The target animal batch safety test: a non suitable tool to demonstrate the safety of veterinary vaccines

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Veterinary Vaccines (Ph.Eur.)

- 1. DEFINITION

  … vaccine (live) is a preparation of *a/one or more* suitable strains of [virus]. This monograph applies to vaccines intended for the *active immunisation* of [animals] *and/or for passive protection of their progeny against [disease] caused by* [*virus*].

- 2. PRODUCTION
  - 2-1. PREPARATION OF THE VACCINE

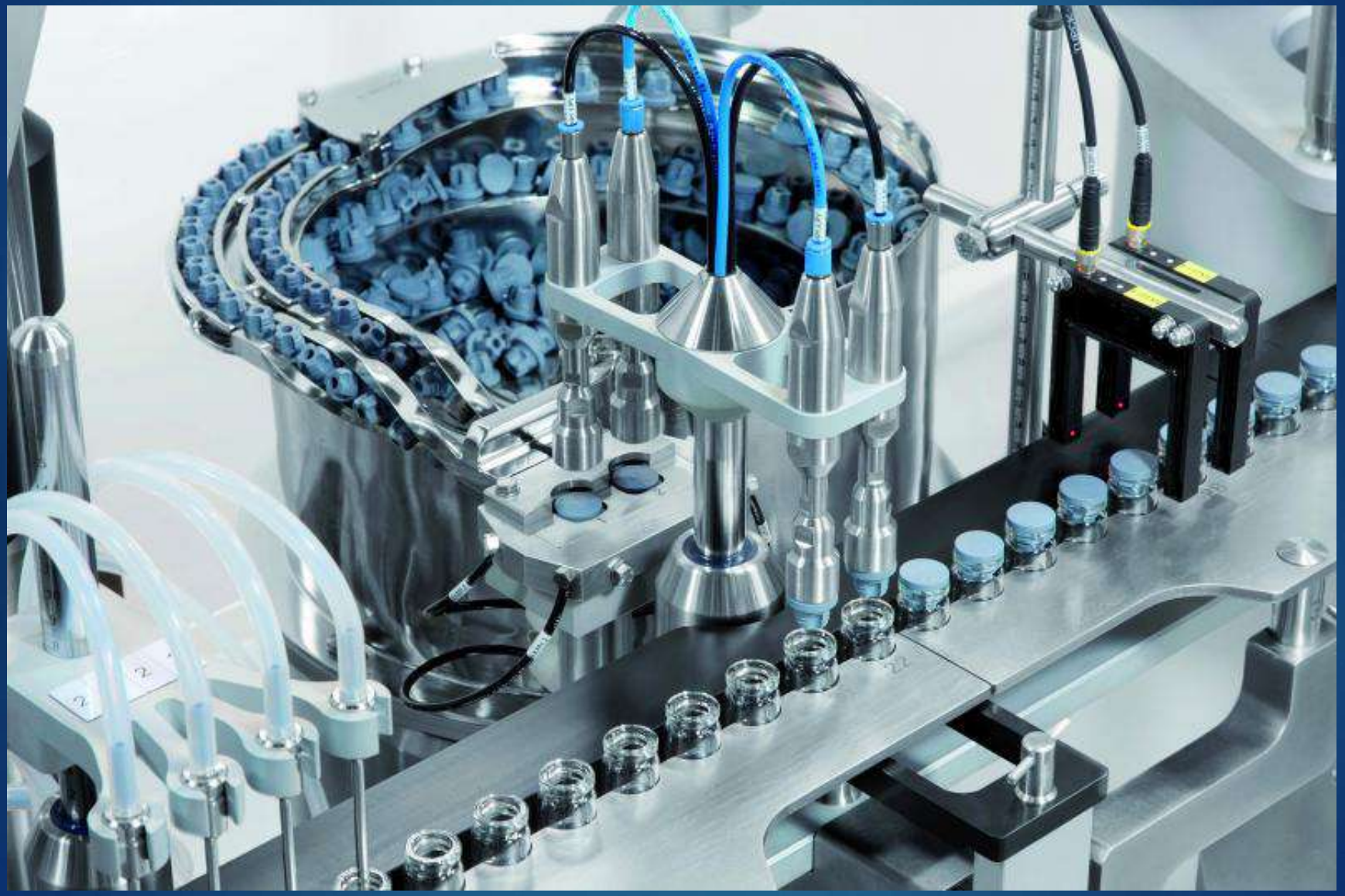
    The vaccine virus is grown *in embryonated hens' eggs or in cell culture*. ...*The vaccine may be adjuvanted*.

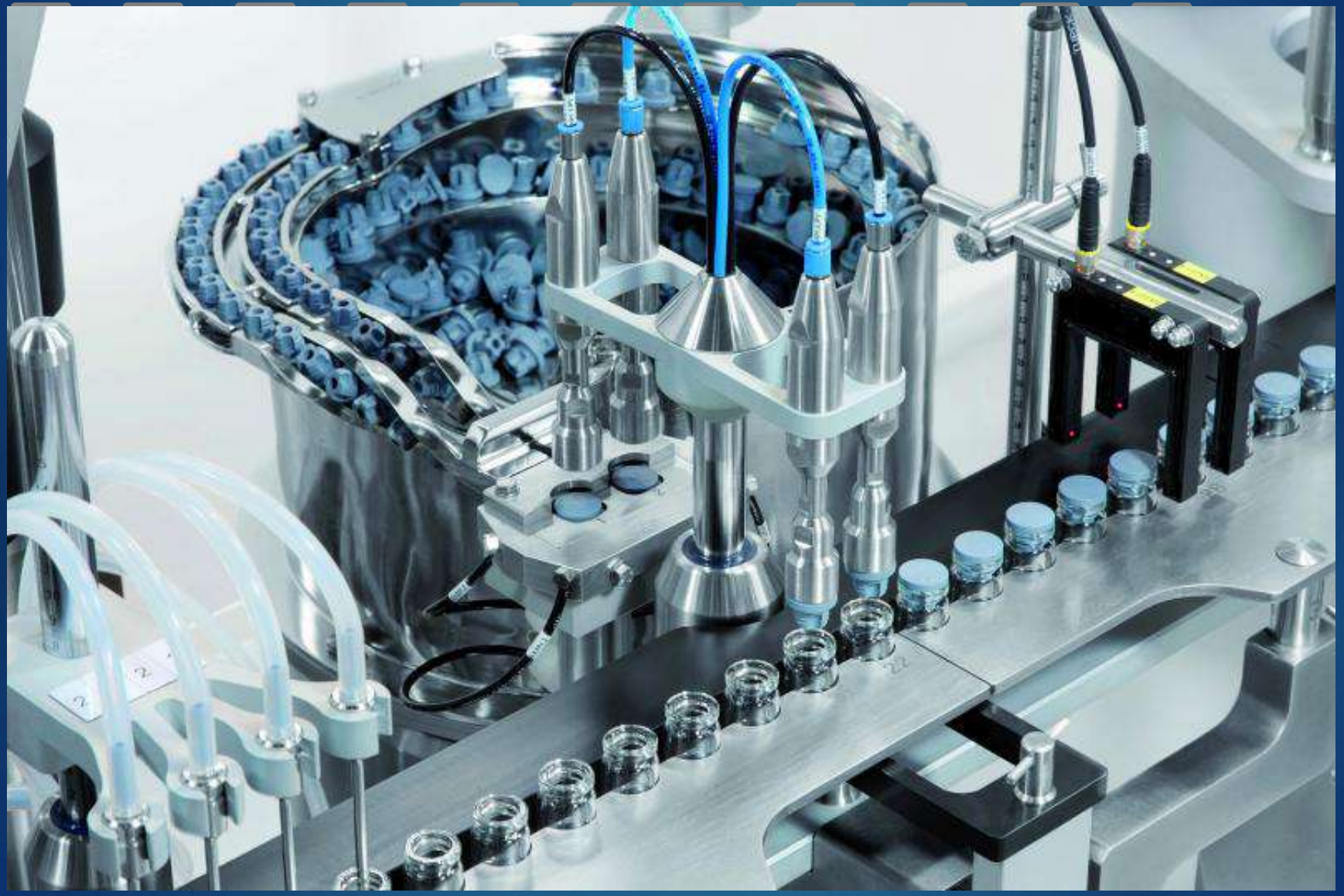
  …
  - 2-4. CHOICE OF THE VACCINE VIRUS

    The vaccine virus is shown to be satisfactory with respect to safety (*5.2.6*) and efficacy (*5.2.7*) for the [animals] for which it is intended.

Production in large fermenters

Filling in Vials





Ph.Eur. until **2013**

3. BATCH TESTS

- 3-1. Identification
- 3-2. Formaldehyde
- 3-3. Phenol
- 3-4. Sterility
- 3-5. Extraneous agents
- 3-6. Mycoplasmas
- 3-7. **Safety**
- 3-8. Potency

3-7. Safety

In general, 2 doses of an inactivated vaccine and/or 10 doses of a live vaccine are injected by a recommended route. It may be necessary to reduce the prescribed number ….. The animals are observed for the longest period stated in the monographs.

No abnormal local or systemic reaction occurs.

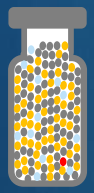
…

During development studies, the type and degree of reactions expected with the vaccine are defined in the light of safety testing. This definition is then used as part of the operating procedure for the batch safety test to evaluate acceptable and unacceptable reactions.

The immune status of animals to be used for the safety test is specified in the individual monograph…

Safety Test, critical issues

- Low concentration of harmful contaminant: Outcome is depending on sampling



- Positive Result

- False Negative Result

Safety Test, critical issues

- Immune status of test animals

  Antibodies against harmful contaminant may lead to **false** negative result

    Live IBR vaccine, contaminated with BVD-2 virus in the mid nineties

- General condition of the test animals
  e.g. subclinical infection may lead to a false positive result

The Ph. Eur. Approach

PHARMEUROPA Vol. 23, No. 1, January 2011

Target animal batch safety test (formerly section 3-7).

As a consequence of the harmonisation with VICH Guidelines 41 and 44 regarding the safety test, and since the results obtained with this test are used to assess the results obtained with the target animal batch safety test (TABST), it was decided to revise the TABST for consistency. Since the TABST was considered inappropriate to detect real defects of a vaccine, it was proposed to delete it for inactivated vaccines as an initial step. Since there was no reason to have a different approach for inactivated and live vaccines, it was decided to delete the TABST for live vaccines too. …

VICH GL 44 (TARGET ANIMAL SAFETY)

July 2008

2.1. Laboratory Safety Tests

2.1.1. Overdose Test for Live Vaccines

For live vaccines shown to retain residual pathogenicity by induction of disease specific signs or lesions, overdose testing of the live vaccine component should be conducted as part of the risk analyses for the acceptability of the micro-organism as vaccine strain. ... A 10X dose based on the maximum release titer for which the application is submitted shall be administered. ...

Generally 8 animals per group should be used unless otherwise justified. ...

In general other vaccines do not require overdose testing.

Dilemma of the Ph. Eur.

- VICH Guideline 44 did no longer foresee overdose testing for safety testing for inactivated vaccine
- Overdose testing for safety is used in Ph.Eur. to establish the type and degree of reactions expected with the vaccine are defined in the light of safety testing.

3-7. Safety

In general, 2 doses of an inactivated vaccine and/or 10 doses of a live vaccine are injected by a recommended route. It may be necessary to reduce the prescribed number ….. The animals are observed for the longest period stated in the monographs.

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During development studies, the type and degree of reactions expected with the vaccine are defined in the light of safety testing. This definition is then used as part of the operating procedure for the batch safety test to evaluate acceptable and unacceptable reactions.

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Dilemma of the Ph. Eur.

- VICH Guideline 44 did no longer foresee overdose testing for safety testing for inactivated vaccine
- Overdose testing for safety is used in Ph.Eur. to establish the type and degree of reactions expected with the vaccine are defined in the light of safety testing. *This definition is then used as part of the operating procedure for the batch safety test to evaluate acceptable and unacceptable reactions.*

Basis to evaluate results in batch safety testing got lost

Further arguments to waive the target animal batch safety test

- Strict application of the seed-lot system
  - Master seed virus
  - Master cell seed
- Extensive testing of starting materials
  - Master seeds
  - Any substance used for production
    - biological substances
      - Bovine serum
      - …
- Implementation of Good Manufacturing Procedures (GMP)
  - Standard Operating Procedures
  - Control of Equipment, Production facilities
  - …

Conclusions Ph.Eur. Expert group 15V
(veterinary vaccines and sera)

Target Animal Batch Safety Test

- Does not contribute to the safety of batches of veterinary vaccines
- Has no added value for veterinary vaccines

Ph. Eur. SUPPLEMENT 7.7 (2013)

Target-animal batch safety test (section 3-7)

As a consequence of implementation of VICH Guidelines 41 and 44, the TABST has been deleted for all veterinary vaccines. This goes a step further than the option, available since 2004, of waiving the use of the TABST for established vaccines. The section explaining the immune status of animals to be used in the safety tests has been moved to general chapter *5.2.6.*

The O.I.E. approach

Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2018

2.3.4 Minimum Requirements for the Production and Quality Control of Vaccines

2.4.1.2 Batch or Serial Safety Test

Safety tests are not required by many regulatory authorities for the release of each batch or serial where the seed-lot system is used. Other regulatory authorities may allow waiving of target animal batch safety tests in line with VICH GL50 and 55.

Thank you for your attention