16 January 2012
EMA/675371/2011
Veterinary Medicines and Product Data Management

EMA report on the implementation of the possibility for waiving the target animal batch safety test for immunological veterinary medicinal products in the European Union

This paper addresses the efforts to waive the target animal batch safety tests (TABST) among European marketing authorisation holders (MAHs) for veterinary vaccines. MAHs argue that the current process to generate documentation is time consuming and needs significant resources. This paper discusses the main issues raised by the companies and gives an overview of the current situation regarding the number of products for which a waiver of the TABST was obtained.

Introduction

In the beginning of this millennium the revision of the European Pharmacopoeia (Ph. Eur.), General monograph 0062, Vaccines for Veterinary Use established the possibility of the target animal batch safety tests (TABST) to be waived in the interests of the animal welfare by the competent authority. In a position paper on data requirements for removing the TABST for immunological veterinary medicinal products in the EU (EMEA/CVMP/865/03/final) the Committee for Medicinal Products for Veterinary Use (CVMP) clarified that when a sufficient number of consecutive batches have been produced and found to comply with the test, the consistency of the manufacturing process has been demonstrated and the possibility of waiving the TABST can be taken up by the manufacturer by means of a variation procedure.

In 2010 the European Medicines Agency wrote to all major MAHs of veterinary vaccines in the European Union (at the time 8 companies) to establish the status of implementation of this waiver for the immunological veterinary medicinal products registered through these companies in the European Union.

Replies were received from all eight MAHs as well as the European Federation for Animal Health Europe (IFAH-Europe). The number of products where the TABST was waived varies greatly among the companies, from 0 to 18 products while the number of applications for waiver ranges between 0 and 11 (*Table 1*). There is no information available on planned submission of waivers.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8447
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Report

While IFAH-Europe and the MAHs welcome the possibility to waive TABST, on the CVMP position paper in principle they commented that as long as there is no worldwide harmonisation regarding the waiving of the TABSTs, waiving is unlikely to be adopted broadly by industry since the tests would still have to be done for countries outside the EU.

Two regulatory challenges at the European level were cited as the reason for preventing the effective implementation of the reduction of TABST. Firstly, the Ph. Eur. requirement for extraneous agents(EA) testing of all inactivated veterinary viral vaccines for food production, which states that these kind of tests must be combined with the TABST, makes it currently difficult for the companies to comply with the scheme for waiving of the TABST. Secondly, the CVMP position paper is not considered a strong enough incentive for the industry. It was argued that the process to generate documentation is time consuming and needs significant resources. The relevance of the data requested, especially for well established products (such as those renewed or indefinitely renewed) was also questioned, as the same data was already assessed by European authorities in national released activities or post marketing surveillance, or any variation possibly impacting on the safety.

The discussions generated over the requested data defined four different issues regarding the practical viability to implement TABST waivers to all vaccines where it is applicable.

The first issue raised was regarding the batch data. According to CVMP proposal the manufacturers should submit this data on at least 10 consecutive batches from separate final bulks, unless justified. For the companies the added value of re-assessing safety tests is questionable, as once a sufficient number (10) of consecutive batches are produced and found to comply with the test approved at the time of registration, these batches clearly comply with the safety requirements.

The second issue considered was the pharmacovigilance data used to support the removal of the batch safety test. The assessment of the Periodic Safety Update Report (PSUR) by the competent authorities is an integral part of the routine post marketing surveillance for any product, and such assessment also has to be performed in light of the expected acceptable safety reactions. Therefore, the added value of re-assessing the pharmacovigilance data already provided, particularly for products that have already been marketed for several years, is questionable and resource demanding.

The necessity to have an expert report was listed as the third issue. Considering the batches were released on the basis of conformity to the safety test release requirements, pharmacovigilance was already assessed as part of the post marketing surveillance programme and, safety assessed variations having a possible negative impact, the added value of the expert report is also questioned.

The last issue was regarding the variation type applied in this circumstance. The current type of variation for waiving the TASBT is usually a standard type II variation, which was considered a rather heavy regulatory burden given that companies should be incentivised to reduce the number of animals used for testing.

The MAHs then went on to propose a variety of measures to incentivise the waiving of the TABST for well established products such as the handling of such a waiver as a type IA variation and the deletion of the need of an expert report which they believe will reduce costs, simplify gathering of documentation, usefully use existing regulatory framework, avoid double reassessment and reinforce the importance of the EU routine surveillance system.

The Agency also received feedback from the MAHs regarding their current effort to comply with the scheme. Eight of them liaised with the Agency providing figures for their vaccines, which are summarised in Table 1. Some companies gave details regarding the number of marketing

authorisations (MA) obtained per product submitted to waive TABST whereas others only mentioned their intentions towards the scheme, without specifying any numbers. MAH (B) provided a good example of a detailed report towards the waiving of TABST. Additionally MAHs also stated the current number of the MAs recently submitted, which involves six products and a total of 70 national authorisations.

As not all the results were quantitatively measurable, the table below reflects an overall view of the current situation.

Table 1. List of companies and products (quantity) to which the removal of TABST has been granted and/or submitted

MAH	TABST waiver obtained / product	TABST waiver requested / product	No. of MA *MRP/National	No. of MA Centralised procedure
Company A	1	1	Not specified	None
Company B	8	7	140	1
Company C	2	None	Not specified	None
Company D	None	11	Not specified	None
Company E	2	None	Not specified	None
Company F	1	None	Not specified	None
Company G	18	3	Not specified	None
Company H	Several	Several	Not specified	None

Table 1 displays in detail the feedback received by the Agency from MAHs towards the proposal of waiving TABST
*MRP= Mutual Recognition Procedure

The companies listed at least 32 products which have been granted the removal of TABST. They also expressed the total number of current applications under assessment, approximately 22 products. However, none of them have listed the expected number of products to be submitted in the near future. Not all replies were quantitatively measurable.

The MAHs as a whole consider that the acceptance of their proposals would certainly be an incentive for companies to implement the waiving of the TABST scheme but on the other hand they point out that for certain types of immunological products (i.e. inactivated vaccines), which require combined tests like the EA tests, the compliance with the waiving TABST will still not reduce the use of animals in safety tests. Additionally, since the manufactured batches are not intended for only European countries, this variation can only be implemented from the moment when all the concerned national authorities have officially approved this change.

Conclusion

While it is in the common interest of regulatory agencies and industry to reduce animal experiments through the development and implementation of *in vitro* analytical tests, it seems that the lack of international harmonisation and the specific tests required for some products remain an obstacle for the implementation of the waiving of the TABST which needs to be addressed by all interested parties.

It should be noted that the EU proposal for developing an internationally harmonised guideline on criteria for waiving TABST for veterinary vaccines at VICH has been accepted and a draft VICH guideline regarding inactivated vaccines has now been released for public consultation.

The CVMP has taken the suggestions of the MAHs on board and a revised guideline on data requirements for removing the target animal batch safety test for immunological veterinary medicinal products in the EU is planned to be published in January 2012.

The CVMP will ask the Agency's Joint CVMP/CHMP Ad-hoc Expert Group on 3Rs to review how the reluctance of MAHs to implement the possibility of waiving the TABST for vaccines can be overcome.