
- Product labelling

SME office: dedicated to addressing the particular needs of smaller companies
smeoffice@ema.europa.eu
EMA Scientific advice

- **Scientific advice** is advice to a company on the appropriate tests and studies in the development of a medicine.

- Companies can request scientific advice from the European Medicines Agency at any stage of development of a medicine, whether eligible for the centralised procedure or not.

- **Answers to questions** posed by companies in the light of the current scientific knowledge, based on the documentation provided by the company.

- Scientific advice is prospective in nature focused on development strategies

- Not legally binding with regard to any future marketing-authorisation applications for the medicine concerned.
Key points

- Choice of authorisation procedures in the European Union
- Eligibility for ‘polypill’ (known ASs) under optional scope for centralised procedure determined by CHMP: adequacy of justification of innovation/interest to patients at community level
- CHMP Guidance on clinical development of fixed dose combinations being reviewed
- Scientific advice available
- smeoffice@ema.europa.eu
- Adequacy of clinical development program ultimately decided only during assessment of a marketing authorisation procedure
Council of Europe
International Conference on Harmonisation (ICH)
FDA
World Health Organisation
European Institutions
European Medicines Agency (EMA)
EU EEA Countries
Mutual Recognition Agreements
Candidate Countries
European and International Partners
Thank you

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