Review of requirements for immunological medicinal products and their evolution since the start of Community legislation on medicines

Dr. Carmen Jungbäck
Paul-Ehrlich Institut, Germany

London, March 2015
First legislative steps

Dir. 81/851  approximation of laws of MS relating to VMPs
Dir. 81/852  approximation of laws of MS relating to analytical, pharnaco-toxicological and clinical standards and protocols in respect of the testing of VMPs
Dir. 90/677  extending the scope of Dir. 81/851 to VMPs and laying down additional provisions for IVMPs
Dir. 92/18   modifying the Annex to Dir. 81/852
Dir. 2001/82 assembling all future Dir. in a single text
Dir. 2004/28 amending Dir. 2001/82
Dir. 2009/9  amending Dir. 2001/82
Review of requirements for IVMPs and their evolution......

**Directive - quality testing**

- General Requirements
  validated test procedures on the current state of scientific progress
- Qualitative and Quantitative Particulars of the Constituents
- Description of Method of Preparation of the Finished Product
- Production and Control of Starting Materials
- Specific Measures Concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
- Control Test during Production
- Control Test on the Finished Product
- Stability Test
Review of requirements for IVMPs and their evolution……

Directive- safety testing

- General Requirements
  - Target species
  - Maximum titre or potency
  - Batches produced according to application

- Laboratory Trials

- Field Trials

- Ecotoxicity
Review of requirements for IVMPs and their evolution......

**Directive - safety - laboratory trials**

- Safety of the administration of one dose
- Safety of the administration of an overdose
- Safety of the repeated administration of one dose
- Examination of reproductive performance
- Examination of immunological functions
- Special requirements for live vaccines
  - Spread of the vaccine strain
  - Dissemination in the vaccinated animal
  - Reversion of virulence of attenuated vaccines
  - Biological properties of the vaccine strain
  - Recombination or genomic reassortment of strains
- Study of residues
- Interactions
Directive - safety - ecotoxicity

- Assessment of potential harmful effects to the environment
- Identification of precautionary measures, if necessary

**First phase:**

Assessment on the basis of the results of the safety tests and former experiences of use of the product in question

- Target species
- Method of administration
- Possible excretion and persistence

**Second phase:**

Additional experimental investigations on:

- Extent and duration of exposure to the environment
- Physical/chemical and pharmacological/toxicological properties
- Impact of the product on the environment
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Directive - efficacy

General Requirements

- Choice of vaccine strains on epizoological data
- Target species of each category
- Each route of administration
- Vaccine scheme including other vaccinations
- Influence of maternal antibodies
  - broilers
  - layers
- Duration of protection
  - broilers
  - layers
- Each component of multivalent or combined vaccines
- Minimum titre or potency
- Batches produced according to application
Review of requirements for IVMPs and their evolution......

Directive - field trials

- Summary
- Investigator in charge
- Place and date of administration
- Details of the trial protocol
- Control animals
- Identification of the animals
- Description of rearing and feeding of the animals
- Observations, performances, results
- Observations and results of studies
- Number of animals withdrawn
- Side-effects
- Intercurrent diseases
- Details of medicinal products used
- Discussion of results
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Directive since 1992

Reasons for changes:

Lessons learnt: from discussions between assessors
from questions posed by applicants
from validation procedures

New developments: new extraneous agents
new diseases

Scientific reasons: 3R
VICH

Consequences: addition / modification / deletion of requirements
Review of requirements for IVMPs and their evolution……

**Directive — lessons learnt**

**Quality:**  
Media for cell cultures

Diluents

Validation:  
Key stages of production  
Whole production process

**Safety:**  
Associations

User safety / risk to humans (ecotoxicity)

**Efficacy:**  
Marker vaccines in DIVA strategies: data on diagnostics
Directive – new developments

**Quality:**
- Detailed data on starting material of animal origin
- Compliance with TSE Guidelines
- Benefit-risk assessment for EA testing in final product

**Safety/Efficacy:**
- **Title III:** Requirements for specific marketing authorisations
- **Title IV:** Documentation for applications in exceptional circumstances
Expert reports and executive summaries for each part merged to detailed and clinical summaries

Efficacy of preservatives

Finished product testing

EA: Risk assessment introduced

Live vaccines:

Reversion to virulence:

Reduction from 6 to 5 animal groups

No in vitro passages between animal groups

Use of “normal” batches allows safety and efficacy testing in one trial
Directive – deleted requirements

**General:**
information from manufacturers provided directly to authorities but not to applicants

**Quality:**
finished product:
- assessment of purity
- test of general characteristics, when performed *in process*
- identification, when not justified
- colouring matters
- inactivation, when performed in process
- TABST

**Safety:**
safety of one dose if overdose testing is performed

safety of an overdose for inactivated vaccines
Guidelines - approach

**Status:** “soft” legislation

**Role:** interpretation of “hard” legislation
no additional requirements
immediate guidance for new developments

**Use:** help for thinking
- manufacturers: planning of trials
- assessors: supporting assessment

!no tick box licensing!
Role of IWP

- Mandate defined by CVMP
- Setting scientific guidance for IVMPs
  - regular situation
  - emergency situation
  - MUMS
  - New development
- Assist in setting scientific requirements on EU level
- commenting on VICH guidelines
- co-operation with other EMA WPs
- co-operation with Ph. Eur.
Decrease in availability of IVMPs

**Reasons:**

- Large companies concentrate on blockbusters
- Impact of overhead structures on flexibility (manufacturers and authorities)
- Manufacturing capacities grow slower than global market
- Small companies struggle with administrative procedures
Wishes for easier licensing

- Facilitate administrative structures (EMA, NCAs, EDQM)
- Facilitate administrative procedures (CP, MRP, DCP, national)
- Dare benefit-risk assessment
- Harmonize scientific requirements globally
Thank you for your attention