GUIDELINE FOR VARIATIONS

TO MARKETING AUTHORISATIONS FOR REGISTERED

VETERINARY IMMUNOLOGICAL PRODUCTS

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1. INTRODUCTION

The holder of a Marketing Authorisation for a registered Veterinary Immunological Product (IVP) is responsible for the registered IVP throughout its life and is required to take into account technical and scientific progress that may affect the product since the Marketing Authorization (MA) was first granted. He or she is required to make any amendment that may be required to enable the registered IVP to be manufactured and controlled by means of generally accepted scientific methods. Marketing Authorisation Holders (MAHs) may also wish to alter, to improve the IVP, or to introduce additional claims or safeguards.

The regulation of Immunological Veterinary Products is dynamic, taking into account changes to the original dossier that was used for registration of the IVP that may become necessary during the lifetime of the product. Any changes to a registered IVP, known as Variations, may involve administrative and/or more substantial changes and are subject to approval by the relevant Regulatory Authorities.

Procedures for the implementation of the different types of variations need to be set out to facilitate the task for both Marketing Authorisation Holders (MAHs) and the Authority to guarantee that variations to the IVPs do not give rise to public health or livestock concerns.

This Guideline is intended to provide guidance to applicants on the conditions to be fulfilled and the type of documentation to be submitted before a Variation can be approved by the AUTHORITY. Four categories of changes that require application for variations have been provided in the guidelines. These include notifications, minor changes, major changes and changes that mean an application for a new IVP must be applied for.

Changes are classified as major only in those instances where the level of risk is considered to be high and it is deemed necessary to provide the AUTHORITY with adequate time for an assessment of the supporting documentation.

2. Objectives

This guideline is intended to:

a) Assist applicants with the classification of changes made to a registered Immunological Veterinary Product

b) Provide guidance on the technical and other general data requirements to support changes to the method of manufacture and testing of the active ingredient or finished product of an IVP, particularly if there is a chance that the change may have an effect on the safety, quality or efficacy of the product.

3. Scope

This guideline applies to applicants intending to make changes to the different sections of a registration dossier for an Immunological Veterinary Product. It should be read in conjunction with other applicable guidelines.

When a variation leads to a revision of the summary of product characteristics (SPC), labelling and packaging leaflet, updated product information has to be submitted as part of the application.

For variations that require the generation of new stability data the studies required, including commitments to test specific batches, should always be continued to cover the currently accepted shelf-life period. The relevant AUTHORITYs should be informed immediately if any problems with stability appear during storage, e.g. if results are outside specification or potentially outside specification.

Applicants should be aware that some variations may require the submission of additional consequential variations. Therefore, for any given change the applicant should consider if one or more variations may be required to be submitted.

If changes to the dossier only concern editorial changes, such changes need not be submitted as a separate variation, but can be included as a notification together with a subsequent variation concerning that part of the dossier. In such a case, a declaration should be provided that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the substance of the variation submitted.

3.1 Changes to Labelling information

For any change to labelling information (SPC, label and package leaflet) not covered by the variation categories described in this document, the Authority must be notified and submission of the revised labelling information is expected.

3.2 When Variations are required

The definitions outlined in the following sections are intended to provide guidance with respect to the classification of administrative, quality, safety and efficacy-related changes. Specific change examples are provided in this guideline. However, it is to be noted that a change not cited in this guideline, should be considered as a major change by default. Whenever the applicant is unclear about the classification of a particular change, the Authority should be contacted. It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality, safety and efficacy of the product.

Individual changes normally require the submission of separate variations. Grouping of variations is acceptable only when variations are consequential to each other, e.g. introduction of a new starting material specification that requires a new analytical procedure.

For the purpose of classification, an application involving two or more types of variations will be considered as the highest risk type, e.g. a variation grouping both a minor change and a major change will be classified as a major change.

Applicants are also advised to exercise caution whenever several changes to the same Finished Product are envisaged. Although individual changes may be classified as a particular reporting type, classification at a higher risk category may be warranted as a result of the composite effect of these changes. In all such cases, applicants are advised to contact the Authority prior to submission of the variation application in order to obtain guidance in classifying such changes.

4. CATEGORISATION OF VARIATIONS

4.1 Notifications

Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the Finished Product. Such notifications do not require prior approval, but must be notified to the Authority immediately after implementation (immediate notification (IN)), or within 12 months following implementation (annual notification (AN)) of the change.

It should be highlighted that an IN or AN may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

For Annual Notifications, Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarised as part of the notification. The indicated documentation is not required to be submitted but should be made available on request or at the time of inspection. ANs should be submitted to the Authority within 12 months of implementation of the changes. For convenience applicants may group several AN changes as a single submission

4.2 Minor Variations

Minor variations are changes that may have minor effects on the overall safety, quality and efficacy of the IVP. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.

Such variations must be notified before the change is implemented. If no objection letter has been issued within 60 days of notification, the change may be introduced. Should questions arise during the specified period; the change can only be implemented on receipt of a letter of acceptance from the Authority.

4.3 Major Variations

Major variations are changes that could have major effects on the overall safety, quality and efficacy of the Immunological Veterinary Product. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by the Authority is required before the changes can be implemented. A letter of acceptance will be issued for all major variations when the variation is considered acceptable. These variation applications will be reviewed within a time period of 90 days.

4.4 Extensions/New Applications

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as changes. For these cases a new dossier must be submitted. Examples of this could be:

i. Adding a new target species

ii. Adding a new antigen or strain.

6.0 Conditions to be fulfilled

For each type of variation, attempts have been made to identify particular circumstances where lower reporting requirements (IN, AN or Minor) are possible. A change that does not meet all of the conditions stipulated for these specific circumstances is considered to be a major variation.

In some circumstances categories may be specifically stated for a given variation. This has been done to indicate to applicants what documents should be provided. This is for informational purposes only. The list of documentation is not intended to be comprehensive and further documentation may be required. For all changes it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not have a negative effect on the safety, quality or efficacy of the IVP.

7.0. Documentation required

Examples of variations are organised according to the dossier structure given in the guidelines for registration of immunological veterinary product.

a) A variation application form can be downloaded from Authority's website: All sections of this form should be completed and the document signed. Electronic versions of the application form, both as a Word document and as a scanned signed pdf file should be provided.

b) Replacement pages of the relevant sections of the dossier are required.

d) Copies of SPC, labels and package leaflet, if relevant.

c) It is to be noted that the Authority reserves the right to request further information.

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that the Authority may request information or material, or may define conditions not specifically described in this guidance, in order to adequately assess the safety, efficacy and quality of an IVP.

TYPES OF VARIATIONS:

1. CHANGES AFFECTING INFORMATION IN PART 1

No.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1	Change in the name and/or corporate address of the supplier of the finished product	1,2,3	1,2,3	IN
	Conditions to be fulfilled			
	1. The supplier is an authorized Local Technical Representative (LTR) 2. Must hold a valid wholesale dealer's licence. 3. Confirmation that the supplier of the product remains the same legal entity.			
	Documentation required			
	1. Letter of appointment of the LTR by the manufacturer or marketing authorization holder 2. Letter of acceptance from the proposed LTR 3. Copy of wholesale dealer's licence			

No.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
2	Change in the name and/or corporate address of the Marketing Authorisation Holder (MAH)	1	1,3	IN
	Change of MAH from one company to another	2	2,3	IN
	Conditions to be fulfilled			
	1. Confirmation that the supplier of the product remains the same legal entity 2. All legal requirements for change of MAH have been met & Legal transfer of change has been completed			
	Documentation required			
	1. A formal document from a relevant official body (e.g. regulatory authority) in which the new name and/or address is mentioned. 2. Notarized transfer documents 3. Company registration certificate from the relevant jurisdiction			

No.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
3	Change in the name and/or address of a manufacturer of the finished product	1	1 - 3	IN
	Conditions to be fulfilled			
	1. No change in the location of the manufacturing site and in the manufacturing operations.			
	Documentation required			
	1. Confirmation that the supplier of the product remains the same legal entity. 2. Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. Regulatory Authority) in which the new name and/or address is mentioned. 3. Two (2) commercial samples of the product			

No.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
4	Deletion of a manufacturing site or manufacturer involving:			
	Production of the IVP starting material	1	1,2	AN
	Production or testing of the IVP intermediate or IVP	1 - 2	1 -3	IN
	Production, packaging Or testing of the intermediate or FPP	1 - 2	1 - 3	IN
	Conditions to be fulfilled			
	1. No change in the location of the manufacturing site and in the manufacturing operations. 2. At least one other site continues to perform the same function(s) as the site(s) intended to be deleted. 3. The deletion of site is not a result of critical deficiencies in manufacturing			
	Documentation required			
	1. Revised product information 2. Samples of the product 3. Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application. 4. Two (2) commercial samples of the product required **ONLY** if deleted manufacturing site appears on registered product label. 5. Updated manufacturers information and their roles			

No.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
5.	Change in the name of the finished product	1	1,2,3,4	Vmin
	Conditions to be fulfilled			
	1. No change in the location of the manufacturing site and in the manufacturing operations. 2. The brand name should not have been accepted for another product. 3. The brand name should not resemble available product in the market. 4. The brand names should not contain exaggerated claims			
	Documentation required			
	1. Revised product information 2. Tow commercial samples of the product			

No.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
6	Change of LTR	-	1,2,3,4 ,5	Vmaj
	Documentation required			
	1. Power of attorney from the MAH revoking the previous power of attorney, and appointing the new LTR. 2. Letter of no objection for the change by the previous LTR 3. Letter of appointment from the product Marketing Authorization Holder 4. Letter of acceptance from the proposed LTR and a copy of termination notice of previous LTR. 5. List of affected products, including registration numbers. Affected products should appear on the current Drug Register. 6. License to deal with pharmaceuticals issued by the Authority to the LTR			

2. CHANGES AFFECTING MANUFACTURE AND CONTROL

No.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
7.	**Addition or replacement container type**	1	1 - 6	V min
	Conditions to be fulfilled			
	1. The new container is made of the same material as the registered container(s) 2. The closure system is the same as that for the registered container(s)			
	Documentation required			
	1. Two (2) commercial samples of the product as packaged in the new container-closure system. 2. Data on the suitability of the container closure system demonstrating equivalent or superior protection compared to the current packaging system. 3. Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications, if appropriate). 4. Stability summary and conclusions, with results of tests for a minimum of two (2) batches of pilot or production scale batch and three (3) months of long-term testing. 5. Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of the product in the proposed new container into the long-term stability programme, unless data was provided in documentation 4.			

Note: Addition or replacement of a primary container with a container made from different material requires a Major Variation with supporting data to show that the safety and efficacy of the product in the new container is equivalent to that of the product in the original container.

No.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
8	Change in the package size involving:			
	a. change in the number of units (e.g. ampoules etc.) in a package	1 - 2	1 - 3	IN
	b. change in the fill weight/fill volume of parenteral multi - dose products	1 - 2	1 - 3	Vmin
	Conditions to be fulfilled			
	1. The change is consistent with the posology and treatment duration accepted in the SPC. 2. No change in the primary packaging material.			
	Documentation required			
	1. Justification for the new pack-size, indicating that the new size is consistent with the dosage regimen and duration of use as accepted in the SPC. **2.** A written commitment that stability studies will be conducted. **3.** Two (2) commercial samples of the product			

No.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
9	Change in the shelf-life of the Final Product (as packaged for sale) involving:			
	a. Reduction	1-3	2	IN
	b. Extension	1-3	1- 3	Vmin
	Conditions to be fulfilled			
	1. No change to the primary packaging type in direct contact with the Final Product and to the recommended condition of storage. 2. Stability data was generated in accordance with the currently accepted stability protocol. 3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.			
	Documentation required			
	1. Proposed shelf-life with test results for a minimum of two pilot or production scale batches and justification for change 2. Copy of the currently accepted shelf-life specifications and, where applicable, specifications after dilution/reconstitution. 3. Two (2) commercial samples of the product			

No.	Description of change	Conditions to be filled	Documentation required	Reporting type
10	Change in the in-use shelf life of the Final Product (after first opening or after reconstitution or dilution):			
	a. Reduction	1	1, 3-4	IN
	b. Extension	None	1-4	Vmin
	Conditions to be fulfilled			
	1.The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.			
	Documentation required			
	1. Proposed in-use period, test results and justification of change. 2. Copy of currently accepted end of shelf-life FPP specifications and where applicable, specifications after dilution/reconstitution. 3. The revised label information 4. Two (2) commercial samples of the product			

No.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
11	(i) Change in the storage conditions of the final Product (as packaged for sale), or (ii) the product during the in-use period, or (iii) the product after reconstitution or dilution	1	01-Mar	Vmaj
	Conditions to be fulfilled			
	1. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.			
	Documentation required			
	1. Stability and/or compatibility test results to support that the change to the storage conditions has no negative effects on the safety and efficacy if the product in the target species. 2. Updated post-acceptance stability protocol and stability commitment and justification of change. 3. Two (2) commercial samples of the product			

No.	Description of change	Conditions to be fulfilled	Documentatio n required	Reporting type
12	Replacement or addition of a new manufacturing site of the active immunogenic substance or the finished product	1,2,3,4	1,2,3,4	VMaj
	Conditions to be fulfilled 1.The new manufacturer has a valid GMP Certificate 2. The mew manufacturer produces three pilot scale batches and carries out the registered quality control tests on them. 3. The results of these three pilot scale batches are compared with the batch release test results from three batches produced by the previous manufacturer and shown to be equivalent. 4. The pilot scale batches are tested by AU-PANVAC or OIE accredited Laboratories			
	Documentation required			
	1. GMP Certificate of new manufacturer, and /or Site Master File 2. Manufacturing Licence of new manufacturer 3. Evidence of a technical transfer between the previous and the new manufacturer. 4. Batch Protocols for three batches produced by previous manufacturer. Batch protocols for three batches produced by new manufacturer. 5. AU-PANVAC QC Certificates for the pilot scale batches			

OTHER VARIATIONS

For Immunological Veterinary Products, many changes to the product, especially those involving methods of manufacture and testing, must be treated as Major Variations.

Appropriate supportive data must be provided. This will, for example, require the reporting of studies conducted to demonstrate that the requested change has no adverse effect on the safety and efficacy of the product in the target species when used according to the SPC. Evidence may be provided by demonstrating the equivalence of batch safety and potency/titre results of the changed product with the results of those tests when carried out with the approved product manufactured and tested according to the descriptions provided in the registration dossier. Date from each of 3 batches of the old and 3 batches of the new product should be provided.