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BIOLOGICAL REFERENCE STANDARDS FOR MULTIVALENT VACCINES QUALIFICATION STRATEGIES AND CHALLENGES FROM A NATIONAL CONTROL LAB PERSPECTIVE

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Legal Framework

Council Directive 2001/83/EC, amended by Directive 2004/27/EC, formerly Council Directives 89/342/EEC and 89/381/EEC.

Article 114 of the codified Directive relating to medicinal products for human use, allows but does not require a Member State laboratory to test a batch of an immunological medicinal product or a medicinal product derived from human blood or plasma before it can be marketed.

In Europe, 100% of the batches are tested by an Official Medicines Control Lab before being marketed (roughly 1250 batches per year in our lab).

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Biological Reference Standards for multi-valent vaccines

Biological Reference Materials

Potency testing:

- **biological reference vaccines** *(in vivo* and *in vitro)*
- **biological reference standards** *(in vitro*)

Validity of assay:

- **biological controls** *(in vitro)*

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Biological Reference Standards for multi-valent vaccines

Some compendial reference standards are available through EDQM / WHO:

- Reference vaccines: BRP3 (Tetanus), BRP4 (Diphtheria) for challenge tests
- Reference standard: Bordetella pertussis mouse antiserum BRP batch 2 for serology tests on mice

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Biological Reference Standards for multi-valent vaccines

Manufacturers prefer in-house reference standards for the following reasons:

- homologous reference
- representative of own production
- easier to manage (supply, qualification, bridging schedule)

But mandatory to qualify in-house reference standard *versus* the International reference standards and to monitor consistency of results overtime

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Biological Reference Standards for multi-valent vaccines

From the OMCL point of view:

Compendial reference standards are:

- easier to manage (single bridging study)
- products from different manufacturers can be analysed in the same run, with reduced use of animals
- International standards are qualified through collaborative studies (EDQM / WHO)
- Same units for each user

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Biological Reference Standards for multi-valent vaccines

From the OMCL point of view: (cont')

Non-compendial reference standards:

- one reference vaccine for each product (e.g. aP)
- increased use of animals for routine tests and bridging studies
- Subject to more variability (lack of qualification by collaborative studies)
- no comparability between manufacturers (different units)
- Less assured continued availability

Biological Reference Standards and Bridging Studies

- A **switch** from one reference standard to another may lead to a **shift** in the results obtained, therefore bridging study is required
- In any bridging study, **influences** due to other factors (e.g. assay reagents or materials) should be evaluated
- Changes of reference material should be **anticipated** in order to facilitate qualification and **continuity** of routine testing results from an OMCL perspective

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Biological Reference Standards

- For the **bridging of controls,** the data obtained (e.g. mean, coefficient of variation) are evaluated (control chart) to keep previous **limits** of acceptability or **define new limits**
- Apply **manufacturer's control limits** in the OMCL control charts e.g. if the **same method** is used and no indication of **systematic** differences at the OMCL

Refer to :

- https://www.edqm.eu/sites/default/files/omcl-handling-and-use-noncompendial_reference_standards.pdf for further guidance (OMCL guidelines)

- Recommendations for the preparation, characterization and establishment of international and other biological reference standards (WHO TRS 932, 2006)

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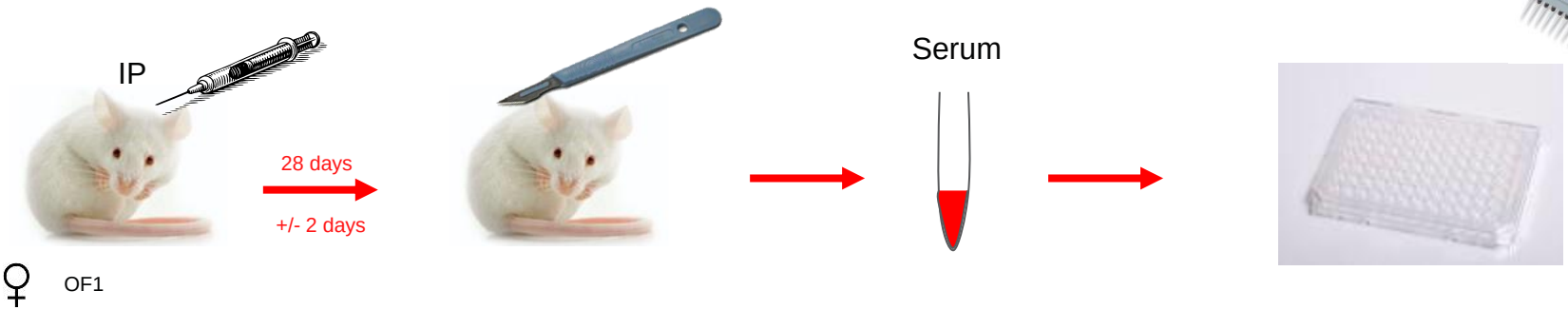
Acellular pertussis test design: SEROLOGY

Immunization | Bleeding | Centrifugation | ELISA



1 dilutions of vaccine and **reference** - 10 animals / dilution
Negative mice - 5 animals

Calculations: based on geometric mean of 10 values then Relative potency or no significant difference between vaccine and reference vaccine

The **first reference vaccine** is usually a lot used in clinical trials.
The bridging of the reference vaccine is thus of high importance !

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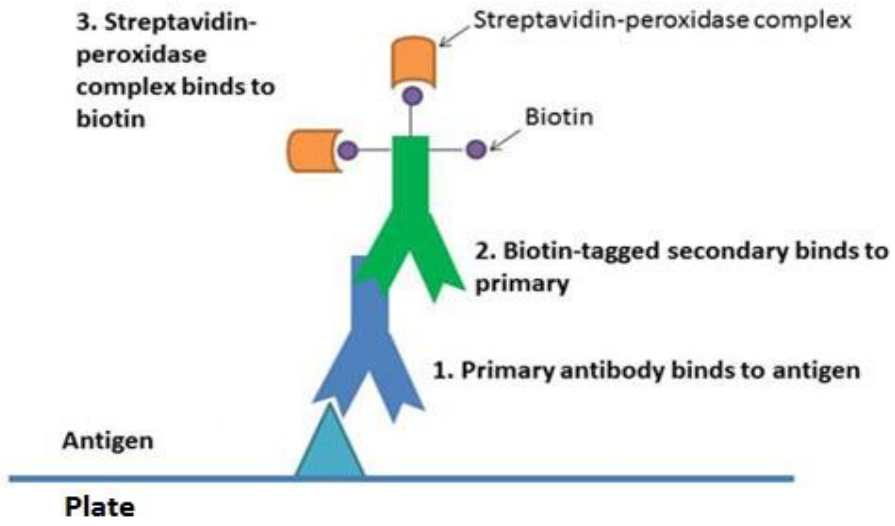
(*) Ph.Eur: 2.7.16. Assay of acellular pertussis vaccine

Biological Reference Standards

ELISA Pertussis Immunogenicity Testing



A few words about the ELISA test. First , antigens are coated on the plate. Then the primary antibody from mouse serum binds to the coated antigen. The test uses then secondary biotin-tagged antibodies. The detection is amplified with streptavidin-peroxidase complex which strongly binds to the biotin. The peroxidase can then converts the substrate which shows a colour change depending on antibody concentration.

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Biological Reference Standards

Biological standards are often used to **ensure traceability** to the **first clinical lot**

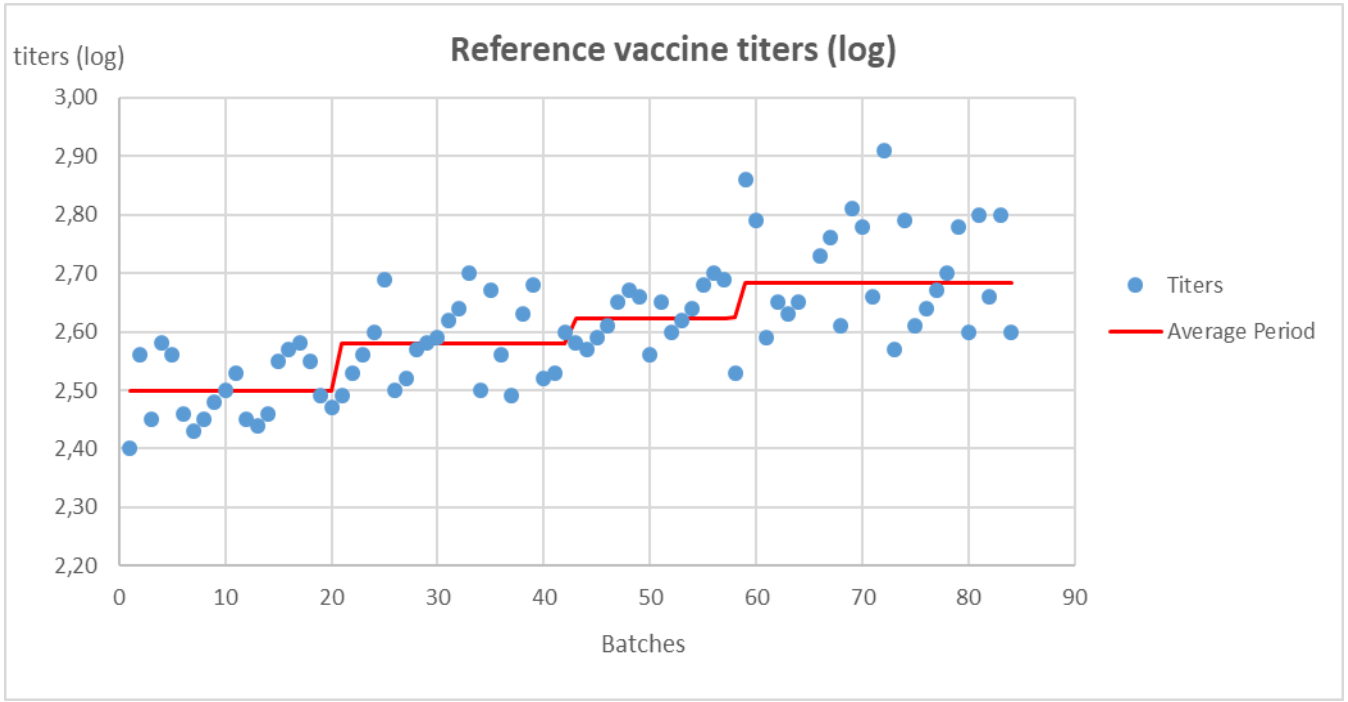
Potential strategies:

- Bridging study *versus* primary
- Successive bridging studies to align test results over time (with or without determination of **correction factors**)

Biological Reference Standards

Case study

How to handle such a case?: upward drift from the manufacturer's point of view but no drift for the OMCL



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Biological Reference Standards

It is **strongly recommended** to communicate in an appropriate and timely manner with the manufacturer to avoid shortage of reagents and materials and facilitate smooth performance of bridging studies

New Manufacturer Reference (shelf-life 3-5 years)

Bridging and lifetime use within OMCL

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Biological Reference Standards

New Manufacturer Reference (shelf-life 3-5 years)

Bridging and lifetime use within OMCL

Risks:

- due to gaps (i.e. time and stability trends), the results between OMCL and manufacturer may be significantly different
- increased workload, due to lack of time/material to qualify new reference

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Biological Reference Standards: Future challenges for an OMCL

- Serology assays with multiplex technology (Luminex®, Meso-Scale®,…): implies increase use of in-house standards and related workload
- Use of GMU specification instead of the use of a reference vaccine should limit the complexity of bridging studies
- Move from *in vivo test* to *in vitro test* (3R's regulation, Vac2Vac IMI project): should limit use of animals, testing variability and discrepant results between manufacturers and OMCLs but will increase the need to select and qualify new international or in-house standards

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Biological Reference Standards: Future challenges for an OMCL

- More complex vaccines (2 to 5 components for pertussis, 15-valent pneumococcal vaccines need a reference standard and biological control for total polysaccharide content, free polysaccharide content !)
- Different testing procedures and specifications between OMCL and manufacturers

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