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VICH Concept Paper on harmonisation of the batch safety test for immunological veterinary medicinal product

1. Background

At the 21st VICH SC meeting, the EU presented a Discussion Paper for the Harmonisation of the Target Animal Batch Safety Test (TABST) for immunological veterinary medicinal products. The SC agreed that the EU would prepare a Concept Paper for review at the next SC meeting.

2. Problem Statement

The target animal batch safety test (TABST) on final product can be considered as a general safety test. It should provide some assurance that the product will be safe in the target species even when an overdose is injected, i.e. it should reveal "abnormal local or systematic reactions" (European Pharmacopoeia) or "unfavourable reactions attributable to the biological product ..." (Title 9. United States Code of Federal Regulations).

Over the last two decades, its relevance has been questioned by representatives of regulatory authorities and vaccine manufacturers (Roberts and Lucken, 1996; Zeegers et al., 1997; Pastoret et al., 1997; Cussler et al., 2000). Particularly, as the introduction of Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) into the manufacture of vaccines has greatly increased their safety and quality.

In the EU, based on the retrospective analysis of TABST data provided by Official Medicines Control Laboratories (OMCLs) in EU Member States and vaccine manufacturers (AGAATI, 2002), it was concluded that a) the TABST is no longer relevant and should be omitted as a routine batch release test and b) in special cases, where the TABST might still be required, (e.g. for new products or for a certain period after licensing, or for vaccines which have caused serious pharmacovigilance problems), clear guidance should be given on the test design (animal number, dosage) and on the evaluation criteria (acceptable/non-acceptable local and systemic reactions, test repetitions).

In 2005, the revised European Pharmacopoeia (Ph.Eur.) general monograph on vaccines for veterinary use came into force allowing manufacturers to waive the TABST after having demonstrated consistency of production (see 3.). In addition, the CVMP issued a position paper (EMEA/CVMP/865/03/Final) for harmonising the data requirements for removing the TABST within the European Union.

Nevertheless, the TABST is still performed for routine batch release, mainly due to the lack of international harmonisation. A review document on animal welfare progress in European Pharmacopoeia Monographs states that *"... Manufacturers have concerns over liability in case of adverse reactions and since this possibility has been introduced only in Europe and not in other regions there has been reluctance to apply it on part of manufacturers who supply a vaccine in different regions"* (Castle, Pharmeuropa, 2007).

In drafting the concept paper and reviewing the data requirements in the different regions and comments received at the 21st SC meeting it became apparent that the approach to the batch safety testing and consequently the tests required differ considerably between the regions. In addition confirmation of the completeness of information available on the regional requirements was required.

Therefore, in order to identify the potential for international harmonisation and the scope of any future VICH guideline (i.e. whether the harmonisation could cover both batch safety testing in target animals and laboratory animals or only target animal batch safety testing, and whether both live and inactivated vaccines should be addressed) the EU circulated on 12 December 2008 a discussion paper that comprised key questions regarding the scope for review and response by the VICH partners. Responses were received from all regions.

3. Regional requirements

Significant variations are evident between different regional requirements, however, these are more related to the products for which a TABST is stipulated than in the test design.

Europe

In the EU the only batch safety test is a test in the target animal for both live and inactivated vaccines. The test in laboratory animals (mice and guinea pigs, abnormal toxicity test) is since 1996 no longer required in Europe for safety testing of veterinary immunologicals (Schwanig et al, 1997).

The Ph.Eur. general monograph on *Vaccines for Veterinary Use* has recently been revised (Pharmeuropa, 2001; adopted in 2004) and now states that for an established vaccine the routine application of the TABST can be waived provided that a sufficient number (e.g. 10) of consecutive batches have been produced and have complied with the test (European Pharmacopoeia, 2008a). For special cases, e.g. significant changes in the manufacturing process or products with inherent risk it might, however, be necessary to perform the TABST. The specifications of the TABST are laid down in the Ph.Eur. general text *"5.2.9 Evaluation of safety of each batch of veterinary vaccines and immunosera"* (European Pharmacopoeia, 2008b), i.e. route of administration (application route), target animal species (minimum age, most sensitive target species), animals numbers (2 mammals, 10 birds, 10 fish), observation period (at least 14 days), definition of local and systemic reaction and criteria for repeating the test.

In the light of these changes, the CVMP issued in 2005 a position paper for harmonising the data requirements for removing the TABST (EMEA/CVMP/865/03/Final).

United States

In the United States the regulatory programme implementing the requirements of the *The Virus-Serum-Toxin Act of 1913 ('VST Act')*, as amended, 21 U.S.C. Section 151-159, is administered by the Center for Veterinary Biologics. Administrative regulations duly promulgated and with effect of law are published in Title 9. Code of Federal Regulations (9 CFR) Parts 101-118.

Veterinary biologicals must meet certain basic criteria including safety requirements: the product must be safe in the target species and, if live, in species exposed to shed organisms. In addition, safety tests in mice or guinea pigs are required. General requirements for live and killed bacterial

vaccines, live and killed viral vaccines and antibody products as well as the detailed requirements for each type of product are described in Title 9 CFR Part 113.

- *Live bacterial vaccine:* In addition to safety tests in mice or guinea pigs, safety tests for mammalian vaccines are carried out in two animals of the target species, which are injected with the equivalent of two doses by the recommended route and observed for 14 (cat, dog vaccines) or 21 (calves, sheep, swine vaccines) days. Live bacterial avian vaccines are only tested in the target species (10 animals, 10-fold dose, 10 days).
- *Inactivated bacterial vaccines:* Safety tests for mammalian vaccines are carried out in mice or, if lethal for mice, in guinea pigs. For inactivated bacterial poultry and fish vaccines, the vaccinates are observed for unfavourable reactions during the postvaccination period of the potency test.
- *Live viral vaccines:* In addition to safety tests in mice, safety tests for mammalian vaccines are carried out in two animals (pigs and cattle) or ten animals (cats and dogs) of at least one target species, which are injected with the equivalent of ten doses (pigs and cattle) or one dose (cats and dogs) by the recommended route and observed for 14 (cat, dog vaccines) or 21 (calves, sheep, swine vaccines) days. For some vaccines, the postvaccination period of the potency test constitutes the target animal safety test. Live viral avian vaccines are only tested in the target species (25 animals, 10-fold dose, 21 days).
- *Inactivated viral vaccines:* Safety tests are carried out in mice or guinea pigs. For safety in the target species the vaccinates of the potency test are used, i.e. they are observed during the postvaccination period for unfavourable reactions. Inactivated viral vaccines in avian species are exempted from this requirement.
- *Antibody products:* The safety is tested in mice or guinea pigs.

Japan

In Japan, medicinal products that are exclusively used for animals, including veterinary biologicals, are under the jurisdiction of the Ministry of Agriculture, Forestry and Fisheries, and ensuring their quality, efficacy and safety is included in the Pharmaceutical Affairs Law. It should be noted that the term “lot” is commonly used instead of “batch”. The quality assurance has come into force for the final product-vaccine according to a notification on “Minimum Requirements for Veterinary Biological Products (MRVBP)” under the Pharmaceutical Affairs Law. In principle, MRVBP stipulates “the lot safety test” in the target animal species for all vaccines, with the exception of inactivated vaccines for cattle and horses, although it varies depending on the characteristics of vaccine concerned. The specification of the lot safety testing for the target animals are also laid in MRVBP.

4. Responses to questions regarding the scope of a future VICH guideline

The following questions were asked:

1. Do you support aiming for a VICH harmonized position on:

a) batch safety testing (target animal batch safety testing **and** batch safety testing in laboratory animals) ☐
or
b) target animal batch safety testing ☐

2. Do you support aiming for a VICH harmonized position applicable to:
a) Inactivated vaccines ☐

or
b) Live and inactivated vaccines ☐

Summary of responses received from VICH SC members and observers regarding the scope of the concept paper and future VICH guideline

	BST[1]	TASBT	Inactivated vaccines	Live and inactivated vaccines	Comments
AHI	x			x	Recognition that regulatory obstacles at present
UDSDA	x			x	Support of proposal in principle. Would require support by robust pharmacovigilance system. Regulatory needs to be considered.
JMAFF		x	x		
JVPA	x			x	
IFAH-Europe	x			x	(a) The first priority should be to harmonise the criteria for waiving the BST, and to promote this world-wide. To begin work on harmonising the BST, without delaying (a) above.
EU	x			x	
AUS/NZ		x		x	
Australia Animal Health Alliance		x		x	Support discontinue obligatory batch release safety testing after an appropriate commercial history has been established, say 3-5 production batches, and upper potency limits determined. However, opportunity should remain for batch release safety testing, in target animal and/or surrogate laboratory animals, when potency measures are in excess of defined limit.
Health Canada	x			x	Preferred option

[1] TABST & BST in laboratory animals

The responses from the VICH partners to the questions in the EU discussion paper of 12 January are presented in the Annex to this Concept paper.

5. Impact on animal health and animal welfare

The waiving of the (TA)BST for routine batch release will not affect the quality of the vaccines. As demonstrated in the retrospective analysis of (TA)BST data provided by OMCLs and vaccine

manufacturers, the (TA)BST does not contribute to the safety of veterinary vaccines (AGAATI, 2002).

Furthermore, the strengthened pharmacovigilance network established in VICH regions ensures that in the case of safety problems due to inconsistent quality for a vaccine despite the first proof of quality consistency in production, this could be identified promptly and appropriate action be taken to ensure adequate and consistent quality.

The harmonisation of the (TA)BST would reduce the numbers of animals used for the quality control of vaccines. Based on the data collected from 14 European manufacturers for 11.386 batches released during 1997-1999, it was calculated that at least 66.184 animals were needed for the TABST (AGAATI, 2002).

6. Anticipated benefit for industry and regulatory authorities

Harmonisation of requirements across the different regions would result in reduced testing and as such reduce the costs for the manufacturers. It would also reduce the overall number of animals needed for the quality control of veterinary vaccines.

International harmonisation of batch safety testing would help manufacturers to comply with animal welfare legislation and commitments in the VICH regions for not performing unnecessary animal tests.

7. Discussion

The responses to the questions asked in the discussion paper of 12 December 2008 confirm the support for embarking on the topic in principle. However, the differences in regional requirements and legislation and possibilities for implementation suggest that the topic can only be approached in a phased approach.

The following approach is proposed:

1. In a first step harmonization for the waiving of TABSTs for inactivated vaccines would be sought, and the EWG would establish criteria for this in a VICH GL.
2. The EWG would explore possibilities for harmonizing BSTs and waiving of BSTs including laboratory animal tests and live vaccines and report back to the SC for consideration of future extension of the topic and VICH GL.

8. Recommendation (action plan, issues to be addressed, mandate, etc.)

The VICH SC agreed at the 21th meeting that the work on a guideline should be carried out by the Biologicals Quality Monitoring (BQM) EWG. This should be confirmed or otherwise a specialized EWG or Task Force under the BQM EWG be established.

Each VICH member/observer should nominate an expert to participate.

The EU would be willing to be the topic leader.

It is proposed that the VICH SC gives this group the mandate of preparing a guideline on establishing harmonized criteria for the waiving of the requirement for the TABST for inactivated

vaccines and to prepare a discussion paper for harmonizing BSTs and waiving of BSTs including laboratory animal tests and live vaccines.

9. Timetable

The EWG or TF should meet prior to the 23rd VICH SC meeting to prepare an outline for a guideline establishing harmonized criteria for the waiving of the requirement for the TABST for inactivated vaccines and to discussion possibilities for harmonizing BSTs and waiving of BSTs including laboratory animal tests and live vaccines in the future.

Further details to be established following report of EWG/TF at 23rd VICH SC.

10. Milestones

Nomination of experts by end March 2009
Meeting of EWG or TF by September 2009

Further details to be established following report of EWG/TF at 23rd VICH SC.

References

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Annex

Responses received from VICH SC members and observers regarding the scope of the concept paper and future VICH guideline:

AHI	The US supports efforts to harmonize batch safety testing for biologics. Our desire is for this to encompass all batch safety testing, both target animal and laboratory animal. With this stated, please understand that there may regulatory obstacles to implementation in the US that are not present in the EU, Japan or the other regions. However, we are committed to participating in a good faith effort to harmonize in this important area.
USDA	We have interest in looking at TABST in both laboratory and target animals for both live and inactivated products. Having said that, we also believe that a robust pharmacovigilance program would play an integral role in building a level of assurance that products continue to be monitored for safety performance long after the initial work is completed demonstrating consistency of manufacture. As you may be aware, the U.S. efforts (from the biologics perspective) to develop that more robust pharmacovigilance program have been delayed while that topic is being considered by our expert working group, and haven't been funded to this point by our Congress either. So, in summary, we support your proposal, would certainly like to discuss how this could be made to work, and need to ensure that from a regulatory perspective, that we can cover the associated regulatory needs given our current funding levels.
JMAFF	Scope: b) target animal batch safety testing a) Inactivated vaccines
JVPA	We wish the discussion paper including both live and inactivated vaccines and both batch safety testing in target animals and laboratory animals.
IFAH Europe	2. FAH-Europe appreciates the preparation of this discussion paper and the useful overview that it provides of the different batch safety test (BST) systems in the VICH regions. 3. IFAH-Europe supports the widest scope of this discussion document, i.e. in response to the questions presented in Section 6 of the discussion document, IFAH-Europe supports 1(a) (both target animals and laboratory animals) and 2(b) (both live and inactivated vaccines). 4. IFAH-Europe strongly recommends: (a) The first priority should be to harmonise the criteria for waiving the BST, and to promote this world-wide. (b) To begin work on harmonising the BST, without delaying (a) above. Additional comments: - Up to now we have little experience of selling EU vaccines, which have had the TABST removed, in other regions however this practice is increasing. We possibly have one example of a non-EU country insisting on TABST and are investigating this further at the moment. - We fully support a VICH harmonisation on batch safety tests for live and inactivated vaccines and are also of the opinion that as long as the rest of the world does not accept the possibility to waive such batch safety test, it will be kept indefinitely. Having a VICH guideline will greatly help to have these other countries accepting the withdrawal of such a

	test. - However, as expressed before at IFAH-Europe meetings, we have some doubts about outcome of VICH process for harmonising sensitive tests like batch safety test. Indeed, the USDA which does not work with GMP system and which does not really ask for fully controlled starting materials of animal origin, might be very reluctant to waive the test as it is the way to hopefully detect a problem in the target species… We do not know about Japan. Again why not, but with reasonable effort. We still have to harmonise the ways of test waiving inside the European Union. Special comments: 1) It is not reasonable to test live vaccines in laboratory animals. It is especially true, when mouse or guinea pig is not sensitive to the microorganism. These expensive tests would not present additional information on vaccine safety and animal welfare reasons do also support their omission. 2) With inactivated mammalian vaccines - provided that safety was proven in the target species during development, and laboratory species has well demonstrated reactions observed/expected in the target species - manufacturer can replace routine target animal safety test with test in laboratory animals, in case the vaccine safety data do not allow the total waiving of the batch safety test. - Global harmonisation of the batch safety test is a nice goal but given the regional differences also a far away goal. In first instance, a global agreement on waiving the batch safety test seems more readily obtainable. Such an agreement is essential if the possibility given by the Ph. Eur. for waiving the batch safety test will have any significance. As long as the rest of the world does not accept this principle, we have to keep the batch safety test in place indefinitely. Our experience with a vaccine licensed by CP in the EU and in many countries all over the world (except US and Canada) shows that it is already difficult to get waiving the batch safety test accepted in a central variation application in the EU, whereas the variation applications in non-EU countries (in Africa, South-America and Asia) have all been rejected. It should be realized that in many countries the use of “experimental animals” and the 3R principles are not regarded as an issue at all. This even more so if these “experimental animals” are a few (2-10) target animals in which the vaccine is tested for safety before being administered to tens of thousands other target animals. Unity within VICH on waiving the batch safety test seems a minimum requirement before other countries may accept the principle as well. And when waiving the batch safety test is accepted within VICH, the differences existing in the batch safety test systems between the various VICH regions automatically become less important …. We therefore propose: • to express the appreciation of the IHAH-Europe members for the useful overview in the discussion paper of the different batch safety test systems, • to suggest omitting the use of the term Target Animal Batch Safety Test, as in some regions small laboratory animals are (still) in use for batch safety testing, • to advise focusing the goal of the discussion paper solely on waiving of the batch safety test and • to advise dropping the subject of harmonization within VICH of the batch safety tests until agreement on waiving the batch safety test has been reached and the seed lot system has been fully implemented in Japan.

AUS/NZ:	Scope: b) target animal batch safety testing b) Live and inactivated vaccines
Australia Animal Health Alliance	Scope: b) target animal batch safety testing **We support provision to discontinue obligatory batch release safety testing after an appropriate commercial history has been established, say 3-5 production batches, and upper potency limits determined. However, opportunity should remain for batch release safety testing, in target animal and/or surrogate laboratory animals, when potency measures are in excess of defined limit** b) Live and inactivated vaccines **We support harmonisation, with such harmonisation aimed at allowing commercial imperatives without compromise to product safety, likely to include live and inactivated vaccines**
Health Canada	Scope: 1. Do you support aiming for a VICH harmonized position on: a) batch safety testing (target animal batch safety testing and batch safety testing in laboratory animals)- yes preferred option or b) target animal batch safety testing -yes 2. Do you support aiming for a VICH harmonized position applicable to: a) Inactivated vaccines -yes or b) Live and inactivated vaccines -yes preferred option Other comments from CFIA (prepared by Dr. Donna Hutchings) Evaluating animal safety testing for serial release, and perhaps developing VICH guidelines was discussed at the a meeting of the target animal safety EWG in 2006. It would be a useful exercise, but also a very large project. CFIA does not know how often serials from vaccines licensed for use in Canada might have been rejected because of unsatisfactory results from a safety test, in either target animals or laboratory animals - that would be a significant part of the puzzle in terms of deciding whether or not to continue with this requirement. The USDA would probably have this data available for the US-licensed products sold in Canada, though (we just stipulate that only USDA-released serials are eligible for import). We could probably pull together some data on products actually manufactured in Canada. In some cases (eg. AI vaccines in chickens - perhaps some of the fish vaccine safety tests as well) the safety test and the potency test are combined, so those tests should probably be left alone, since they don't represent additional animal use. The suggestion in the discussion document that this testing could continue for a certain period after licensing or for certain products that have caused serious pharmacovigilance problems is a useful one. The guidance on safety test design and evaluation criteria in these cases could be

	difficult to summarize (we evaluate it case by case usually...would be different for vaccines with residual neurovirulence vs local reactions, and some products are toxic to some laboratory species, etc.). CFIA agrees with the concept of the 3 R's (reduce, refine, replace, as per the new CCAC microsite - http://www.ccac.ca/en/alternatives/index.html) but if 2 target animals are vaccinated for release of a serial consisting of thousands of doses, that is a minimal use of animals, and provides some reassurance that there's no significant problem with the product. CFIA took a look at one of the key papers referenced in the concept paper (copy attached), and it does include a small summary of #s of batches tested in target animals from 1994 to 1997 in Europe, and says that most of them were eligible for release, although a few safety tests had to be repeated. This paper does not include any data from animal safety testing conducted in North America, it would be premature to conclude that this serial release animal safety testing was not useful here. The general requirement for 2x dose for target animal safety tests of inactivated vaccines and 10x dose for live vaccines reflects that there is some variability in animal size (all target animals generally receive the same dose) and that the most sensitive class of livestock is not necessarily available for test (eg. newborn animals might be more susceptible than the older animals used in testing), so it is a margin to increase the sensitivity of this testing. In conclusion, regarding the questions, we would support aiming for a VICH harmonized position on batch safety testing in both target animals and laboratory animals, for both live and inactivated vaccines. CFIA does not have the necessary data available to recommend not looking at safety testing in laboratory animals, or safety testing for live vaccines at this point...in response to their questions, we answered yes - preferred option and yes to the "either - or" options presented.