Virtual Workshop

"Novel in-vitro model as alternative to in-vivo toxoid vaccines testing: *Clostridium septicum* vaccine as proof of concept"

Session 4: Regulatory process

Regulators' perspective - Europe

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Disclaimer

I attend this webinar as an individual expert and I express here my personal views.

The information contained in this presentation does not necessarily reflect the opinion or the position of the Paul-Ehrlich-Institut, the Committee for Veterinary Medicial Products or the Immunological Working Party.

Agenda

- Role of the Paul-Ehrlich-Institute (PEI) in 3R projects
- BSP 130 and proposed changes to monographs
- Documents related to the use of *in vitro* methods and containing requirements and principles regarding 3Rs
- How does is work in practice – view of a competent authority

Role of the Paul-Ehrlich-Institute (PEI) in 3R projects

Role of PEI in 3R projects

- **Research Programme** – three key cross-divisional research areas
  Regulatory Research & Innovative Medicinal Product Testing
  - New experimental product testing approaches and standardised evaluation criteria.
- **Veterinary Department - 3R Approaches in Product Testing**
  "*The main objective of our research is focused on the* ***development of non-animal test methods*** *as an alternative to extensive animal testing in potency and safety testing of IVMPs. Further goals are* ***to refine animal tests*** *to avoid suffering of the animals and* ***to reduce the number of animals required****. …*
  A number of activities are targeted on the enhancement of strategies and methods for the testing of vaccines and biomedicines. The purpose is to sustain the standardisation of tests carried out in a number of different laboratories and to advance the implementation of alternative methods."

Role of PEI in 3R projects

Development of 3R methods (revised Ph. Eur. monograph)

- Potency tests*: Inactivated *E. rhusiopathiae* vaccines, Rabies vaccines vet, Tetanus vaccines, Inactivated Newcastle Disease vaccines
- Abnormal toxicity test (ATT) – deleted from vet Ph. Eur. Monographs, *
- ….

Ongoing 3R projects

- Development & validation of an in vitro assay for the determination of tetanus toxicity/ for the potency determination of botulinum neurotoxins.
- "VAC2VAC" – contribution in the context of the `consistency approach´, focus on Diphtheria-, Pertussis-, Tetanus- and *Leptospira* vaccines.
- Development of an alternative assay for tuberculin testing.

BSP 130 and proposed changes to monographs

Clostridia toxoid vaccines

BSP130: Validation of cell line assays for toxicity and antigenicity testing of *Clostridium septicum* vaccines

- Vero cell-based alternatives to the mouse tests currently in use for in-process quality control of *Clostridium septicum* vaccines.

Proposed changes in monograph

- Residual toxicity: immediately after detoxification by a test in suitable cell cultures (e.g. Vero cells) & deleted from tests on the final product.
- Antigen content to monitor consistency of production: by a suitable *in vitro* method such as total combining power (TCP) using Vero cells as indicators of toxicity, an ELISA or any other validated method.
- (Batch potency test & identification).
- Comparable proposals for *C. perfringens* and *C. novyi* Type B vaccines

Documents related to the use of *in vitro* methods and containing requirements and principles regarding 3Rs

European Pharmacopoeia

Ph. Eur. general chapter 5.2.14

Substitution of *in vivo* method(s) by *in vitro* method(s) for the quality control of vaccines

- Guidance to facilitate the implementation of *in vitro* methods as substitutes for existing *in vivo* methods, in cases where a typical one-to-one assay comparison is not appropriate for reasons unrelated to the suitability of one or more *in vitro* methods.
- Outlines approaches on replacement of *in vivo* potency and safety tests and describes the most important criteria *in vitro* methods would need to fulfil.
- Therefore, in order to comply with the provisions of Directive 2010/63/EU and Ph. Eur. and to secure an undisrupted supply of medicinal products to the European Market, MAHs should take all necessary actions to introduce 3Rs Ph. Eur. methods including submission of variations to marketing authorisations as appropriate.

EMA guidance

Reflection paper providing an overview of the current regulatory testing requirements for veterinary medicinal products and opportunities for implementation of the 3Rs (EMA/CHMP/CVMP/3Rs/164002/2016)

- **Example:** Different Ph. Eur. monographs for ***Clostridia* vaccines** are included for which the residual toxicity test in mice is required
- For clostridial vaccines, validation work involving the EDQM to replace the test in mice by a test in cells - ongoing work.
- BSP130: Validation of cell line assays for in-process testing of *Clostridium septicum* vaccine antigens.

EMA guidelines

Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)

- Describes the process for submission & evaluation of a proposal for regulatory acceptance of 3R testing approaches for use in the development and quality control for human & veterinary products.
- Presents scientific and technical criteria for validation of 3R testing approaches and explains the pathways for their regulatory acceptance.
- Definition of regulatory acceptance of a new 3Rs testing approach.

EMA guidance

Guidance for individual laboratories for transfer of quality control methods validated in collaborative trials with a view to implementing 3Rs
(EMA/CHMP/CVMP/3Rs/94436/2014)

- Applies to regulatory testing used for quality control of medicinal products where animals have been traditionally used.
- Aims to facilitate transfer of quality control methods validated in collaborative trials with a view to implementing the 3Rs – replace, reduce and refine – principles to testing in a product-specific context.
- By implementing methods validated through collaborative studies, various scenarios are possible and summarized.

EMA guidance

- **Recommendation to MAHs, highlighting the need to ensure compliance with 3Rs methods described in the Ph. Eur.** - applicable to all medicinal products regardless of type. (EMA/CHMP/CVMP/JEG-3Rs/252137/2012)
- **Recommendation to MAHs, highlighting recent measures in the veterinary field to promote 3Rs measures described in the Ph. Eur.** - applicable to veterinary vaccines from 01/01/2017. (EMA/CHMP/CVMP/3Rs/336802/2017)
- **Statement of the CVMP position on the ethical use of animals in the testing, development and manufacture of veterinary medicines** (EMA/CVMP/3Rs/506841/2017)

"In conclusion, it is considered incumbent on MAHs to integrate the 3Rs and ethical principles and welfare standards for the treatment of animals in all aspects for the development, manufacture and testing of veterinary medicinal products: from the sourcing of starting materials and active ingredients, through to the studies to generate safety and efficacy data and for any tests used as *in process* and final product controls for batch release of the product."

EU-Regulation 2019/6 Draft Annex 2

SECTION IIIb REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

IIIb.2D. Control tests during the manufacturing process

IIIb.2E. Control tests on the finished product

- In accordance with the provisions of Directive 2010/63/EU and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, tests shall be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm**. If available, an alternative *in vitro* test shall be used when this leads to replacement or reduction of animal use or reduction of suffering.**

How does is work in practice – view of a competent authority

How does is work in practice – view of a competent authority

- **New products - During marketing authorisation process**
  Assessment of proposed test methods → check if alternative methods are available → request to applicant to justify not using alternative methods → commitment to establish such a method post-authorisation.
- **Authorised products - post marketing authorisation**
  JEG 3Rs group: Reviewed animal tests included in product release for centrally authorised medicinal products and check compliance with current Ph. Eur. monographs. Recommended updates to release specifications, where appropriate.
  Letter to concerned MAHs and follow up.
- **Authorised products - post marketing authorisation**
  NCA contact MAHs if new alternative methods are developed and accepted. Recommend replacement of a used *in vivo* method by an alternative method

How does is work in practice – view of a competent authority

- **Development & validation of alternative methods by MAHs**
  Scientific and regulatory advice during the different steps of the establishment of a new method and replacement of the old one (e.g. presentation of interims results, exchange of data).
- **Replacement or change of established methods**
  Submission of variations according to the variation regulation and guidelines.

➡ Procedures to get advice from regulatory authorities on the possible use of new methods as well as procedures for filing variations are in place for authorised products

Examples for implementation of alternative methods

- Potency test of rabies vaccines – change from infection of mice to serological assay.
- *in vitro* antigen mass ELISA for a Rotavirus component.
- AE vaccine: replacement of the hatch of chicks and the development of clinical signs in the animals by an antigen ELISA on the embryos before hatching.
- Replacement of the animal test (in-prozess) for determination of the toxin content in *C. botulinum* Type C cultures before inactivation by botulinum-neurotoxin antigen ELISA.
- Replacement of the hamster challenge test for *Leptospira* vaccines by an antigen quantification.

Clostridia toxoid vaccines

- Publication & implementation of the revised monograph texts.
- Promote variations to replace the mouse tests currently in use for in-process quality control after development and validation of methods for a product.
- *C. septicum* vaccines: suitability of Vero cells shown, however differences can not be excluded, suitability & sensitivity have to be shown.
- *C. perfringens/C. novyi* type B vaccines: Identify suitable toxin- specific cell lines & confirm sensitivity.
- Optimisation of protocol & validation of methods – Robustness, repeatability, intermediate precision, acceptance criteria, pass/fail thresholds …
- Correlation studies.

PEI welcomes the introduction of *in vitro* alternatives into monographs & supports implementation of new methods to replace animal tests.

Thank you for listening.