Mutual Recognition Procedure in Europe

Vaccines

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Marketing Authorisation

- Any veterinary medicinal product placed on the EU market must have a marketing authorisation ('Product Licence')
- Four routes to authorisation
  - National
  - Mutual Recognition
  - Decentralised Procedure
  - Centralised Procedure
- Same technical requirements for all procedures defined in Directive 2001/82/EC, as amended

Routes to Authorisation

Type of Authorisation	National	Mutual Recognition	Decentralised	Centralised
Issued by	National Authority	National Authority through CMDv	National Authoriy through CMDv	European Commission through EMEA/CVMP
Validity	One Member State	Several Member States	Several Member States	All Member States
Legal Base	Directive 2001/82/EC	Directive 2001/82/EC	Directive 2001/82/EC	Regulation 726/2004
Time to authorisation (standard)	210 days	210 days	210 days	210 days
Appeal &/or arbitration	National appeal systems	Appeal to CMDv then arbitration by CVMP	Appeal to CMDv then arbitration by CVMP	Re-examination by CVMP
Types of product	Conventional, novel actives and generics	Conventional, novel actives and generics	Conventional, novel actives and generics	Novel, biotech, GMO and generics of CAPs

Mutual Recognition Procedure

- Based on 'mutual recognition' of a national marketing authorisation = a member state accepts the authorisation issued by another member state
- National authority of original Member State as the 'Reference Member State' (RMS) for the product
- Between 1 and 26 'Concerned Member States' (CMS) plus EEA countries (Norway, Iceland and Lichtenstein)
- Coordinated through the Coordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv)
- Veterinary Mutual Recognition Index (products)
  http://www.hma.eu/vmri.html

Mutual Recognition Procedure

- Applicant sends dossier to RMS.
- RMS: Preparation/Updating of assessment report within 90 days -> send to CMS
- CMS: Checking dossier and assessment report, or trusts without checking. Questions to RMS if disagreement. RMS and Applicant try to solve. (90 days total)
- 60 more days for referral to CMD(v) group, if no agreement
- If still no agreement: Arbitration by the Committee for Medicinal Products for Veterinary Use (CVMP)
- (in the previous legislation a member state could withdraw from the procedure instead)

Legal Framework

- Harmonised legal framework covering pharmaceutical products as part of the *Acquis Communautaire*
- Basic requirements in Directive **2001/82/EC** and Directive **2004/28/EC** with amendments.

Key factors are:

- GMP production (Good Manufacturing Practice)
- Obligatory monographs from EDQM – General/specific monographs apply for many vaccines
- Technical/scientific requirements for the application dossier in Directive 9/2009, ”Annex 1”.

GMP Requirements for manufacture

- Manufacturing authorisation issued by national competent authority
  - Recognition of compliance with requirements of GMP in line with Directive 91/412/EEC
- Facility inspection
- Product related inspection
- "Qualified Person" certifies compliance of each batch with terms of marketing authorisation

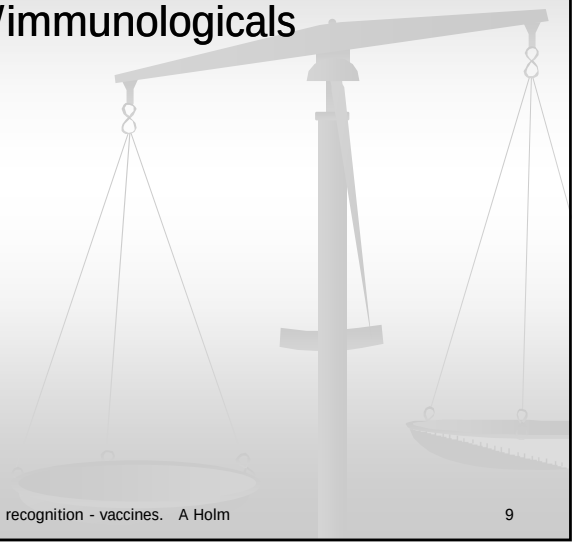
Monographs

- EDQM: *European Directorate for Quality of Medicines and healthcare* issues legally binding texts, which include minimum requirements for many vaccines:
- "European Pharmacopoeia"
  - qualitative and quantitative composition of medicines
  - the tests to be carried out on medicines, raw materials and intermediates etc.
- General monographs/texts
  - (f.ex. endotoxin test)
- General vaccine monographs apply to all vaccines
  - (f.ex. Safety of veterinary vaccines...)
- Specific monographs for vaccines against specific diseases
  - by diseases/ animal species /infective agents (f.ex. Swine fever vaccine...) - based on authorised vaccines

Directive 9/2009, Annex 1 Scientific/technical requirements

- Pharmaceutials/immunologicals

- Quality
- Safety
- Efficacy



Directive 9/2009, Annex 1 Scientific/technical requirements

Quality part

- **Composition,**
- **Manufacturing process**
- **Controls of starting materials**
- **In-process controls**
- **Controls of finished product**
- **Consistency of production**
- **Stability**

Directive 9/2009, Annex 1 Scientific/technical requirements

Safety part

- **Laboratory tests (batch with maximum titre)**
  - **Administration of one dose, of an overdose**
  - **Repeated administration of a dose**
  - **Reproductive performance**
  - **Immunological functions**
  - **Special requirements for live vaccines**
    - spreading, dissemination, reversion to virulence, recombination/rearrangement, biological properties (ex : tropisms)
  - **Interactions**
- **User safety**
- **Field study**
- **Environmental safety**

Directive 9/2009, Annex 1 Scientific/technical requirements

Efficacy part

- Laboratory tests (Batch with minimum titre)
- Vaccination-Challenge, unvaccinated controls
  - Choice of the challenge strain
  - Animals representative of target population
    - Passive / Active Immunisation
    - Physiological status
    - Age at injection
  - Onset and Duration of immunity
- Field study

Challenges and solutions

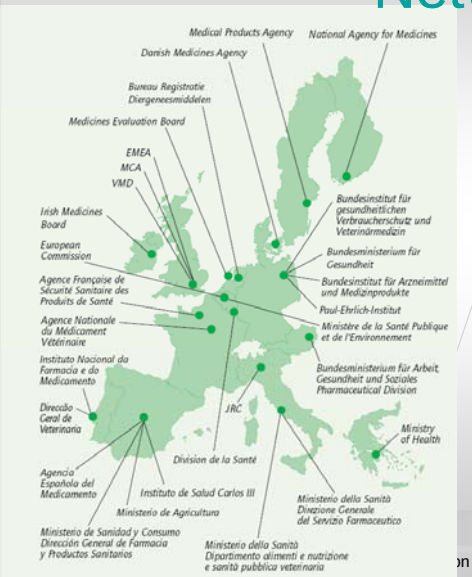
- Differences in opinion (member states disagree)
  - Acceptance, eg. if there is
    - changes in product information, warnings or conditions/restriction of use
    - Follow-up measures, post-authorisation requirements
  - Rejection: Arbitration (final voting in CVMP)
- Differences in needs between member states
  - Different diseases (geographical, husbandry, climate)
  - Strains (does the vaccine cover the circulating strain)
  - Surveillance programmes (eradication vs. vaccination)
    - Legal possibility to restrict the use of an authorised product

Does Mutual Recognition work?

- Many vaccines has been authorised through Mutual Recognition in recent years.
- Only few arbitrations on vaccines

- Reduces repetition of assessment
- High quality assessment of the dossier with ”peer-review” from other member states
- Provides vaccines to small markets because it is easy to include extra member states
- More harmonised requirements - dialogue
- Better predictability for Industry

European Medicines Network



Elements of the network

- National Competent Authorities coordinated by Heads of Medicines Agencies (HMA)
  - Human/Joint Agencies/Authorities
  - Veterinary Agencies/Authorities
  - Inspection Agencies/Authorities
    42 agencies, including EEA
- European Medicines Agency (EMA)
- European Commission
- European Directorate for the Quality of Medicines & Healthcare (EDQM)
- Network of Official Medicines Control Laboratories
- MRA partners

The European Medicines Regulatory Networking Model

- Essential components for an effective network
  - Harmonised legal and technical requirements
  - An effective infrastructure for coordination and cooperation
    - Buildings and physical facilities
    - Coordinatory body
    - Established and agreed procedures
  - Effective IT systems
    - EU Telematics programme
      - e.g. http://eudrapharm.eu/eudrapharm/welcome.do
  - A common language
  - Mutual trust and transparency
  - Interest in work sharing

The European Medicines Regulatory Networking Model

- Lessons learnt during building of European Regulatory Network
  - Sharing of resources can be effective and efficient
  - Mutual trust and transparency are essential and increase with experience
  - Gains to industry and competitiveness can be considerable
    - Time
    - Resource
    - 'Level playing field'= same rules for all
    - Predictability
  - Resource constraints drive ever greater efficiency

The European Medicines Regulatory Networking Model

- Prospects for the future
  - Harmonised interpretation of requirements is a continuous challenge
  - 'Old' products particularly difficult
  - Compulsory arbitration and referral leading to greater harmonisation and predictability
  - Emphasis and drive for improved IT systems

The European Medicines Regulatory Networking Model

- Prospects for the future
  - increasing trend for 'Centres of Excellence'
  - increase in worksharing
  - emphasis on training and cooperation
  - European Commission is currently reviewing the legislation to assess the need for
    - simplification
    - ensuring a proportionate regulatory burden
    - adapting to the needs of the veterinary sector

Thank you for your attention