EDQM WORKSHOP

EUROPEAN PHARMACOPOEIA REQUIREMENTS FOR FISH VACCINES

8 SEPTEMBER 2015

17th International Conference on ‘Diseases of Fish and Shellfish’, Las Palmas de Gran Canaria, Spain

PRESENTATIONS
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BIOGRAPHIES

Øystein Evensen

Øystein Evensen obtained his degree in Veterinary Medicine from the Norwegian School of Veterinary Science in 1984 and his PhD in pathology from the same institution in 1987. He has worked for more than 10 years after his PhD as research scientist at the Norwegian Veterinary Institute in Oslo, Norway, more than 7 years in pharmaceutical industry with development of vaccines for finfish, particularly salmon. Over the last 12 hears he has been full professor at the Norwegian University of Life Sciences, Faculty of Veterinary Medicine and Biosciences, where he heads a research group of more than 15 people, including research scientists, post docs and Phd students, and done research on viral and bacterial diseases of farmed salmon with a focus on host-pathogen interactions, mechanisms of infection and vaccine development.

Catherine Lang

Catherine Lang is a Scientific Officer in the European Pharmacopeia Department at the EDQM. She holds a master’s degree in Sciences (Biochemistry) from the University Louis Pasteur de Strasbourg (1992) and a DESS in Applied Microbiology from the Pharmaceutical University of Strasbourg (1993). After graduation, she worked for one year as a researcher in the R&D laboratory of a large food company. From 1994 to 2000, she was Head of the microbiological quality control laboratory responsible for quality control and batch release. In 2000, she worked in quality, safety and environment management for a large pharmaceutical company, and in 2001 she obtained a master’s degree in this field.

She joined the EDQM in 2001 and has a large experience at the EDQM as a Scientific Officer to the groups of experts for human blood and blood products, human and veterinary sera and vaccines, and the working parties for Botulinum toxin and homoeopathic raw materials and stocks. She is also involved in the ISO 9001 certification of the European Pharmacopoeia Department.

Céline Lorteau DVM

Dr Céline Lorteau holds a DVM (1994, Nantes, France) and followed an advanced course in aquaculture and an externship at the University of Brest (1993, France), focusing on the immune response of shellfish as biological indicator of pollution. She also holds the equivalent of a Master’s of Science degree (2001) in the area of statistics, immunology and immunopathology, virology, and molecular biology and pathology.

She is a senior assessor in the unit for immunologicals at the ANSES ANMV (French Agency for veterinary medicinal products). In addition, she served for 12 years as an expert of Group 15V of the EDQM (in charge of sera and vaccines for veterinary use) and was elected Chair of the Group 15V in 2011.
European Pharmacopoeia texts for the control of IVMPs

Mrs Catherine LANG
Scientific Officer, responsible for Group 15V
European Pharmacopoeia Department,
EDQM, Council of Europe

Agenda

❖ The European Pharmacopoeia or how to turn challenges into opportunities and successes

❖ Structure of the European Pharmacopoeia and how to use the European Pharmacopoeia
The European Pharmacopoeia

➢ Lays down common, compulsory quality standards for all medicinal products in Europe.

➢ Mandatory on the same date in 37 states (CoE) and the EU 640 millions Europeans (European Union Directives 2001/82/EC, 2001/83/EC, and 2003/63/EC, as amended, on medicines for human and veterinary use). 28 Observers (26 countries, TFDA and WHO)

➢ The Ph. Eur. is legally binding but the legislation also includes a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market.  an excellent tool to ensure that monographs are not cast in stone but routinely updated to reflect the state-of-the-art.

Relationship with European Regulators: A strength of the Ph. Eur.!

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The Ph.Eur. - one decision body ...

The Ph. Eur. Commission:

- 3 sessions per year
- 38 delegations (37 member states + EU) of up to three representatives
- All technical decisions by consensus
- Observers welcome!

... and more than 70 groups/800 experts coordinated by the European Pharmacopoeia ...
... going into one direction: The Ph. Eur. 

 ➔ A success story!

• A unique example of an efficient collaborative process:
  37 national secretaries contributing resources to this
  collaborative process rather than developing national standards
  (2 member states interested in one topic ➔ added on the Ph. Eur. work
  programme)

• Opportunities:
  • saving of resources
  • no subsequent need to harmonise national positions

• Concrete outcomes ➔ More than 2200
  monographs and 340 general chapters adopted

The Ph. Eur. network: An asset!

• 800 members in Ph. Eur. Groups
• Proposed by national secretariats from member states
• Nominated by the Ph. Eur. Commission
• With a well balanced expertise:
  ➢ Approx. 1/3 from Health Authorities
  ➢ Approx. 1/3 from Industry
  ➢ Approx. 1/3 from University, Hospital
• and the support of nearly 60 observers (from e.g. Algeria, Armenia, Australia, Belarus, Canada, Israel, Malaysia, Russian Federation, TFDA)
The European Pharmacopoeia: a transparent process

- All revised and new texts published online in Pharmeuropa (the European pharmacopoeial forum, free access) for public enquiry
- Work programme available on EDQM website
- Style guide and technical guides freely available and downloadable on EDQM website
- Knowledge database (free access) ➔ useful information
- Organisation of hearings of interested parties
The Ph. Eur. needs …

... to keep pace:

- with the regulatory needs of licensing, control and inspection authorities in the public health area,
- with technological and scientific advances,
- And with industrial constraints.

Staying “State of the Art” – a constant challenge -

Developments in Regulatory Environment

Increased demand for Generic and Biosimilar products

Scientific / technical evolutions

Need to regularly review & update and create new Ph Eur texts

Developments in Manufacture and Globalisation

New risks to Public Health

Dr Susanne Keitel ©2015 EDQM, Council of Europe. All rights reserved.
Agenda

- The European Pharmacopoeia or how to turn challenges into opportunities and successes
- Structure of the European Pharmacopoeia and how to use the European Pharmacopoeia

Ph. Eur. – General organisation

- Introduction
- General notices
- General chapters
- General monographs
- Individual monographs


- apply to all monographs and other texts of the Ph. Eur.
- instructions to understand texts, conventional expressions
- essential reading before starting to use monographs
Ph. Eur. texts (cont’d)

- Standard analytical methods
- General requirements for equipment e.g.:
  - 2.6 Biological tests
    - 2.6.1 Sterility
    - 2.6.7 Mycoplasmas
    - 2.6.8 Pyrogens
    - 2.6.24 & 2.6.25
  - 5.1 General texts on microbiology
  - etc

- Editorial convenience: avoid repeating standard methods in each monograph
- Provide standard methods that can be used where there is no monograph
- Give general requirements for equipment, equipment verification
- Not mandatory *per se*
- When referred to in a monograph, they become part of the standard

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Ph. Eur. texts

- Classes of substances, dosage forms
  - *Substances for pharmaceutical use* (2034)
  - *Pharmaceutical preparations* (2619)
  - *Vaccines for veterinary use* (0062)
  - *Immunosera for veterinary use* (0030)

- Quality aspects that cannot be dealt with in each individual monograph
- Quality aspects that are common to a class of products
- Classes defined by different criteria: production method, origin, risk factors
- General monographs apply to all substances and preparations within the scope of the DEFINITION section of the general monograph, except where a preamble limits its application

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General monographs

- General monographs are ALL mandatory and apply to ALL substances and preparations within the scope of the Definition section of the general monograph.
- No cross-reference in individual monographs: Check in the Introduction & Definition which monograph applies!

Ph. Eur. texts (cont’d)

- based on approved specification(s) backed up by batch data
- specifications for drug substance or finished products
- analytical procedures and acceptance criteria to demonstrate that the substance meets required quality standards

<table>
<thead>
<tr>
<th>General chapters</th>
<th>Individual monographs</th>
</tr>
</thead>
<tbody>
<tr>
<td>General monographs</td>
<td>Reference standards</td>
</tr>
</tbody>
</table>

DEFINITION: defines the scope of the monograph – suitable strain

PRODUCTION: safety and Immunogenicity, antimicrobial preservatives, stability.

MANUFACTURER’S TESTS: Batch potency test, inactivation test

BATCH TESTS: Identification (alternative tests may be used), Sterility/Bacteria and fungi, Potency (must comply if tested)

STORAGE & LABELLING: Items necessary for use of the monograph
Ph. Eur. reference standards

- Established specifically for use in monographs or general chapters of the Ph. Eur., as prescribed in the methods given
- **Chemical Reference Standards** (CRSs) and **Biological Reference Preparations** (BRPs)

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Ph. Eur. Group 15V
- Experts of Group 15V, under the Chairmanship of Dr. Céline Lorteau (and the former Chair Dr. Lukas Bruckner)

EDQM team
- Cathie Vielle, Head EPD and Emmanuelle Charton, Deputy Head EPD

Useful links

- **Website** [www.edqm.eu](http://www.edqm.eu) and [Ph Eur training sessions](http://www.edqm.eu/ph Eur training sessions) (next on 8-9 December 2015)
- **Helpdesk** [www.edqm.eu/hd](http://www.edqm.eu/hd) and [Readers’ tribune](http://publications.info@edqm.eu)
- **Pharneuropa online** [http://pharmeuropa.edqm.eu](http://pharmeuropa.edqm.eu) (set notification for Group 15V)
Thank you for your attention

European Directorate for the Quality of Medicines & HealthCare (EDQM)
The Ph.Eur. : general texts and specific monographs for fish vaccines
08/09/2015

Céline Lorteau
DVM - French Agency for Veterinary Medicinal Products
Chair Group 15V Ph. Eur.

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CONCLUSION
PH. EUR. TEXTS APPLICABLE TO FISH VACCINES (1/4)

General texts

General monograph

0062: vaccines for veterinary use

Gives the general rules applicable to all the vet. vaccines including fish vaccines:

- Quality of the starting materials
- Production of the antigen in a seed lot system
- Inactivation process and control
- How to perform the developmental safety and efficacy tests
- ...

PH. EUR. TEXTS APPLICABLE TO FISH VACCINES (2/4)

General texts

General chapters

to avoid repetitions of general rules broadly applicable

- 2.6.1: Sterility
- 5.1.1: Methods of preparation of sterile products
- 5.1.3: Efficacy of antimicrobial preservation
- 5.2.5: Substances of animal origin for the production of vaccines for veterinary use
- 5.2.6: Evaluation of safety of vet. vaccines and immunosera
- 5.2.7: Evaluation of efficacy of vet. vaccines and immunosera
Specific monographs

FURUNCULOSIS VACCINE (INACTIVATED, OIL-ADJUVANTED, INJECTABLE) FOR SALMONIDS – 1521

VIBRIOSIS (COLD-WATER) VACCINE (INACTIVATED) FOR SALMONIDS – 1580

VIBRIOSIS VACCINE (INACTIVATED) FOR SALMONIDS – 1581

YERSINIOSIS VACCINE (INACTIVATED) FOR SALMONIDS - 1950

Specific monographs

Provide specific information:

• Target species, vaccine strains…
• The minimum level of protection (potency/immunogenicity)
• Batch potency testing
• Any specific test, i.e. safety characteristics of live vaccine strains
• …
**How to use the Eur.Ph.?**

1- Read the General Notices  
2 – Read the general monograph  
3 – Read the specific monograph  

Applying at the same time the general chapters cited in the monographs

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### COMPLEX INTERACTIONS BETWEEN TEXTS (1/2)

**GENERAL NOTICES**

Guide for the elaboration and use of the monographs (2009)

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### COMPLEX INTERACTIONS BETWEEN TEXTS (2/2)

- General chapters
- General monograph
- Specific monograph

Guide for the elaboration and use of the monographs (2009)
EXAMPLE (1/2)

VIBRISOSIS VACCINE (INACTIVATED) FOR SALMONIDS

Vaccinum vibrivosis inactiitum ad salmonidos

1. DETECTION

Vibrivosis vaccine (inactivated) for salmonids is prepared from cultures of one or more suitable strains or varieties of Lactobacillus angulatus (L. vibriosis), inactivated while maintaining adequate immunogenic properties.

2. PRODUCTION

2.1. PREPARATION OF THE VACCINE

The vaccine is prepared by the mixed culture method, and is usually produced in a biological laboratory. The vaccine is administered to the fish in a manner specified by the manufacturer.

2.2. STABILITY

The vaccine is stable at 4°C and should be stored at this temperature until use. The shelf life of the vaccine is at least 12 months from the date of manufacture.

2.3. IMMUNOREACTIVITY

Carry out a separate test for each fish species and each vaccine included in the vaccine, according to a protocol defining water source, water flow and temperature limits, and period of observation.

EXAMPLE (2/2)

3.2.2. IMMUNOREACTIVITY

Carry out a separate test for each fish species and each vaccine included in the vaccine, according to a protocol defining water source, water flow and temperature limits, and period of observation.

4. LABELING

The label states information on the fish needed for the development of immunity after vaccination under the conditions corresponding to the recommended use.
VIBRIOSIS - SCOPE

1. DEFINITION

Gives the scope (target species, route, effect…)

Vibriosis vaccine (inactivated) for salmonids is prepared from cultures of one or more suitable strains or serovars of Listonella anguillarum (Vibrio anguillarum), inactivated while maintaining adequate immunogenic properties; the vaccine may also include Vibrio ordalii. This monograph applies to vaccines intended for administration by injection or immersion for the active immunisation of salmonids against vibriosis.

VIBRIOSIS – PRODUCTION (EXTRACTS)

2. PRODUCTION
2-1. PREPARATION OF THE VACCINE

Gives some particulars regarding production:

The strains of L. anguillarum and V. ordalii are cultured and harvested separately. The harvests are inactivated by a suitable method. They may be purified and concentrated. Whole or disrupted cells may be used and the vaccine may contain extracellular products of the bacterium released into the growth medium.

Beside this, the general monograph 0062 & chapters 5.2.2, 5.2.4, 5.2.5… provide details on:
- Seed material (production and testing)
- Quality of starting materials
- Inactivation process
- …
2. PRODUCTION
2-1. PREPARATION OF THE VACCINE
2-1-3. Seed lots
2-1-3-1. Bacterial seed lots

2-1-3-1-1. General requirements. The genus and species (and varieties where appropriate) of the bacteria used in the vaccine are stated. Bacteria used in manufacture are handled in a seed-lot system wherever possible. Each master seed lot is tested as described below. A record of the origin, date of isolation, passage history (including purification and characterisation procedures) and storage conditions is maintained for each master seed lot. Each master seed lot is assigned a specific code for identification purposes.

2-1-3-1-2. Propagation. The minimum and maximum number of subcultures of each master seed lot prior to the production stage are specified. The methods used for the preparation of seed cultures, preparation of suspensions for seeding, techniques for inoculation of seeds, titre and concentration of inocula and the media used, are documented. It shall be demonstrated that the characteristics of the seed material (for example, dissociation or antigenicity) are not changed by these subcultures. The conditions under which each seed lot is stored are documented.

2-1-3-1-3. Identity and purity. Each master seed lot is shown to contain only the species and strain of bacterium stated. A brief description of the method of identifying each strain by biochemical, serological and morphological characteristics and distinguishing it as far as possible from related strains is recorded, as is also the method of determining the purity of the strain. If the master seed lot is shown to contain living organisms of any kind other than the species and strain stated, then it is unsuitable for vaccine production.

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2-1-3-1-1. General requirements. The **genus** and **species** (and varieties where appropriate) of the bacteria used in the vaccine are stated. Bacteria used in manufacture are handled in a **seed-lot system** wherever possible. Each master seed lot is tested as described below. A record of the **origin**, **date of isolation**, **passage history** (including purification and characterisation procedures) and **storage** conditions is maintained for each master seed lot. Each master seed lot is assigned a **specific code for identification** purposes.
### MONOGRAPH 0062 – PRODUCTION (3/3)

#### 2-1-3-1-3. Identity and purity.
Each master seed lot is shown to contain only the species and strain of bacterium stated. A brief description of the method of identifying each strain by biochemical, serological and morphological characteristics and distinguishing it as far as possible from related strains is recorded, as is also the method of determining the purity of the strain. If the master seed lot is shown to contain living organisms of any kind other than the species and strain stated, then it is unsuitable for vaccine production.

### VIBROSIS – PRODUCTION (EXTRACTS)

#### 2. PRODUCTION
2-2. CHOICE OF VACCINE COMPOSITION

Gives the level of efficacy expected – part of the efficacy demonstration

2-2-2. Immunogenicity. Carry out a separate test for each fish species and each serovar included in the vaccine, […]for each route and method of administration to be recommended.

 […] Vaccinate not fewer than 30 fish according to the instructions for use. Perform mock vaccination on a control group of not fewer than 30 fish; […] Challenge each fish at a fixed interval after vaccination, corresponding to the onset of immunity claimed, by a suitable route with a sufficient quantity of cultures of L. anguillarum or V. ordalii whose virulence has been verified. Observe the fish at least daily until at least 60 per cent specific mortality is reached in the control group. […]

The test is not valid if […].

The vaccine complies with the test if the RPS is not less than 60 % for vaccines administered by immersion and 75 % for vaccines administered by injection.

Beside this, the general monograph 0062 and chapter 5.2.7. provide details on administration routes, how to demonstrate onset and duration of immunity…
VIBRIOSIS – PRODUCTION & IN-PROCESS TESTING

2. PRODUCTION

2-3. MANUFACTURER’S TESTS

2-3-1. Batch potency test. The potency test (section 3-3) may be carried out for each batch of vaccine […] When the test is not carried out, an alternative validated method based on antibody response may be used, the criteria for acceptance being set with reference to a batch of vaccine that has given satisfactory results in the test described under Potency. The following test may be used.

Use […] fish from a population that does not have specific antibodies […] Inject into each of not fewer than 25 fish 1 dose of vaccine, according to the instructions for use. Perform mock vaccination on a control group of not fewer than 10 fish. Collect blood samples at a defined time after vaccination. Determine for each sample the level of specific antibodies against L. anguillarum included in the vaccine and where applicable against V. ordalii, by a suitable immunochemical method (2.7.1). The test is not valid […] The vaccine complies with the test if the mean level of antibodies in the vaccinates is not significantly lower than that found for a batch that gave satisfactory results in the test described under Potency.

Scope of 3Rs:
- Reduction
- Refining
- Replacing

VIBRIOSIS – BATCH TESTING

3. BATCH TESTS

3-1. Identification. When injected into fish that do not have specific antibodies against L. anguillarum and, where applicable, V. ordalii, the vaccine stimulates the production of such antibodies. (under revision to avoid reference to animal test)

3-2. Bacteria and fungi. The vaccine, including where applicable the diluent supplied for reconstitution, complies with the test for sterility prescribed in the monograph Vaccines for veterinary use (0062).

3-3. Potency. The vaccine complies with the requirements of the test mentioned under Immunogenicity (section 2-2-2) when administered by a recommended route and method.

(Usually replaced by a manufacturer’s test (by serology or challenge)

Beside this, the general monograph 0062 indicates the other tests to be done for batch release of any vet vaccine, i.e. physico-chemical tests
CONCLUSION

Few monographs for fish vaccines (4)
Only for bacterial inactivated vaccines
Numerous fish used / trial
Limited knowledge & availability of *in vitro*
alternatives
Batch potency test to improve (3Rs)
Will to improve in collaboration with experts
EDQM Fish vaccines conference
Oslo 10-11 May 2016

THANK YOU FOR YOUR ATTENTION!
Towards in vitro methods for potency testing of fish vaccines

EVENSEN, Ø., LANG, C., BRADY, A.-M., LORTEAU, C

Introduction

Background and motivation for developing in vitro methods potency testing for fish vaccines
Definitions of in vitro methods
Regulations
Examples – feasibility
Way forward – next steps
Background

Fish used in experimental studies in Norway in 2014 was 5.5 million
- 4.9 million were accounted for in 3 different field experiments
- 180 000 fish used in experiments imposing pain on the animals

Use of fish for potency testing
- Classical testing methods based on vaccination and challenge
- Mortality as end-point
- Humane end-points

Alternatives
- In vitro potency studies
- In the spirit of the 3R’s

In vitro potency – some considerations

Classical approach
- Based on circulating antibodies
- Build correlation with in vivo challenge studies (during development) using dose-response studies
- Purpose – define a cut-off that separates potent from sub-potent batches as defined during development studies

Should the antibodies react with the protective antigen?
- Not necessarily as long as the method used can be sufficiently defined
- Antibodies against bacteria (and also viruses) that are important for protection against infection or disease would react with surface antigens of the bacterium – a flagellum as a typical one
- For many pathogens, the protective antigen(s) has/have not been defined
Further, antibodies typically “collaborate” with soluble components like complement and circulating cells like macrophages/phagocytes to kill/inactivate the intruder.

**In vitro** potency – additional considerations

**Species**
- Would it have to be target species?
  - Not necessarily as long as a correlation can be defined
  - There will be practical challenges with species being very small
  - And complexity of the immune system would also have to be considered (and how this can impact)
Examples

• I will present two examples related to developing in vitro methods for vaccine potency testing of furunculosis vaccines in salmon
• This shows a step-wise approach towards establishing a correlation between antibody responses and vaccine potency
Purpose of this study

- [understand] how the antibody response against *A. salmonicida* develops with time in Atlantic salmon held in different water temperatures
- to which degree it *[antibody levels]* correlates with protection following *in vivo* challenge
- optimise and standardise an antibody-based ELISA potency test procedure

- deviation from EP requirements
  - Challenge carried out by cohabitation

Materials and methods

- used two vaccine doses (Full dose (FD) and reduced dose (RD – 1/20 of FD)) + adjuvant control
- sampled serum over time (time course study); 3, 6, 9, and 12 weeks post vaccination
- challenge at 6 and 12 weeks post vaccination
Results

A.B. Rometal et al. / Biologicals 48 (2020) 67–71

6 weeks post vaccination

12 weeks post vaccination

Cumulative % mortality

Days post challenge (DPC)

Phys saline
FD vaccine
RD vaccine
AD group

ELISA analysis

A.B. Rometal et al. / Biologicals 48 (2020) 67–71
Dose - effect

- We obtained a very nice relationship between antigen dose and RPS in this experiment
- Caution should be exercised – no dose-response study as such

Conclusions

- The results show that an ELISA assay for serum antibody level against *A. salmonicida* correlates well with protection after an immunisation period of approximately 500 degree days, and this assay revealed a significant difference between a full dose
Aim

- evaluate the ability of different vaccine evaluation methods to identify sub-potent furunculosis vaccines, using ELISA as in vitro assay

- Deviation from EP: cohabitation challenge as in vivo assays but injection challenge was also included

Antibody responses correlate with antigen dose and in vivo protection for oil-adjuvanted, experimental furunculosis (Aeromonas salmonicida subsp. salmonicida) vaccines in Atlantic salmon (Salmo salar L.) and can be used for batch potency testing of vaccines

Anne Berit Romstad\textsuperscript{a,c,*}, Liv Jorun Reitan\textsuperscript{b}, Paul Midtlyng\textsuperscript{c}, Kjersti Gravningen\textsuperscript{b}, Øystein Evensen\textsuperscript{c}
Antigen/vaccine preparations

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Antigen content</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. salmonicida virulent strain</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>10%</td>
</tr>
<tr>
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</tr>
<tr>
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<td>200%</td>
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<tr>
<td>A. salmonicida avirulent strain</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Saline control</td>
<td>0%</td>
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</tbody>
</table>

Fine-tuned the antigen dosage – dose-effect study

Results

<table>
<thead>
<tr>
<th>Antigen content</th>
<th>Intra peritoneal challenge</th>
<th>Cohabitation challenge</th>
<th>ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CM%</td>
<td>RPShod</td>
<td>RPShod</td>
</tr>
<tr>
<td>0%</td>
<td>87.5</td>
<td>29.1</td>
<td>3.4</td>
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<td>2%</td>
<td>50.0</td>
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<td>200%</td>
<td>0</td>
<td>100.0</td>
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</tr>
<tr>
<td>A. salmonicida</td>
<td>0%</td>
<td>54.8</td>
<td>17.2</td>
</tr>
<tr>
<td>A-layer</td>
<td>100%</td>
<td>58.2</td>
<td>24.1</td>
</tr>
<tr>
<td>Control</td>
<td>0%</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Antigen content and challenge results

In (A) we see that vaccines with antigen content as low as 5% of standard will come out as potent using RPS60 evaluation. In (B) we see that only vaccines with 40% of standard ag content will pass (RPS>80).

Antigen content and ELISA (OD)
OD relative to antigen and potency

- Here the OD ELISA values have been plotted against antigen content and at the same time result from potency test – endpoint mortality by injection challenge
- As seen – OD values above 0.6 is found for potent vaccines, i.e. vaccines that meet the RPS>80 criterion

Conclusions

- The results indicate that there is a close correlation between the antigen dose and the antibody response against Aeromonas salmonicida as measured by ELISA.
- There is also a close correlation between the antibody response and protection for both i.p. and cohabitation challenge models
- The ELISA method identified sub-potent batches not identified when using an RPS60 assessment protocol
- In vitro methods based on antibody responses for furunculosis vaccines potency testing carry potential as a batch release method considering 3R’s principles and animal welfare
Additional – back-ups given questions about challenge models etc.
Antibody response relative to time post vaccination

Correlation between antigen content and RPS

Fig. 2. Relative Percent Survival (RPS) calculated for the different vaccines and challenge methods versus % antigen content in A. salmonicida vaccines: (1) Oral challenge; (2) intraperitoneal challenge at 60% control mortality, and (3) intraperitoneal challenge at end of the trial. Challenge 9 weeks post vaccination (750 days). N = 32 per group. Relative Percentage survival (RPS) calculated across parallel trials according to Amund (1981).
EDQM / European Pharmacopoeia: Assuring the quality of medicines

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Introduction

The Council of Europe is one of the oldest international organisations dedicated to fostering co-operation in Europe, through the promotion of human rights, democracy and rule of law. It was founded in 1949 and has 47 member states. The European Directorate for the Quality of Medicines and HealthCare (EDQM) is a Directorate of the Council of Europe that traces its origins and statutes to an international treaty enabling an international cooperation for the elaboration of a common pharmacopoeia in Europe. This poster focuses on the work and different activities of the EDQM / European Pharmacopoeia (Ph. Eur.).

The EDQM’s Mission: Protecting public health

The mission of the EDQM is to contribute to the basic human right of access to good quality medicines and healthcare and to promote and protect human and animal health by:

- establishing and providing official standards which apply to the manufacture and quality control of medicines in all signatory States of the Convention on the Elaboration of a European Pharmacopoeia (OMCL) and beyond;
- ensuring the application of these official standards to substances used in the production of medicines;
- co-ordinating a network of Official Medicines Control Laboratories (OMCL) to collaborate and share expertise among Member States and to use limited resources effectively;
- proposing ethical, safety and quality standards:
  - for the collection, preparation, storage, distribution and appropriate use of blood components in blood transfusion;
  - for the transplantation of organs, tissues and cells;
- collaborating with national, European and international organisations in efforts to combat counterfeiting of medical products and similar crimes;
- providing policies and model approaches for the safe use of medicines in Europe, including guidelines on pharmaceutical care; and
- establishing standards and coordinating controls for cosmetics and food packaging.

EDQM Reference Standards

The EDQM supplies chemical reference substances (CRS) and biological reference preparations (BRP) as well as reference spectra for the tests and assays to be carried out in accordance with the official methods prescribed in the European Pharmacopoeia.

Working with the EDQM – your opinion counts!

Give us your feedback and contribute to the work of the EDQM by:

- Participating in public enquiries on draft texts published in PHARMEUROPA.
- Register for free access: pharmeuropa.edqm.eu/home
- Joining a GROUP OF EXPERTS to the European Pharmacopoeia
- Contributing an article to PHARMEUROPA via the Readers’ Tribune

Interested in joining a European Pharmacopoeia Group of Experts?

If yes, contact your national authority for more information.

OMCL Network - Market surveillance

In 1994, the Commission of the European Union and the Council of Europe created a Network of Official Medicines Control Laboratories (OMCL) to measure the quality of commercialised medicinal products for human and veterinary use.

Key Fact & Figures

- The EDQM publishes a new edition of the Ph. Eur. every three years, both in English and French – the official languages of the Council of Europe.
- The current 8th Edition contains over 2200 monographs and 350 other tests – mostly covering excipients and active pharmaceutical ingredients.
- The Ph. Eur. Commission adopts on average 200 texts per year.
- More than 70 expert groups and 800 European experts, from all the member states, participate in the work of the Ph. Eur.
- Over 2600 reference standards of chemical, biological or herbal origin are available in the Ph. Eur. Catalogue.
- More than 3800 valid CEPs have been granted by the EDQM.
- In 2014, the EDQM carried out 34 site inspections – located mainly in Asia - with the participation of inspectors from national supervisory authorities.
- Certification of Suitability to the Ph. Eur. Monographs (CEP): The Certification Procedure is based on the assessment of quality dossiers provided by manufacturers on the manufacturing processes and quality control tests of their active pharmaceutical ingredient or excipient. Certification indicates that the Ph. Eur. monograph(s) suitably control the quality of this substance. In addition, the EDQM carries out inspections of manufacturing and/or distribution sites of substances covered by Certificates of Suitability (CEPs), to ensure that Good Manufacturing Practices (GMPs) are enforced and the information supplied under the Certification Procedure is accurate.
- What are the advantages of a CEP?
  - Centralised and harmonised assessment by the EDQM.
  - Recognised in all Ph. Eur. Convention member States and many non-European countries.
  - Saves time and resources for all stakeholders, manufacturers and authorities.
  - Facilitates management of applications for marketing authorisation applications (MAA) and variations for medicinal products.
- A CEP simplifies marketing authorisation applications for regulatory authorities and the industry.

Products & Services: Order our publications and reference standards online via: edqm.eu/store

References

5. Reference Standards Database: http://rsv.edqm.eu/