Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

www.pei.de

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, pharmaco-toxicological and clinical standards and protocols in respect of the testing of VMPs
Dir. 90/677	extending the scope of Dir. 81/851to 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

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

Directive- safety testing

- General Requirements
  - Target species
  - Maximum titre or potency
  - Batches produced according to application
- Laboratory Trials
- Field Trials
- Ecotoxicity

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

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

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

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**

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

Directive – modifications

General: Expert reports and executive summaries for each part merged to detailed and clinical summaries

Quality: Efficacy of preservatives

Finished product testing

EA: Risk assessment introduced

Safety: Live vaccines:

Reversion to virulence:

Reduction from 6 to 5 animal groups

No *in vitro* passages between animal groups

Field trials: 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