

Vaccines for veterinary use (Supplement 7.7)

Harmonisation with VICH Guidelines 41 and 44 and deletion of the TABST, adopted at the 142nd Session of the European Pharmacopoeia Commission (April 2012)

What has changed and why

Following their publication in Pharmeuropa 23.1, around 80 vaccine-specific monographs, the general monograph *Vaccines for veterinary use (0062)* and 2 general chapters (5.2.6. *Evaluation of safety of veterinary vaccines and immunosera* and 5.2.9. *Evaluation of safety of each batch of immunosera for veterinary use*) were adopted at the 142nd Session of the European Pharmacopoeia (Ph. Eur.) Commission and published in Supplement 7.7. The main improvements were:

- a new format for the monographs to avoid unnecessary repetitions;
- harmonisation with VICH Guidelines 41 (test for reversion to virulence) and 44 (developmental safety tests), which came into force in 2008 and 2009 respectively, and, as a consequence, the deletion of the target animal batch safety test (TABST) from the Ph. Eur. (however, a statement was introduced allowing for the performance of a TABST under particular circumstances, e.g. significant changes to the manufacturing process, reports of unexpected adverse reactions observed in the field, or reports that final batches do not comply with the data initially provided during licensing).

Further to VICH harmonisation and to ensure consistency with European regulations, the Ph. Eur. harmonised all of the monographs for veterinary vaccines, including monographs for vaccines intended for species that are outside the scope of the VICH guidelines.

As a consequence, the safety tests and the tests for increased virulence performed during development of the vaccines were harmonised as described below; this will greatly reduce the number of animals used for testing.

Wherever possible, the following updates were made in accordance with VICH Guidelines 41 and 44.

- **General chapter 5.2.6. *Evaluation of safety of veterinary vaccines and immunosera* was fully revised and improved by adding general acceptance limits**, which are not repeated in each vaccine-specific monograph and which apply to all vaccines, even if there is no vaccine-specific monograph. As a consequence and to avoid unnecessary repetitions, in vaccine-specific monographs the examination of reproductive performance is no longer described unless the vaccine is intended only for breeders (e.g. *Neonatal piglet colibacillosis vaccine (inactivated) (0962)*) or the protocol/acceptance limits differ from general chapter 5.2.6 (e.g. *Feline infectious enteritis (feline panleucopenia) vaccine (live) (0251)*). This is not a lowering of requirements but a standardisation, since these tests must still be performed when the vaccine is recommended for use in, or may be used in, pregnant

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animals or laying birds, according to ► the general monograph *Vaccines for veterinary use* (0062) and as described in ◀ general chapter 5.2.6. This is the case, for example, for *Porcine actinobacillosis vaccine (inactivated)* (1360) and *Canine distemper vaccine (live)* (0448).

- **General chapter 5.2.9. Evaluation of safety of each batch of immunosera for veterinary use**, dedicated to the TABST for veterinary vaccines and immunosera, was revised so that it is only applicable to immunosera for veterinary use.
- **All the veterinary vaccine monographs were revised**, even if VICH Guidelines 41 and 44 only apply to certain species (bovine, ovine, caprine, feline, canine, porcine, equine, chickens and turkeys). Indeed, *Directive 2001/82/EC on the Community code relating to veterinary medicinal products*, which applies to all medicines and which describes the studies to be included in marketing authorisation applications, already includes some of the provisions of the guidelines. To ensure consistency between Ph. Eur. texts and with European regulations, the principles of VICH Guidelines 41 and 44 were therefore also applied to vaccines intended for species that are outside of the scope of the guidelines, but in a more flexible way and based on scientifically justified criteria (e.g. it was not considered advisable to use groups of 8 individuals for fish species).
- **The following updates were made in accordance with VICH Guideline 44 (developmental safety tests), where scientifically acceptable.**
 - For vaccines intended for use in birds older than 3 weeks and in mammals, safety tests are performed using, in general, 8 animals per group (previously the tests were usually performed using 20 birds or 10 mammals). However, if the initial test is performed using 5 mammals, this number is not increased to 8.
 - For vaccines intended for use in birds younger than 3 weeks, the safety tests are performed using, in general, 10 animals per group (previously the tests were usually performed using 20 birds). This deviates from VICH Guideline 44, but allows the retention of an acceptance limit of 10 per cent of non-specific mortality known to occur in young birds, and is scientifically justified.
 - The observation period is 14 days after vaccination (previously it was 14 or 21 days).
 - Overdose testing is only required for live vaccines. A single route of vaccination may be tested.
 - For repeated dose testing, a single route of vaccination may be tested.
 - For the examination of reproductive performance, a test is carried out when the vaccine is recommended for use in, or may be used in, pregnant animals or laying birds. This is no longer an overdose test, but a test performed according to the vaccination schedule. A standard protocol has been added to general chapter 5.2.6 as an example. A single route of vaccination may be tested.
- **The following updates were made in accordance with VICH Guideline 41 (test for increased virulence), where scientifically acceptable.**
 - First administration is carried out using the master seed lot (previously 'the least attenuated passage').
 - 4 passages are required instead of 5.

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- If the micro-organism has not recovered from any intermediate *in vivo* passage, the passage is repeated, but in 10 animals (previously the entire test was repeated).
- A minimum of 2 mammals or 5 birds are used for the first 4 groups, and of 8 mammals or 10 birds for the last group.
- For the final evaluation, the need for a control group (a group receiving the initial inoculum at the same time as the last group) has been deleted and comparison is now made with the reactions of animals used in another existing test (safety of a single dose). If there is an indication of an increase in virulence, an additional test is carried out to characterise better this increase. This test includes 2 groups of 8 mammals or 10 birds, with 1 group receiving the initial inoculum and the other group, for comparison, receiving the micro-organism re-isolated from the last passage.

As a consequence:

- **The target animal batch safety test (TABST) has been deleted for all veterinary vaccines.** In the interest of the 3Rs, the Ph. Eur. Commission also adopted the deletion of the TABST from the Ph. Eur. for all veterinary vaccines. The deletion of the TABST goes a step further than the option, available since 2004, of waiving the use of the TABST for established vaccines.

This test was an overdose test using either 2 mammals or 10 birds, performed on each batch of vaccine to ensure that it was safe. For live vaccines, this was an overdose test using 10 doses of vaccine. Under such tests, no animal should show notable signs of disease or die from causes attributable to the vaccine during the observation period. The same applied to inactivated vaccines, but using 2 doses of vaccines, with acceptance limits that were set based on a developmental overdose test. Since this test was no longer requested by VICH Guideline 44 and had been deleted from the monographs, the need for revision and even the relevance of the TABST were questioned, taking into account a number of parameters (e.g. poor sensitivity despite using numerous animals each year, very limited number of batches failing this test, observation of field safety issues with batches compliant with the TABST). In the context of the 3Rs and of the new *Directive 2010/63/EU on the protection of animals used for scientific purposes*, it was particularly justified to question the use of the TABST. Taking into account new developments (e.g. general improvements in the manufacturing process of veterinary vaccines in recent decades, introduction of new requirements regarding in-process testing and controls on the starting materials), the risk/benefit balance no longer supported retaining such a test for routine batch release and it was therefore decided to delete it. This would also greatly reduce the number of animals used for the control of veterinary vaccines, while maintaining the same level of safety for all veterinary vaccines.

There are, however, 3 exceptions to this general rule: *Porcine actinobacillosis vaccine (inactivated) (1360)*, *Porcine progressive atrophic rhinitis vaccine (inactivated) (1361)* and *Tetanus vaccine for veterinary use (0697)*, for which the former TABST with 2 doses of vaccines was kept because there was an inherent batch-dependent safety risk. The name of the test has been changed to 'Residual toxicity test' to avoid any misunderstanding.

- **A new statement on 'particular circumstances' has been introduced in the Ph. Eur.** The deletion of the TABST from the Ph. Eur. was agreed provided that a statement, to cover the need to perform, on an *ad-hoc* basis, further testing and in particular safety tests, was

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introduced in the general monograph *Vaccines for veterinary use (0062)*. In the context of the 3Rs and of the new *Directive 2010/63/EU on the protection of animals used for scientific purposes*, this statement would facilitate the investigation and performance of any necessary additional tests without having to wait unnecessarily long to obtain the authorisation to do so.

The following modifications were also introduced.

- In the general monograph *Vaccines for veterinary use (0062)*, it was clarified that the relaxation of the requirement of sterility for non-parenteral avian vaccines (administered orally or by spray) only made sense when the vaccine was produced in eggs (and not in cell cultures for which methods exist to test and ensure sterility) and when the method for storage of the vaccine (in freeze-dried or frozen form) did not allow bacterial growth in the vaccine. This had an impact on some monographs (e.g. live avian vaccine monographs) for which the wording of the test also had to be changed.
- For vaccines intended for fish (monographs 1521, 1580, 1581, 1950), the number of fish to be used for the immunogenicity test was reduced based on experience gained over the past few years.
- The title of the extraneous agent test for inactivated viral vaccines intended for food-producing animals (in particular the porcine monographs 0744, 0963, 0965, 1360, 1943), and also for inactivated avian vaccines (monographs 0870, 0959, 0960, 1202, 1392), was changed to 'Specified extraneous agents' to clarify that only specified extraneous agents were checked.
- Monographs were amended in line with the *Guide for the elaboration of monographs on vaccines for veterinary use* (i.e. not new requirements): a 'general' developmental safety test was not always present in vaccine-specific monographs, and was therefore added. This is not a new requirement (as this test has to be carried out in accordance with ► the general monograph *Vaccines for veterinary use (0062)* and as described in ◀ general chapter 5.2.6), but a standardisation of all vaccine-specific monographs. This is the case for the *Clostridium* vaccine monographs (0360, 0361, 0362, 0363, 0364), *Rabies vaccine (inactivated) for veterinary use (0451)*, *Swine erysipelas vaccine (inactivated) (0064)*, *Newcastle disease vaccine (inactivated) (0870)*, *Avian infectious bronchitis vaccine (inactivated) (0959)*, *Avian infectious bursal disease vaccine (inactivated) (0960)*, *Egg drop syndrome '76 vaccine (inactivated) (1202)*, *Avian paramyxovirus 3 vaccine (inactivated) for turkeys (1392)* and *Mycoplasma gallisepticum vaccine (inactivated) (1942)*.

All monographs on vaccines for veterinary use have been similarly updated.

As explained in the *Technical Guide for the elaboration and use of monographs for immunological veterinary medicinal products*, any veterinary vaccine has to comply with the requirements of the general monograph *Vaccines for veterinary use (0062)*.

With regard to the demonstration of safety, since the general monograph *Vaccines for veterinary use (0062)* refers to general chapter 5.2.6. *Evaluation of safety of veterinary vaccines and immunosera*, the requirements of general chapter 5.2.6 apply to any veterinary vaccine.

Furthermore, when a given vaccine falls within the scope of a specific monograph, any additional requirements of the specific monograph also apply.

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A revised *Guide for the elaboration of monographs on vaccines for veterinary use* and a revised *Technical Guide for the elaboration and use of monographs for immunological veterinary medicinal products*, taking into account all of these modifications, are planned for publication soon.

These guides and their subsequent revisions are available to download for free from our website: <http://www.edqm.eu/en/technical-guides-589.html>.

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