EMEA- Regulatory up-to-date topics - Approval Procedure for Pharmaceutical Products

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- Expansion of EU- Legal Basis for EU Drug Approval Procedures
- Revision 2001; Regulatory Bodies involved in EU Procedures
- Submission Documents/ Centralized- vs Mutual Recognition Procedure
Expansion of EU -
Legal Basis for EU Drug Approval Procedures
The European Union

- 25 Member States
- 21 Languages
- About 450 Mio citizens
- Council of Ministers
- European Parliament
- EU Commission
# The EU Member States

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Background - History

- **EU a common market without any Trade-borders**
- **Free Trade (including Drugs) among the Member States**
- **New Drug-Approval Procedure implemented in 1995**
  - Central Procedure (highly innovative products)
  - Mutual Recognition (general products)
- **2001 Revision; Review of Provisions of 1995 suggested**
  - Part of the new Revision accommodating accession of new EU Member States implemented in May 2004; remaining part in Sept./Oct. ‘05
Revision 2001;
What are the new Regulatory Bodies?
Regulatory Bodies (1/3)

- CPMP Committee for Proprietary Medicinal Products renamed to

- CHMP Committee for Human Medicinal Products
  - Scientific Body of EMEA responsible for the evaluation of medicinal products, both new and marketed products
  - Consists of 1 representative of each EU member state plus Norway, Iceland and Liechtenstein (Before May 1, 2 representatives per country)
  - Monthly meetings for 3 days
  - Chairman: Daniel Brasseur from Belgium
  - Co-Chairman: Eric Abadie from France
CHMP working parties and ad hoc groups, e.g.

- Biotechnology Working Party
- Efficacy Working Party
- Pharmacovigilance Working Party
- Joint CHMP/CVMP Quality Working Party
- Safety Working Party
- Scientific Advice Review Group
- Ad hoc Working Group on Blood products
- Herbal Medicinal Products Working Party
Regulatory Bodies (3/3)

- MRFG Mutual Recognition Facilitation Group
- MRCG Mutual Recognition Coordination Group
  - Representatives from EU member states, Norway, Iceland, CADREAC observers
  - Chairmanship by EU Presidency
  - Meets once a month in CHMP week

- Task:
  - Coordination and facilitation of mutual recognition procedure
  - Provide a forum to reach common understanding of the procedure and develop SOPs
  - Translate legal interpretations into practical recommendations
  - Hold break-out sessions on individual applications in order to facilitate agreement
Revision 2001;
- Submission Documents
- Submission Procedures
Submission Documentation

- So far:
  - USA: New Drug Application
  - Europe: Notice toApplicants
  - Japan: Gaiyo

Common Technical Document

- Mandatory for EU (centralized submissions) and Japan since July 2003
- Mandatory for national submissions in EU from November 2003
- US, highly recommended but yet not mandatory
The Structure of the Common Technical Document (CTD)

- **Dossier presented in a modular fashion**

- **Logical order of documents, reflecting sequential pathway of drug development**
Revision 2001;
- Submission Documents
- Submission Procedures
Possible procedures for approval in EU

- **Centralized Procedures**
  - Mandatory for:
    - Biotech Products,
    - Oncology, Diabetes, AIDS,
    - Neurodegenerative diseases
    - Orphan Drugs also open for NCEs
  - Decentralized Procedure

- **Mutual Recognition Procedure**
  - Possible for NCEs containing small molecules and known chemical entities
  - National submissions
    - For products that will only be marketed in one EU Member State and line extensions to nationally approved products
The Centralised Procedure
List A Products (mandatory)

Products developed by:
- Recombinant DNA Technology
- Gene-Technology
- Antibody Methods

List B Products (optional)

- Innovative Products Processes, Manufacturing Methods, delivery systems
- Therapeutic Interest
- Products from human blood or plasma
- New Active Substance
Centralised Procedure (1/2)

- **Day 70**: Procedure start after CHMP (Committee on Human Medicinal Products) Meeting
- **Day 120**: Preliminary assessment report
- **Day 121**: Consolidated list of questions
- **Clock stop**: Submission of responses and restart of the clock
Centralised Procedure (2/2)

1. Day 180
   - Clock stop if oral explanation is needed

2. Day 181
   - Restart of clock and oral explanation

3. Day 210
   - Adoption of CHMP Opinion

4. Day 240
   - Transmission of opinion to EU Commission

5. Day 15
   - For appeal to this decision

6. ~90 days later
   - EU Commission decision and final approval

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Dr. Nikolaus Mueller, Head of R&D Operations, Nihon Schering K.K.
The Outcome

- Marketing Authorization Granted by the EU-Commission
- Results in one European Approval
- Harmonized SPC (Summary of Product Characteristics) and PIL (Packaging Insert Label)
- Variations Regulated by Regulation 542/95
De-centralised Procedure; modification of the Centralized Procedure
New Decentralized Procedure

- Similar Process as for Centralized Procedure but
- Choice of Rapporteur possible
- Selection of participating countries possible
- No possibility to withdraw application after process was started
- MRCG to coordinate process in case of differing opinions
  - arbitration last resort.
The Mutual Recognition Procedure (MRP)
Relevant aspects of the MRP

- MRP can be initiated by the Applicant or the Member States
- Concerned Member States and Reference Member State can be selected by the Applicant
- Based on the Assessment Report and the Marketing Authorisation of the Reference Member State (RMS)
- Marketing in RMS possible after Marketing Authorization (before and during the MRP)
- Can also be used for elder products
- Withdrawal (from selected countries) possible
Mutual Recognition Procedure - National Phase

210 days + clock stop
~150 days
~90 days?
~60 days
90 days

- Submission to Reference Member State (RMS)
- Deficiency Letter
- Clock Stop for reply preparation
- Assessment of reply
- Approval
- Assessment Report
Mutual Recognition Procedure - MR Phase

- Submission by affiliates to CMS (Start day scheduled with CHMP meeting plan)
- Validation Period by CMS
- Objections
- Submit reply
- MRFG (Mutual Recognition Facilitation Group)
- Final Decision
- National decisions

Timeframes:
- ~7 days
- 10 days
- day 50
- day 60
- day 75
- day 90 (~30 days later)
- day 100
- day 90 (30 days later)
- day 100
- ~90 days later
If Mutual Recognition cannot be achieved and no decision for withdrawal!

- **Serious Public Health Concern remains**
  - Within 90 days Referral to CHMP
  - Within 60 days CHMP opinion

- **Commission decision**
  - Within 60 days Final CHMP Opinion
  - Company Appeal possible
National Submissions:

- Initial phase same as MRP
- Difference:
  the Procedure stops with the approval of the RMS which is the only State where the applicant does want to market the Product
Summary and Conclusion (1/2)

- Expansion of the EU into a Free-Trade-Community of 25 States has triggered the revision of the Marketing Authorization Procedure of Medicinal Products
- Regulatory Bodies involved in EU Procedures have been newly set up
- The National-, the MR-Route and the new Decentralised procedure result in National Approvals, while the Centralised Procedure ends with a Community Marketing Authorisation
The community procedures (i.e. MRP, the Decentralised- and the Centralised Procedure) do result into a harmonized Summary of Product Characteristics (SPCs) and Package Insert Labels (PILs)
Aspects to be assessed during evaluation

➢ Back-up
Revision 2001;
What is new: Terms/ Procedures?
Definitions for medicinal products

- **Medicinal product is defined by the mode of action**
  - pharmacological
  - immunological
  - metabolic

- **Borderline products are medicinal products by definition**
Data protection

- Rules harmonised all over the EU (8+2+1 rule)
  - Data protection for 10 years Europe-wide after first marketing authorization
  - Submission of data for generic application possible after 8 years (but not marketing)
  - 1 year extension of data protection for originator, if during first 8 years after marketing authorisation an authorization for one or more therapeutic indication, with significant clinical benefit has been obtained
Support of generic industry

- Bolar provision
- EU reference product
- Choice of procedure for centrally approved originator products (Centralised or MRP)
- Bio-similar products, still to be accompanied by major data, however discussion about feasibility has begun
- Derivatives can be considered to be the same
- Most of line extensions are now included in a marketing authorization
Procedures

- Centralised procedure: mandatory also for some indications (accelerated decision process, fast track procedures, conditional licence)
- Mutual Recognition Procedure for products with an existing MA, Decentralised Procedure for products without MA
- Both procedures result in mandatory arbitration in case of serious public health concern
- Public Assessment Report for all procedures
- Package insert now included in all procedures
- Legal power for MRCG
Pharmacovigilance

- More frequent safety reports
  - every 6 months for the first 2 years
  - once a year for the following 2 years
  - every 3 years thereafter
- Increased co-ordination between MS
- Use of MedDRA for safety reporting
- Any regulatory action has to be reported immediately
- Notification to competent authority if marketing of product is ceased
GMP

- GMP requirements for active substances and certain excipients (list for latter to be established by a directive)
- Increased co-ordination and communication of inspection results via a community database
- GMP certificates to be issued within 90 days after a successful inspection
- Regular, unannounced and repeated and outside of the EC regulated
Other Provisions

- Obligation of continuous supply
- Compulsory licensing possible
- Compassionate use implemented
- Sunset clause
- Renewal only once after 5 years (submission 6 month before expiry the latest)
Important to know

- Initiated by the Applicant
- Reserved to certain kind of Products
- Application made to the EMEA (all of the Member States)
- Assessment made by the Rapporteur and Co-Rapporteur
- Opinion (Majority Decision) by the CPMP
MUTUAL RECOGNITION PROCEDURE

Application to first Member State

210 days

Assessment report (including SPC)

First Authorisation

Max. 90 days

Applicant requests mutual recognition of the reference authorisation

Update and issue of assessment report

(Parallel) applications in other Member States

May suspend evaluation

Mutual Recognition process

Continued to next page
Mutual Recognition process

55 days

No

Objections

Yes

Clarification and dialogue
Point of view of applicant

30 days

Mutual Recognition

Resolution of issues

No

Serious objections remain

Yes

Arbitration

90 days

‘Stand stop’ possible for input by applicant

FIRMP

Opinion

60 days

Company Appeal

60 days

Opinion (final)

Final National Decisions

Commission Decision
Renewals

Currently:

- Marketing authorizations (MAs) valid for 5 years, renewals to be filed 3 - 6 months before expiration

Future:

- MAs have to undergo only one renewal after the first 5 years then valid indefinitely

and

- "Sunset clause": Products not marketed within 3 years after MA has been granted lose their MA
Variations

- All textual changes in SmPC, PIL and Packaging Material need to be approved prior to implementation. (Except Urgent Safety Restrictions)

- Relevant Changes to the manufacturing of drug substance or drug product and/or release testing that impact the approved documents need to be approved prior to implementation.
3 Variation categories

- **No Assessment**
  - notification
  - validity check
  - implementation („tell and do“)

- **Assessment**
  - short assessment
    (as in current Type I) („tell, wait and do“)
  - full assessment

Type IA
Type IB
Type II