International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH/12/056
FINAL

PUBLIC CONSULTATION AT STEP 4 OF THE VICH PROCEDURE
OVERVIEW OF COMMENTS RECEIVED

VICH draft Guideline GL59 on Harmonization of criteria to waive laboratory animal batch safety testing for vaccines for veterinary use

VICH EWG: BIOLOGICALS QUALITY MONITORING

Name & Country of individual, organisation, or VICH delegation that commented

Comment n°	Name - Country
1	International Council on Animal Protection in Pharmaceutical Programmes (ICAPPP, USA)
2	Federation of Veterinarians of Europe (FVE) and European Veterinarians in Education, Research and Industry (EVERI)
3	Dogs Trust
4	Sindicato Nacional da Indústria de Produtos para Saúde Animal (Brazil)
5	Seiji Narihira (an individual)

Discussion of comments

GENERAL COMMENTS – OVERVIEW		
Comment N°	**Comment received**	**Outcome of consideration**
1	International Council on Animal Protection in Pharmaceutical Programmes (ICAPPP) The ICAPPP welcomes the creation of this guideline, which provides internationally harmonized recommendations for criteria to waive laboratory animal batch safety testing (LABST) of veterinary vaccines to encourage global implementation and a reduction in animal use. However, it is not clear why the USA and Japan still require the LABST in mice and guinea pigs when the EU removed this requirement over 20 years ago. Experience in several regions is that these tests do not add confidence in the safety of batches of product and they therefore represent an additional burden for industry (over and above other regions) and unnecessary use of animals. Therefore, these requirements should be deleted in the US and Japan (and other regions) as a matter of urgency. At the very least, a justification should be included to explain why these tests are still deemed necessary in these regions. It is also not clear why such a discrepancy exists between the human and veterinary sectors when it comes to testing requirements in regions outside of the EU. For example, in 2015, the US Food and Drug Administration (FDA) stated that the general safety test (GST) for human vaccines (which is comparable to LABST for veterinary vaccines) is no longer required for testing the safety of licenced human vaccines and the test was revoked from biological regulations (FDA, 2015). Prior to this, in 2003, a Rule was published in the Federal Register to permit manufacturers of biological products to apply for an exemption from the GST requirement "*provided they submit information to demonstrate that they use appropriate production controls and quality assurance safeguards*". However, the case is very different for veterinary vaccines as the United States Department of Agriculture (USDA) still requires the LABST in mice and guinea pigs (https://www.govinfo.gov/content/pkg/CFR-2019-title9-vol1/pdf/CFR-2019-title9-vol1-part113.pdf). Similarly, in 2019, the World Health Organization published a 'proposal to discontinue the test for undue toxicity (chapter 3.7) in the international pharmacopoeia' (WHO, 2019). According to the proposal, current manufacturing processes were considered to be "*more appropriate than the innocuity test in assuring the quality and safety of vaccines and other biological products*". Their Expert Committee concluded that "*its complete omission would not compromise the quality and safety of vaccines and other biological products" and recommended that that the test be removed from all future WHO recommendations, guidelines and manuals for biological*	The VICH EWG BQM acknowledges these general comments. In the light of the comments, the first sentence of the guideline was modified to: *Submission of batch safety test data from target or laboratory animals is a requirement for batch release of veterinary vaccines in several regions participating in the VICH and may also be required in other regions.*

	products published in the TRS [Technical Report Series], and that a clear indication be made in its report that the inclusion of this test in previously published WHO TRS documents be disregarded". It is not clear why similar exemptions have yet to be provided for LABST requirements in the testing of veterinary biologicals in all regions (apart from the EU). We urge the VICH to strongly encourage the US and Japan to reconsider their testing requirements for veterinary vaccines and ensure that they, at the very least, publish official guidance demonstrating that they will accept LABST waivers based on supportive data. Also, the proposed text specifies that the guideline's aim is to harmonize LABST waiver policies in VICH-participating regions but omits information that would assist OIE member countries – which are encouraged by OIE to use VICH guidelines – in adopting harmonized policies.	
2	<u>Federation of Veterinarians of Europe (FVE) and European Veterinarians in Education, Research and Industry (EVERI)</u> FVE and its Section EVERI welcome the development of the VICH GL59 on Harmonisation of criteria to waive laboratory animal batch safety testing for vaccines for veterinary use and agree with the principles that have informed this paper. The concept of this guideline is in the interests of replacing, reducing, and refining the use of animals in research, and also promotes animal welfare. We suggest, however, that the term "*laboratory animals*" should be more clearly defined within the document and support the testing products in the proposed target species, beyond guinea pigs and mice, as it is more valid and generates more appropriate data. Further to this, authorities from other countries are encouraged to recognize the principles of the 3Rs and also move towards acceptance of a waiver for LABST.	The VICH EWG BQM acknowledges these general comments. The term laboratory animal is defined in section 3 ("Glossary") of this guideline. Safety tests are carried out in the target species during the development of veterinary vaccines and, in some regions for batch release (target animal batch safety test; TABST) purposes as well. Please note that VICH GL50R and 55 establish waiving criteria for the TABST.
3	<u>Dogs Trust</u> Dogs Trust is in agreement in finding a way to remove laboratory animal batch safety testing where possible. The concerns outlined below are around the mechanism of pharmacovigilance predominantly and how this is achieved effectively in each state. Dogs Trust has concerns regarding people not reporting problems with vaccines. For example, owners may fail to notice or not be concerned by their pets showing adverse responses to a	The VICH EWG BQM acknowledges these general comments.

	vaccine, which could indicate it has not been effective. More public awareness of the importance of reporting any side effects following a vaccine is needed. Reporting within the industry is also needed to improve pharmacovigilance. We understand unclear roles and responsibilities, complex reporting rules implemented differently by different Member States, a lack of robust safety studies and complex decision-making at EU-level have led to the current EU system of medicines safety monitoring being insufficient. We welcome the paper that looks at batch safety testing for vaccines for veterinary use. However, we also want to raise the importance of efficacy, as well as safety. A study (https://www.researchgate.net/publication/13864571_Outbreak_of_canine_distemper_in_vaccinated_dogs_in_Finland) looking at the outbreak of distemper in Finland in the 1990s found, of the confirmed cases 631 (73 per cent) were between three and 24 months of age; 487 of these had been vaccinated at least once and 351 (41 per cent) had a complete vaccination history. Among the 351 confirmed cases of distemper with a known vaccination history, the proportion of dogs vaccinated with the most popular vaccine was significantly larger than would have been expected from its market shares on the assumption that all the vaccines had equal efficacy. The study concluded that the adequacy of vaccination policy and the efficacy of vaccines should be reviewed periodically to maintain the population immunity at an adequate level. Dogs Trust questions how useful it is to test vaccines on animals that are not the target animal.	The efficacy of veterinary vaccines is ensured by the strict authorisation process and established pharmacovigilance systems (see also VICH guidelines). Moreover, efficacy does not fall within the scope of this guideline. Safety tests are carried out in the target species during the development of veterinary vaccines and, in some regions for batch release (target animal batch safety test; TABST) purposes as well. Please note that VICH GL50R and 55 establish waiving criteria for the TABST.

SPECIFIC COMMENTS ON THE TEXT OF THE GUIDELINE

SECTION: Guideline cover page and title

Paragraph	Comment N°	Comment received and rationale; proposed change	Outcome of consideration
Title	1	**FVE/EVERI** Refer to "**minimum** criteria" for waiving LABST for veterinary vaccines	In order to be in line with VICH GL50(R) and 55, the VICH EWG BQM did not amend the text.
Section on VICH process	2	**FVE/EVERI** Please include a reference to the VICH process - https://vichsec.org/en/about/process/process-to-develop-harmonised-guidelines.html.	VICH EWG BQM rejected this comment since it is not appropriate to add a reference to the cover page of the GL.

SECTION 1

Paragraph	Comment N°	Comment received and rationale; proposed change	Outcome of consideration

2	3	**FVE/EVERI** Refer to "**minimum** criteria" for waiving LABST for veterinary vaccines	In order to be in line with VICH GL50(R) and 55, the VICH EWG BQM did not amend the text.
3	4	**FVE/EVERI** proposed change (if any): …approach for **immunological** products	The following change was made: "The use of this VICH guideline to support a similar approach for ~~products~~ veterinary vaccines for local distribution only …
4	5	**FVE/EVERI** Proposed change (if any): .. (3Rs), **i.e. to replace them with non-sentient alternatives, to reduce to a minimum the number of animals used, and to refine experiments which used animals so that they caused the minimum pain and distress**.	The VICH EWG BQM rejected this comment, since there is no need to explain the 3Rs.
4	6	**ICAPP (to USA)** Regulatory harmonization is one of the major barriers identified by industry and regulatory stakeholders for the local implementation of waivers, deletions or replacement of animal testing. A more direct endorsement of global alignment from VICH would be useful. Proposed change: VICH is committed to the replacement, reduction and refinement (3Rs) of animal testing, and urges countries and regions to consider granting waiver for the LABST, as a means to reduce the use of animals and the time requested for routine batch release.	The following change was made: Global implementation of LABST waivers reduces the use of animals for routine batch release. ~~and should be encouraged in the light of VICH's commitment to replacement, reduction and refinement (3Rs).~~ VICH is committed to the replacement, reduction and refinement (3Rs) of animal testing, and encourages countries and regions to implement this guideline and grant waivers for the LABST.

SECTION 1.1

Paragraph	Comment N°	Comment received and rationale; proposed change	Outcome of consideration
1	7	**FVE/EVERI** Refer to "**minimum** criteria" for waiving LABST for veterinary vaccines	In order to be in line with VICH GL50(R) and 55, the VICH EWG BQM did not amend the text.

SECTION 1.1.1

Paragraph	Comment N°	Comment received and rationale; proposed change	Outcome of consideration
1	8	**FVE/EVERI** Proposed change (if any): Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM rejected this comment, since it is appropriate to use the term "final product" in this context. Moreover, the GL refers to "veterinary vaccines" and not to "veterinary biological product".
1	9	**FVE/EVERI** Proposed change (if any): Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM amended "product" to "vaccine". See also reply to comment No 8.
1	10	**FVE/EVERI** Replace "unfavourable reactions" by "unfavourable local or ***systemic** reactions*" for clarity	The VICH EWG BQM rejected this comment, since the text is a quote from the CFR.

2	11	**FVE/EVERI** There is a brief mention of Please name some examples of '*in vitro*' technologies being used instead of animals.	The VICH EWG BQM rejected this comment, since *in vitro* methods are not in the scope of this guideline. Examples are given in the referenced scientific papers.
3	12	**FVE/EVERI** Refer to "**minimum** criteria" for waiving LABST for veterinary vaccines	In order to be in line with VICH GL50(R) and 55, the VICH EWG BQM did not amend the text.
SECTION 2.1			
Paragraph	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
1	13	**FVE/EVERI** Refer to "**minimum** criteria" for waiving LABST for veterinary vaccines	In order to be in line with VICH GL50(R) and 55, the VICH EWG BQM did not amend the text.
SECTION 2.2.1			
Paragraph	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
1	14	**FVE/EVERI** Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM amended "product" to "vaccine". See also reply to comment No 8.
1	15	**FVE/EVERI** Replace "*These tests*" by "*These **animal safety** tests*" for clarity	The VICH EWG BQM rejected this comment. The sentence before mentions "Other tests in laboratory animals…" and "These tests" refer to those.
3, 4	16	**ICAPPP** According to the guideline, section 2.2. should focus on regional requirements related to laboratory animal batch safety testing. However some requirements for safety testing in target animals are described for the US and Japan (even though these requirements are already covered in separate dedicated guidelines; VICH GL50 AND GL55) If TABST requirements are mentioned in the US and Japan sections, it should also be mentioned that in Europe, the TABST (as well as the LABST) is not a requirement. Proposed change: Include the fact that the TABST is also not required in Europe OR Delete mention of safety testing in 'target animals' in the regional requirements for the United States and Japan.	The VICH EWG BQM acknowledges this comment. References to the TABST have been removed wherever possible.
2, 3, 4	17	**ICAPPP** We understand that the purpose of section 2.2. of the draft guideline is to outline the current requirements in each region, however the requirements are not as clear as they could be. We understand the LABST is not required in Europe and therefore waivers are not necessary - but this is not explicit and, while it appears in the following section (2.3.) that the US and Japan will consider requests to waive the LABST if 10 (or 5 over 3 years) consecutive batches have been tested successfully, given the caveat in section 2.3.1 this far from clear.	The VICH EWG BQM acknowledges this comment. The introduction clearly states: *This guideline addresses laboratory animal batch safety tests (LABST) and harmonization of criteria for waiving it in regions where it is required.* There seem to be a misunderstanding with regard to Table 1 in GL50 and GL55. The table captures the procedures in place

		We suggest that it would be beneficial to present the information in a similar way to Table 1 in GL 50 and 55 on TASBT in order to clarify the situation in each region and to provide further confidence that the US and Japan will indeed accept LABST waivers. Table 1 in the adopted versions of VICH GL50 and GL55 on TABST, clearly shows the requirements in each region alongside a 'remarks' column that highlights the processes in place within each region that would allow these waivers to be considered. We also encourage both regions to work towards harmonization with Europe as much as possible, with the global deletion of the LABST being the ultimate objective.	when the revised GL50 and the new GL55 were published in 2017, i.e. the measures taken to implement the old GL50 after its publication in 2013. Japan added the following statement to its section: "Since 2018, abnormal toxicity tests have been waived for the vaccines that comply with the criteria described in this LABST GL (Section 2.3)."
4	18	**FVE/EVERI** Add "… toxicity limit **(Limit test)** confirmation…"for clarity	The VICH EWG BQM rejected this comment, since it does not enhance clarity.
4	19	**ICAPPP** *"[…] abnormal toxicity test and maximum toxicity limit confirmation test using mice and guinea pigs are carried out in all vaccines for dogs, cats and horses, and in some vaccines for cattle and pigs".* Comment: According to a recent publication by the Japanese Ministry of Agriculture, Forestry and Fisheries (Aihara, 2019), the 'Minimum Requirements for Veterinary Biological Products' in Japan stipulate that "*one of two tests, the abnormal toxicity test (ATT) or toxicity limit test (TLT; also known as the general safety test, innocuity test, or test for freedom from abnormal toxicity), is applied to the final product as appropriate to identify unexpected toxicities*". This contradicts the requirements set out in the draft guideline which states that both tests are required. The same publication also says that while both mice and guinea pigs must be tested in the abnormal toxicity test, only one species is required in the toxicity limit test. Proposed change: *"[…] abnormal toxicity test **or** ~~and~~ maximum toxicity limit confirmation test using mice and/**or** guinea pigs are carried out in all vaccines for dogs, cats and horses, and in some vaccines for cattle and pigs".*	The VICH EWG BQM acknowledges this comment. The following amendments were made: 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 Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (PMD Act). Under the PMD Act, "Minimum Requirements for Veterinary Biological Products (Japan MRVBP; 2002)" 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 down in MRVBP.~~ It should be noted that the term "lot" is commonly used instead of "batch". ~~In addition to~~ As safety tests in ~~the target animal species~~ laboratory animals, abnormal toxicity test ~~and~~ or maximum toxicity limit confirmation test using mice and/or guinea pigs are carried out in all vaccines for dogs, cats and horses, and in some vaccines for cattle and pigs. ~~For avian vaccines, only safety tests in the target animal species are carried out.~~ Since 2018, abnormal toxicity tests have been waived for the vaccines that comply with the criteria described in this LABST GL (Section 2.3).

SECTION 2.2.2.1			
Paragraph	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
1	20	**FVE/EVERI** Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM amended "product" to "veterinary vaccine". See also reply to comment No 8.
SECTION 2.2.2.3			
Paragraph	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
1	21	**FVE/EVERI** Please include a reference to the VICH process - https://vichsec.org/en/about/process/process-to-develop-harmonised-guidelines.html.	The VICH EWG BQM rejected this comment.
1	22	**FVE/EVERI** Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM rejected this comment, since it is appropriate to refer to a product here. See also reply to comment No 8.
SECTION 2.3.1			
Paragraph	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
3	23	**FVE/EVERI** Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM amended "product" to "vaccine". See also reply to comment No 8.
3	24	**FVE/EVERI** Replace "*unexpected adverse events*" by "*unexpected **local or systemic** adverse events*" for clarity	The VICH EWG BQM amended the text as proposed.
4	25	**FVE/EVERI** Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM amended "products" to "vaccines". See also reply to comment No 8.
4	26	**Sindicato Nacional da Indústria de Produtos para Saúde Animal** For products with an inherent safety risk (e.g. residual toxicity of bacterial toxin in bacterial and/or toxoid vaccines, residual live virus in rabies vaccines or other vaccines containing an agent of public health concern), it may be necessary to continue to conduct the LABST on each batch <u>for that specific security risk (residual virus)</u> or apply a different system for waiving LABST considering level of risk and control measures.[2,3] <u>The rest of the security tests could be waived according to the criteria established in the document.</u>	The VICH EWG BQM did consider parts of this comment and made the following changes: For products with an inherent safety risk (e.g. residual toxicity of bacterial toxin in bacterial and/or toxoid vaccines, residual live virus in rabies vaccines or other vaccines containing an agent of public health concern), it may be necessary to continue to conduct ~~the~~ <u>a</u> LABST on each batch <u>for that specific safety risk</u> or apply a different system for waiving LABST considering level of risk and control measures.[2,3] The VICH EWG BQM rejected to add the proposed sentence, since the first three paragraphs of section 2.3.1 already

			describe that the "rest of the LABST" could be waived according to the criteria established in this GL.
SECTION 2.3.1.1			
Paragraph	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
1	27	**FVE/EVERI** Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM amended "product" to "vaccine". See also reply to comment No 8.
SECTION 2.3.1.2			
Paragraph	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
1	28	**FVE/EVERI** …a given **veterinary** vaccine…	The VICH EWG BQM rejected this comment, since the guideline refers to "veterinary vaccines".
1	29	**Seiji Narihira** *"[…] test data of 10 batches (or a minimum of 5 batches if 10 batches are not manufactured within 3 years) is likely to be sufficient for most products."* Comment : The scientific bases regarding "test data of 10 batches […] is likely to be sufficient for most products" should be indicated.	The VICH EWG BQM discussed these figures during the development of the TABST GL50(R) and 55. The experts agreed on these figures since they provide a sufficiently large data set allowing national authorities to decide on a waiver for the given product.
1	30	**FVE/EVERI** …**adverse** reactions observed…	The VICH EWG BQM did consider this comment and made the amendments as proposed.
1	31	**FVE/EVERI** Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM amended "product" to "vaccine". See also reply to comment No 8.
2	32	**FVE/EVERI** Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM amended "product" to "vaccine". See also reply to comment No 8.
2	33	**FVE/EVERI** Replace "*a summary and discussion of the findings*." by "*a **summary, discussion and conclusion** of the findings*."	The VICH EWG BQM amended the text as proposed.
SECTION 2.3.1.3			
Paragraph	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
2	34	**FVE/EVERI** Add "…*Reports **(PSURs)** for…*"	The VICH EWG BQM rejected this comment, since it is not necessary to introduce an abbreviation.
SECTION 2.3.2			
Paragraph	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**

1	35	**FVE/EVERI** Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM rejected this comment, since it is appropriate to refer to "product" here.
1	36	**FVE/EVERI** Replace "*product*" by "***veterinary biological** product*" for clarity	The VICH EWG BQM amended "product" to "vaccine". See also reply to comment No 8.
1	37	**FVE/EVERI** Replace "*any adverse reactions*" by "*any **local or systemic** adverse reactions*" for clarity	The VICH EWG BQM amended the text as proposed.

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