# GUIDELINE ON VARIATIONS TO A REGISTERED VETERINARY PESTICIDE PRODUCT

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ACRONYMS

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|---|---|
| **AN:** | Annual notification |
| **APS:** | Active Pesticide Substance |
| **APSMF:** | Active Pesticide Substance Master File |
| **BP:** | British Pharmacopoeia |
| **CEP:** | European Pharmacopoeia Certificate of Suitability |
| **CTD:** | Common Technical Document |
| **EMA:** | European Medicines Agency |
| **GMP:** | Good Manufacturing Practice |
| **IN:** | Immediate Notification |
| **LTR:** | Local Technical Representative |
| **MAH:** | Marketing Authorization Holder |
| **MRLs:** | Maximum Residue Limits |
| **NPRA:** | National Pesticide Regulatory Authority |
| **The Authority:** | National Regulatory Authorities |
| **Ph. Eur:** | European Pharmacopoeia |
| **Ph.Int:** | International Pharmacopoeia |
| **SmPC:** | Summary of Product Characteristics |
| **SRA:** | Stringent Regulatory Authority |
| **USFDA:** | United States Food & Drugs Administration |
| **USP:** | United States Pharmacopeia |
| **VICH:** | Veterinary International Conference on Harmonization/International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products |
| **VPP:** | Veterinary Pesticide Product |
| **Vmin:** | Minor Variation |
| **Vmaj** | Major Variation |
| **WHO:** | World Health Organization |

## GLOSSARY

The definitions provided below apply to the terms used in this guidance. They may have different meanings in other contexts and documents.

***Active Pesticide Substance -*** Active pesticide substance means the biologically active part of the pesticide.

***Active Pesticide Substance (APS) /Starting Material =*** A raw material, intermediate, or an APS that is used in the production of an APS and that is incorporated as a significant structural fragment into the structure of the APS. An APS starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house.

***Applicant -*** An applicant is a person who applies for registration of a pesticide product to The Authority, who must be the owner of the product. He may be a manufacturer or a person to whose order and specifications, the product is manufactured. The applicant shall therefore be responsible for signing the registration application form. If the applicant wants another person to register the pesticide product on his behalf, then Powers of Attorney, duly notarized in the country of origin, and registered with the Registrar of Companies in the Partner State shall be provided. After the product is registered, the applicant shall be the Marketing Authorisation Holder (MAH)

***Finished Veterinary Pesticide Product (VPP) -***A finished dosage form of a veterinary pesticide product which has undergone all stages of manufacture including packaging in its final container and labelling.

***Formulated Pesticide Product*** - means any formulation containing one or more active ingredients.

***Formulation*** - means the combination of various ingredients designed to render the product useful and effective for the purpose claimed; the form of the pesticide as purchased by users.

***In-Process Control -*** Checks performed during manufacture to monitor or to adjust the process in order to ensure that the final product conforms to its specifications.

***Local Technical Representative (LTR) -*** Every applicant who is not resident in the country where the product is to be marketed, shall appoint a company authorized by The Authority to deal in the pesticide products to be a Local Technical Representative (LTR). The appointment shall be notified to the Authority by submitting a letter of appointment supported by original copy of power of attorney.

***Marketing Authorization Holder (MAH) -*** the company or other legal entity that has the authorisation to market a veterinary pesticide product on a Regulatory Approval.

***Manufacturer -***A company that carries out operations such as production, packaging, repackaging, labelling and re-labelling of pesticide product.

***Pilot Scale Batch -*** A batch of an active pesticide substance or VPP manufactured, by a procedure fully representative of and simulating that to be applied to a full production scale batch.
Product (or pesticide product) means the pesticide active ingredient(s) and other components, in the form in which it is packaged and sold.

***Production Scale Batch*** **-** A batch of an Active pesticide substance or VPP manufactured at production scale by using production equipment in a production facility as specified in the application

***Authority*** means the Veterinary Medicines Directorate responsible for regulating the manufacture and distribution of pesticides in Kenya.

## 1.0 INTRODUCTION

The Marketing Authorisation Holder (MAH) for a registered Veterinary Pesticide Product (VPP) is responsible for the registered product throughout its life-cycle irrespective of the regular reviews by The Authority. The MAH may also wish to alter or to improve the VPP or to introduce an additional safeguard.

Regulation of Veterinary Pesticide Product (VPP) also take into account all changes to the original dossier that was used for registration of the VPP. Any changes to a registered VPP, i.e. variations, whether administrative or substantial, are subject to approval by The Authority.

Guidance for the implementation of the different types of variations is set out in this document to facilitate the task of both the MAHs and the Authority, and to guarantee that variations to the VPP do not give rise to negative effects on animal health as well as public health concerns.

This Guideline is therefore, 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 variation applications have been provided in this guideline. These include notifications, minor changes, major changes and changes that make a new application necessary.

Minor changes in the registration dossier, such as changes to company address or telephone number or in distributors, which do not affect the content of the registration decision, may be handled by a simple administrative arrangement, although they would have a consequence for the labelling of the product.

Major changes in the registration, such as changes to the label or adding new uses (pests or vectors), will require full or partial review of the data package submitted by the registrant and, where necessary, additional data would be requested and evaluated before approval of the request.

Particular circumstances are identified where lower reporting requirements Annual Notification (AN), Immediate Notification (IN) or Minor Variation) are possible.

The change categories are organized in sections according to the administrative, quality, safety and efficacy sections of the product dossier. Specific dossier sections have been identified for individual data requirements in order to assist in the filing of documentation.

In addition, the guideline assists in understanding the possible consequences of the listed changes and may be useful as a risk management tool to promote or enhance best practices within organizations.

The Guideline is an administrative instrument and, as such, allows for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with The Authority to confirm that all the regulatory requirements are met.

It is equally important to note that The Authority reserve the right to request for information or material, or define conditions not specifically described in this guideline, in order to allow for adequate assessment of safety, efficacy

or quality of the pesticide product. The Authority is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

## 2.0 BACKGROUND

The requirements specified in this guideline have been partly adapted from the current European Commission's Guidelines. https://www.ema.europa.eu/en/veterinary-regulatory/post-authorisation. It is intended to provide supportive information on the post-authorasition regulatory requirements for implementing a change to a registered product.

*In adopting part of the European Commission guideline for use in pesticides regulations, consideration has been made of the fact that in some EAC Partner States, pesticides are considered 'drugs", as such, regulated the same way topical veterinary medicinal products are regulated. For many years veterinary ectoparasiticides were also considered as pesticides as such regulated alongside crop pesticides, however, term medicine (or drug) stands for chemicals used to cure diseases, primarily in humans and also in animals. Debate on whether veterinary parasiticides should be drugs or pesticides has come up, so regulators should consider therefore which guideline would be appropriate for use; drugs or pesticides guideline?*

*Reference has also been made of the WHO International Code of Conduct on the Distribution and Use of Pesticides http://www.fao.org/agriculture/crops/corethemes/theme/pests/pm/code/en/*
*(Guideline to a registered Pharmaceutical Product-Code PSS/1/1/21/104), currently published on the EAC website under the link: https://www.eac.int/documents/category/livestock*

### 2.1 Objectives

This guideline is intended to: Assist applicants with the classification of changes made to a registered VPP; Provide guidance on the technical and other general data requirements to support changes to the quality, safety and efficacy attributes of the Active Pesticide Ingredient (APS) or VPP.

### 2.2 Scope

This guideline applies to applicants intending to make changes to a registered veterinary pesticide product. This guideline should be read in conjunction with other applicable guidelines including the *Guideline for Registration of Veterinary Pesticide Products, available at the Authority's website www.vmd.go.ke*.

This guidance document is applicable only to active pesticide substance (APS) and excipients manufactured by chemical synthesis or semi-synthetic processes and VPPs containing such APS and excipients. The applicant is requested to contact The Authority regarding planned variations to such products.

### 2.3 General Guidance

The conditions and documentation stipulated in this guideline for APS-related variations focus primarily on those VPPs that relied upon the provision of full APS information within the VPP dossier.

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

For variations that require generation of stability data on the Active substance or VPP, the stability studies required, including commitment batches should always be continued to cover the currently accepted retest or

shelf-life period. The Authority should be informed immediately if any problems with the stability appear during storage, e.g. if 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.

Applicants are informed that variations will only be accepted and effected for products appearing in the most current Authority drug register.

## 3.0 GUIDANCE FOR IMPLEMENTATION

### 3.1 Reporting Types

The definitions outlined in the following reporting types 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 decided on a case-by-case basis. 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 impurity 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 VPP 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.

### 3.2 Notifications

Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy, and quality of the VPP. Such variations do not require any prior approval by the Authority. However, they must be notified by the MAH to The Authority immediately after implementation in order to ensure the continuous supervision of the product (Immediate notification -IN), or within 12 months following implementation (annual notification - AN).

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

#### 3.2.1 Annual Notification (AN)

Applicants must satisfy themselves that they meet all the prescribed conditions for the change. The change should be summarized as part of the notification, but the indicated documentation is not required to be submitted. The documentation indicated for ANs should be available on request or at the time of inspection. ANs should be submitted to The Authority within 12 months of implementation of the changes.

### 3.2.2 Immediate notification (IN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application.

These variations will be handled within a time period of 60 working days from the date of receipt of application.

## 4.0 CATEGORIZATION OF VARIATIONS TO REGISTERED PRODUCTS

Variations to veterinary pesticide products are classified in different categories, depending on the level of risk to public or animal health and the impact on the quality, safety and efficacy of the pesticide product. This guideline provides minimum requirement for variation per each class as defined below.

### 4.1 Minor Variation (Vmin)

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

These variations will be handled within a time period of 120 working days from the date of receipt of application.

### 4.2 Major Variation (Vmaj)

Major variations are changes that could have major effects on the overall safety, efficacy and quality of the VPP. The documentation required for the changes included in this reporting type should be submitted.
These variations will be handled within a time period of 120 working days from the date of receipt of application.

### 4.3 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 such changes are listed in Appendix 1.

## 5.0 LABELLING INFORMATION

For any change to labelling information (SmPC, Package insert, labels) not covered by the variation categories described in this document, The Authority must be notified and submission of the revised labelling information is expected as per the Guideline for Labelling.

## 6.0 CONDITIONS TO BE FULFILLED

Efforts have been made to indicate the conditions that must be met in order for each type of change to be classified as a notification, minor variation or major variation.

For each variation, attempts have been made to identify particular circumstances where lower reporting requirements (IN, AN, or Vmin) 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 Vmaj categories have been specifically stated for a given variation.

## 7.0 DOCUMENTATION REQUIRED

For each variation, certain documents have been identified and the change categories are organized according to the administrative, quality, safety and efficacy requirement sections of the pesticide registration dossier as supporting data. This has been done to indicate to applicants what documents should be considered to be provided. Applicants should ensure that they have provided all relevant information to support the variation.

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, efficacy or quality of the VPP.

In general, all applicants are required to submit the following in addition to the documentation specified under each type of variation.

a) A variation Application Form. All sections of this Form shall be completed, and the document signed. Electronic versions of the application form, both as a Word document and a scanned signed PDF file, shall be provided.

b) Relevant number of commercial samples of the product in their marketing containers
c) Copies of SmPC, Package leaflet and labels, if relevant.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 1 | Change of the Marketing Authorization Holder (MAH) of the VPP | | | |
| a | Change in the name and/or corporate address of the (MAH) | 1 | 1, 3,4,5 | Vmaj |
| b | Change of MAH from one company to another | 2 | 1,2, 3,4,5 | IN |
| **Conditions to be fulfilled** | | | | |
| 1) Confirmation that the supplier of the product remains the same legal entity<br>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. the national pesticides regulatory authority in which the new name and/or address is mentioned.<br>2) Notarized transfer documents<br>3) A certified copy or notarized company registration certificate from the relevant jurisdiction<br>4) Letter of cessation from previous/current MAH<br>5) Letter of acceptance from proposed MAH | | | | |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 2 | Change in the name or address of a manufacturer of an active pesticide substance | 1 | 1, 2 | IN |
| **Conditions to be fulfilled** | | | | |

| |
|---|
| 1) No change in the location of the manufacturing site and in the manufacturing operations. |
| **Documentation required** |
| 1) A formal document from a relevant official body (e.g. National pesticide regulatory authority) in which the new name and/or address is mentioned.<br>2) An updated Letter of Access in the case of a change in the name of the Active Pesticide Site Master File Holder. |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 3 | Change in the name and/or address of a manufacturer of the VPP | 1 | 1, 2 | Vmin (zero rated) |
| **Conditions to be fulfilled** | | | | |
| 1) No change in the location of the manufacturing site and in the manufacturing operations. | | | | |
| **Documentation required** | | | | |
| 1) Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NPRA) in which the new name and/or address is mentioned.<br>2) Two (2) commercial samples of the product | | | | |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 4 | Deletion of a manufacturing site or manufacturer involving: | | | |
| 4a | production of the Active Substance (AS) starting material | 1 | 1 | AN |
| 4b | production or testing of the AS intermediate or AS | 1-2 | 1 | IN |
| 4c | production, packaging or testing of the intermediate or VPP | 1-2 | 1,2 | IN |
| **Conditions to be fulfilled** | | | | |
| 1) At least one other site continues to perform the same function(s) as the site(s) intended to be deleted.<br>2) The deletion of site is not a result of critical deficiencies in manufacturing. | | | | |
| **Documentation required** | | | | |
| 1) Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application.<br>2) Relevant numbers of commercial samples of the product required **ONLY** if the deleted manufacturing site appears on registered product label. | | | | |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 5 | Change of Local Technical Representative (LTR) | 1 | 1-3 | Vmaj |
| **Conditions to be fulfilled** | | | | |
| 1) Proposed LTR should be licensed by The Authority; in possession of a valid The Authority wholesale permit or licence. | | | | |
| **Documentation required** | | | | |
| 1) Power of attorney from the registered product MAH.<br>2) Letter of acceptance from the proposed LTR and a copy of termination notice of previous LTR.<br>3) List of affected products, including registration numbers<br>4) Letter of acceptance from the previous LTR | | | | |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 6 | Change of Proprietary/Product name | 1,2 | 1,2 | Vmin |

| **Conditions to be fulfilled** |
|---|
| 1) The product name should not have been accepted for another product.<br>2) The product name should not bear close resemblance to that already registered by The Authority; pronunciation and spelling* |
| **Documentation required** |
| 1) Revised product information<br>2) Two (2) commercial samples of the product |

| | **Description of change** | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 10 | Replacement or addition of a new manufacturing site or manufacturer of an Active Pesticide Substance involving: | | | |
| 10a | APS testing only | 1, 3 | 2,3 | IN |
| 10b.1 | Production of APS starting material | 2,3 | No variation is required such changes are handled as amendments to the APSMF by the APSMF holder as part of the The Authority APSMF procedure | |
| 10b.2 | | 3,4 | 1-2, 12 | IN |
| 10b.3 | | None | 1,2,5, 6-7,11, 12 | Vmaj |
| 10c.1 | Production of APS intermediate | 2-3 | No variation is required such changes are handled as amendments to the APSMF by the APSMF holder as part of the The Authority APSMF procedure | |
| 10c.2 | | 3, 5 | 1-2, 11 | IN |
| 10c.3 | | None | 1,2,5, 6-7,11 | Vmaj |
| 10d.1 | Production of APS (full dossier) | 8-9 | 1-2, 4, 7-8 | Vmaj |
| 10d.2 | | None | 1,2,4,5,6-7, 9-10, 12 | Vmaj |

**Conditions to be fulfilled**

1) The transfer of analytical methods has been successfully undertaken.
2) The new site is supported by an APSMF that has been currently accepted through the The Authority APSMF procedure and the VPP manufacturer holds a valid Letter of Access.
3) No change in the VPP manufacturer's APS specifications.
4) The impurity profile of the APS starting material is essentially the same as other accepted sources. The introduction of the new supplier does not require the revision of the APS manufacturer's APS starting material specifications. The route of synthesis is verified as identical to that already accepted.
5) Specifications (including in-process, methods of analysis of all materials), method of manufacture and detailed route of synthesis are verified as identical to those already accepted. The introduction of the new supplier does not require the revision of the APS manufacturer's APS intermediate specifications.
6) No change in the VPP release and end-of-shelf-life specifications.
7) No difference in impurity profile of the proposed APS to be supplied, including organic, inorganic impurities and residual solvents. The proposed APS manufacturer's specifications do not require the revision of the VPP manufacturer's APS specifications.
8) For low solubility APSs the APS polymorph is the same, and whenever particle size is critical (including low solubility APSs) there is no significant difference in particle size distribution, compared to the APS lot used in the preparation of the biobatch.
9) Specifications (including in-process controls, methods of analysis of all materials), method of manufacture (including batch size) and detailed route of synthesis are verified as identical to those already accepted (such situations are generally limited to additional sites by the same manufacturer or new contract manufacturing site with evidence of an acceptable and similar quality system to the main manufacturer).

**Documentation required**

1) (S.2.1) Name, address, and responsibility of the proposed site or facility involved in manufacture or testing (including block(s) and unit(s). A valid testing authorization or a certificate of GMP compliance, if applicable.
2) (S.2.2) A side-by-side comparison of the manufacturing flowcharts for production of the APS, intermediate, or APS starting material (as applicable) at the parent and proposed sites.
3) (S.4.3) Copies or summaries of validation reports or method transfer reports, which demonstrate equivalency of analytical procedures to be used at the proposed testing site.

4) (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the APS from the currently accepted and proposed manufacturers/sites.
5) Relevant sections of (S) documentation in fulfillment of requirements for full information provided in the dossier
6) (P.8.2) If the quality characteristics of the APS are changed in such a way that it may impact the stability of the VPP, a commitment to put under stability one production scale batch of the VPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to The Authority.
7) (S.4.1) A copy of the VPP manufacturer's APS specifications.
8) (S.2) A declaration from the supplier of the registered VPP that the route of synthesis, materials, quality control procedures and specifications of the APS and key (ultimate) intermediate in the manufacturing process of the APS (if applicable) are the same as those already accepted.
9) A discussion of the impact of the new APS on the safety, efficacy and quality of the VPP.
10) For changes to the polymorph of an insoluble APS the applicant should contact The Authority for advice before embarking upon any investigation.
11) Certificates of analysis for at least one batch of APS starting material/intermediate (as applicable) issued by the new supplier and by the APS manufacturer. Comparative batch analysis of final APS manufactured using APS starting material/intermediate (as applicable) from the new source and from a previously accepted source.
12) An analysis of the impact of the change in supplier with respect to the need for APS stability studies and a commitment to conduct such studies if necessary.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 11a | Change or addition of a manufacturing block/unit at a currently accepted site of APS manufacture | 1-3 | 1-4 | IN |
| 11b | | 2-4 | | |

**Conditions to be fulfilled**

1) APS manufacturing block/unit is currently accepted by the NRA's APSMF procedure.
2) The same quality system covers currently accepted and proposed units/blocks.
3) For low solubility APSs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APSs) there is no significant change to the particle size distribution compared to the APS lot used in the preparation of the biobatch.
4) No change in the route of synthesis, quality control procedures and specifications of the APS and key (ultimate) intermediate in the manufacturing process of the APS (if applicable).

**Documentation required**

1) (S.2) A declaration from the supplier of the VPP that the route of synthesis, quality control procedures and specifications of the APS and key (ultimate) intermediate in the manufacturing process of the APS (if applicable) are the same as those already accepted.
2) (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing (including block(s) and unit(s). A valid manufacturing and/or testing authorization and a certificate of GMP compliance, if available.
3) (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the APS from the currently accepted and proposed units/blocks.
4) (S.2.2) A summary of differences between manufacture and control of the APS at the currently accepted and proposed units/blocks

| **Description of change** | | **Conditions to be fulfilled** | **Documentation to be supplied** | **Reporting type** |
|---|---|---|---|---|
| 12a | Change in the manufacturing process of the APS | 1-3, 6 | 1-2, 7 | AN |
| 12b | | 1-2, 5-7 | 3-4, 10-11 | IN |

| | | | | |
|---|---|---|---|---|
| | | | | |
| 12c | | 1-2, 5 | 3-4, 10-11 | Vmin |
| 12d | | None | 2-13 | Vmaj |

**Conditions to be fulfilled**

1) No change in the physical state (e.g. crystalline, amorphous) of the APS.
2) For low solubility APSs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APSs) there is no significant change in the particle size distribution compared to the APS lot used in the preparation of the biobatch.
3) APS manufacturing site is currently accepted through the The Authority APSMF procedure.
4) No change in the route of synthesis (i.e. intermediates remain the same) and there are no new reagents, catalysts or solvents used in the process.
5) No change in qualitative and quantitative impurity profile or in physicochemical properties of the APS.
6) The change involves only steps before the final intermediate.
7) The change does not require revision of the starting material, intermediate or APS specification

**Documentation to be supplied**

1) A copy of The Authority's letter of acceptance for APSMF amendment
2) (P.8.2) if the quality characteristics of the APS are changed in such a way that it may impact the stability of the VPP, a commitment to put under stability one production scale batch of the VPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to The Authority.
3) (S.2.2) A side-by-side comparison of the current process and the new process.
4) (S.2.2) A flow diagram of the proposed synthetic process (es) and a brief narrative description of the proposed manufacturing process (es).
5) (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed APS, where applicable.
6) (S.2.4) Information on controls of critical steps and intermediates, where applicable.
7) (S.2.5) Evidence of process validation, if applicable.
8) (S.3.1) Evidence for elucidation of structure, where applicable.
9) (S.3.2) Information on impurities.
10) (S.4.1) A copy of currently accepted specifications of APS (and starting material and intermediate, if applicable).
11) (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results, in a comparative tabular format, for at least two batches (minimum pilot scale) manufactured according to the current and proposed processes.
12) (S.7.1) Results of two batches of at least pilot scale with a minimum of three (3) months of accelerated (and intermediate as appropriate) and three (3) months of long-term testing of the proposed APS.
13) For low solubility APSs where the polymorphic form has changed or whenever particle size is critical (including low solubility APSs) where there is dissimilar particle size distribution compared to the lot used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the VPP.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation to be supplied** | **Reporting type** |
|---|---|---|---|---|
| 13 | Change in the in-process tests or limits applied during the manufacture of the APS: | | | |
| 13a | any change in the manufacturing process controls | 1 | No variation is required, such changes are handled as amendments to the APSMF by the APSMF holder as part of the The Authority procedure | |
| 13b | tightening of in-process limits | 2-4 | 1 | AN |
| 13c | addition of a new in-process test and limit | 2, 5 | 1-4 | AN |
| 13d | addition or replacement of an in-process test as a result of safety or quality issue | None | 1-4,6-8 | Vmin |
| 13e.1 | deletion of an in-process test | 2,6 | 1-3, 5 | AN |
| 13e.2 | | None | 1-3, 6-8 | Vmaj |
| 13f | relaxation of the in-process test limits | None | 1-3, 4,6-8 | Vmaj |

**Conditions to be fulfilled**

1) APS manufacturing site is currently accepted through the The Authority APSMF procedure.
2) The change is not necessitated by unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
3) The change is within the range of currently accepted limits.

4) The analytical procedure remains the same, or changes to the analytical procedure are minor.
5) Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
6) The affected parameter is non-significant.

**Documentation to be supplied**

1) A comparison of the currently accepted and the proposed in-process tests.
2) (S.2.2) Flow diagram of the proposed synthetic process (es) and a brief narrative description of the proposed manufacturing process (es).
3) (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed APS.
4) Justification for the new in-process test and/or limits.
5) Justification/risk-assessment showing that the parameter is non-significant. ("The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for changing the frequency of testing.")
6) (S.3.2) Information on impurities, if applicable.
7) (S.4.1) Copy of currently accepted specifications of APS (and intermediates, if applicable).
8) (S.4.4) Description of the batches, certificates of analysis or batch analysis report and summary of results, in a comparative tabular format, for at least two batches (minimum pilot scale) for all specification parameters.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 14 | Change in batch size of the APS involving: | | | |
| 14a | up to 10-fold compared to the currently accepted batch size | 1-2,5 | 1,3-4 | AN |
| 14b | downscaling | 1-3 | 1,3-4 | AN |
| 14c | any change in scale (APSMF procedure) | 4 | 1-2, 4-5 | AN |
| 14d | more than 10-fold increase compared to the currently accepted batch size | 1-2,5 | 1,3-4 | Vmin |

**Conditions to be fulfilled**

1) No changes to the manufacturing process other than those necessitated by changes in scale (e.g. use of different size of equipment).
2) The change does not affect the reproducibility of the process.
3) The change is not necessitated by unexpected events arising during manufacture or due to stability concerns.
4) APS manufacturing site and batch size is currently accepted through the The Authority APSMF procedure.
5) The proposed batch size increase is relative to either the originally accepted batch size, or the batch size accepted through a subsequent major or minor variation.

**Documentation required**

1) (S2.2) A brief narrative description of the manufacturing process.
2) (S.2.5) Where applicable, evidence of process validation.
3) (S.4.1) Copy of the currently accepted specifications of the APS (and of the intermediate, if applicable).
4) (S.4.4) Batch analysis data (in tabular format) issued by the VPP manufacturer for a minimum of two batches each of the currently accepted batch size and the proposed batch size.
5) A copy of the The Authority letter of acceptance for APSMF amendment.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 15 | Change to the specifications or analytical procedures applied to materials used in the manufacture of the APS (e.g. raw materials, starting materials, reaction intermediates, solvents, reagents, catalysts) involving: | | | |
| 15a | any change | 1 | No variation is required, such changes are handled as amendments to the APSMF by the APSMF holder as part | |

| | | | | |
|---|---|---|---|---|
| | | | of the The Authority APSMF procedure. | |
| 15b | tightening of the specification limits | 2-4 | 1-3 | AN |
| 15c | minor change to an analytical procedure | 5-7 | 2-3 | AN |
| 15d | addition of a new specification parameter and a corresponding analytical procedure where necessary. | 2,7-9 | 1-3 | AN |
| 15e | deletion of a specification parameter or deletion of an analytical procedure | 2,10 | 1-4 | AN |
| 15f | addition or replacement of a specification parameter as a result of a safety or quality issue | None | 1-3,4, 5 | Vmin |
| 15g | relaxation of the currently accepted specification limits for solvents, reagents, catalysts and raw materials | 4,7,9-10 | 1,3-4 | IN |
| 15h | relaxation of the currently accepted specification limits for APS starting materials and intermediates | None | 1-3,5 | Vmaj |

**Conditions to be fulfilled**

1) APS manufacturing site is currently accepted through the The Authority APSMF procedure.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any change is within the range of currently accepted limits.
4) The analytical procedure remains the same.
5) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method).
6) Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
7) No change to the total impurity limits; no new impurities are detected.
8) Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
9) The change does not concern a genotoxic impurity.
10) The affected parameter is non-significant or the alternative analytical procedure has been previously accepted.

**Documentation to be supplied**

1) Comparative table of currently accepted and proposed specifications.
2) (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed APS, where applicable.
3) (S.2.4) Information on intermediates, where applicable.
4) Justification/risk-assessment showing that the parameter is non-significant.
5) (S.3.2) Information on impurities, where applicable.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 16 | *Changes to the test parameters, acceptance criteria, or analytical procedures of the APS manufacturer that do not require a change to the VPP manufacturer's APS specifications involving:* | | | |
| 16a | a. APS supported through the The Authority APSMF procedure. | 1-2 | No variation is required, such changes are handled as amendments to the associated APSMF | |
| 16b | b. APS not supported through the The Authority APSMF procedure. | 2 | 1-4 | IN |
| **Conditions to be fulfilled** | | | | |

1) The revised test parameters, acceptance criteria, or analytical procedures have been submitted as amendments to the associated APSMF (The Authority APSMF procedure) and accepted.
2) The APS manufacturer has provided the relevant documentation to the VPP manufacturer. The VPP manufacturer has considered the APS manufacturer's revisions and determined that no consequential revisions to the VPP manufacturer's APS test parameters, acceptance criteria, or analytical procedures are required to ensure that adequate control of the APS is maintained.

**Documentation to be supplied**

1) (S.4.1) Copy of the current and proposed APS specifications dated and signed by the APS manufacturer.
2) (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (S.4.3) Copies or summaries of validation reports for new or revised analytical procedures, if applicable.
4) Justification as to why the change does not affect the VPP manufacturer's specifications.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 17 | *Change to the test parameters or acceptance criteria of the APS specifications of the VPP manufacturer involving*: | | | |
| 17a | | *8* | | |
| 17a.1 | deletion of a test parameter | 1-2 | 1,5 | AN |
| 17a.2 | | 7 | 1, 5, 87 | IN |
| 17a.3 | | None | 1, 5 | Vmaj |
| 17b.1 | addition of a test parameter | 1, 4-5 | 1-5 | AN |
| 17b.2 | | 1, 5, 7 | 1-5,7 | IN |
| 17b.3 | | 1,5 | 1-5 | Vmin |
| 17b.4 | | None | 1-6 | Vmaj |
| 17c.1 | replacement of a test parameter | 1, 5 | 1-5 | IN |
| 17c.2 | | 5, 7 | 1-5,7 | Vmin |
| 17c.3 | | None | 1-6 | Vmaj |
| 17d.1 | tightening of an acceptance criterion | 1, 3, 6 | 1,5 | AN |
| 17e.1 | relaxation of an acceptance criterion | 1, 5-7 | 1,5 | IN |
| 17e.2 | | 5, 8 | 1, 5,7 | Vmin |
| 17e.3 | | None | 1,5-6 | 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.
2) The deleted test has been demonstrated to be redundant with respect to the remaining tests.
3) The change is within the range of currently accepted acceptance criteria.
4) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5) For insoluble APSs there is no change in the polymorphic form and whenever particle size is critical (including low solubility APSs) there is no change in particle size distribution acceptance criteria.
6) The associated analytical procedure remains the same.
7) The change has resulted from a revision of the APS manufacturer's specifications and is accepted as part of an APSMF amendment.
8) No change is required in VPP release and shelf-life specifications.

**Documentation to be supplied**

1) (S.4.1) A copy of the proposed APS specifications (of the VPP manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications. In addition, if the change has resulted from a revision to the APS manufacturer's specifications, a copy of the APS specifications (of the APS manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2) (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (S.4.3) Copies or summaries of validation/verification reports issued by the VPP manufacturer, if new analytical procedures are used.
4) (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results in tabular format, for at least one batch if new tests and/or analytical methods are implemented.
5) (S.4.5) Justification of the proposed APS specifications (e.g. test parameters, acceptance criteria, or analytical procedures).

6) For changes to the polymorph of an insoluble APS the applicant should contact The Authority for advice before embarking upon any investigation.
7) Copy of the The Authority letter of acceptance for APS Master File amendment.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 18 | *Change to the analytical procedures used to control the APS by the VPP manufacturer involving:* | | | |
| 18a.1 | Addition of an analytical procedure | 1-3 | 1-3 | AN |
| 18a.2 | | 3, 7 | 1-3, 5 | AN |
| 18a.3 | | 7 | 1-3, 5 | Vmin |
| 18a.4 | | None | 1-3 | Vmaj |
| 18b.1 | Modification or replacement of an analytical procedure | 1-5 | 1-4 | AN |
| 18b.2 | | 2-3, 5, 7 | 1-5 | AN |
| 18b.3 | | 1-3, 5 | 1-4 | Vmin |
| 18b.4 | | 5, 7 | 1-5 | Vmin |
| 18b.5 | | None | 1-4 | Vmaj |
| 18c.1 | Deletion of an analytical procedure | 7 | 1,6 | AN |
| 18c.2 | | 7 | 1, 5, 6 | IN |
| 18c.3 | | None | 1, 6 | Vmaj |

**Conditions to be fulfilled**

1) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) No new impurities have been detected as a result of the use of the new analytical method.
4) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc), but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected.
5) Comparative studies are available demonstrating that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
6) The deleted analytical procedure is an alternate method and is equivalent to a currently accepted method.
7) The new or modified analytical method is identical to that used by the APS manufacturer and has been accepted as part of an amendment to the associated APSMF.

**Documentation to be supplied**

1) (S.4.1) Copy of the proposed APS specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2) (S.4.2) Copies or summaries of analytical procedures, if new or significantly modified analytical procedures are used.
3) S.4.3) Copies or summaries of validation/verification reports issued by the VPP manufacturer, if new or significantly modified analytical procedures are used.
4) (S.4.4) Comparative analytical results demonstrating that the proposed analytical procedures are at least equivalent to the accepted analytical procedures.
5) A copy of the The Authority letter of acceptance for APSMF amendment
6) (S.4.5) Justification for the deletion of the analytical procedure, with supporting data.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 19a | *Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the APS* | 2, 3 | 1-2,4 | AN |
| 19b | | 1, 3 | 2-3 | IN |
| 19c | | 3 | 1-3 | Vmin |

**Conditions to be fulfilled**

1) Results demonstrate that the proposed primary packaging type is at least equivalent to the currently accepted primary packaging type with respect to its relevant properties (e.g. including results of transportation or interaction studies, moisture permeability etc.).
2) The change has previously been accepted through the The Authority APSMF procedure.
3) The change is not the result of stability issues.

**Documentation required**

1) (S.2.5) Evidence of process validation if different from the current process.
2) (S.6) Information on the proposed primary packaging (e.g. description, specifications etc.) and data in fulfillment of condition 1.
3) (S.7.1) Results of a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing of the APS in the proposed primary packaging type.
4) A copy of The Authority letter of acceptance for APSMF amendment

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 20 | *Change in the specifications of the immediate packaging for the storage and shipment of the APS involving:* | | | |
| 20a | tightening of specification limits | 1-2 | 1 | AN |
| 20b | addition of a test parameter | 2-3 | 1-3 | AN |
| 20c | deletion of a non-critical parameter | 2 | 1,4 | AN |
| 20d | any change to the Authority APSMF procedure | 4 | No variation is required, such changes are handled as amendments to the associated APSMF | |

**Conditions to be fulfilled**

1) The change is within the range of currently accepted limits.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4) The change has previously been accepted through the Authority APSMF procedure.
5)

**Documentation required**

1) (S.4.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2) (S.4.2) Details of method and summary of validation of new analytical procedure.
3) (S.6) Certificate of analysis for one batch.
4) Justification to demonstrate that the parameter is not critical.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 21 | *Change to an analytical procedure on the immediate packaging of the APS involving:* | | | |
| 21a | minor change to an analytical procedure | 1-3 | 1 | AN |
| 21b | other changes to an analytical procedure including addition or replacement of an analytical procedure | 2-4 | 1 | AN |
| 21c | deletion of an analytical procedure | 5 | 2 | AN |
| 21d | any change (The Authority APSMF procedure) | 6 | No variation is required, such changes are handled as amendments to the associated APSMF | |

**Conditions to be fulfilled**

1) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method).
2) Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.
3) Comparative studies indicate the new analytical procedure to be at least equivalent to the former procedure.
4) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5) The deleted analytical procedure is an alternate method and is equivalent to a currently accepted method.
6) The change has previously been accepted through the The Authority APSMF procedure.

| **Documentation required** |
|---|
| 1) (S.6) Comparative validation results demonstrating that the currently accepted and proposed procedures are at least equivalent.<br>2) Justification for deletion of the analytical procedure. |

## 3.2. S.7 Stability

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 22 | *Change in the retest period/shelf-life of the APS involving:* | | | |
| 22a | any change to the The Authority APSMF procedure | 4 | 4 | IN |
| 22b | reduction | 3 | 1-2 | IN |
| 22c | extension | 1-2 | 1-3 | Vmin |
| **Conditions to be fulfilled** | | | | |
| 1) No change to the primary packaging in direct contact with the APS or to the recommended condition of storage.<br>2) Stability data was generated in accordance with the currently accepted stability protocol.<br>3) The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.<br>4) The revised retest period has previously been accepted through the The Authority APSMF procedure. | | | | |
| **Documentation required** | | | | |
| 1) (S.7.1) Proposed retest period/shelf-life, summary of stability testing according to currently accepted protocol and test results.<br>2) (S.7.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable.<br>3) (S.7.3) Stability data to support the change<br>4) A copy of the The Authority letter of acceptance for APSMF amendment. | | | | |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 23 | *Change in the labelled storage conditions of the APS involving:* | | | |
| 23a | any change in storage conditions The Authority APSMF procedure | 1 | 1 | IN |
| 23b | any change in storage conditions | 2 | 2 | Vmin |
| **Conditions to be fulfilled** | | | | |
| 1) The revised storage conditions have previously been accepted through the Authority APSMF procedure.<br>2) 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) A copy of the the Authority letter of acceptance for APSMF amendment.<br>2) (S.7.1)Stability and/or compatibility test results to support the change to the storage conditions. | | | | |

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 24a | *Change in the composition of a solution dosage form* | 1-4 | 1,3,6-7 | IN |
| 24b | | None | 1-9 | Vmaj |

**Conditions to be fulfilled**

1) The affected excipient(s) does/do not function as a preservative or preservative enhancer.
2) No change in the specifications of the affected excipient(s) or the VPP.
3) No change in the physical characteristics of the VPP (e.g. viscosity, osmolality, pH).
4) The excipients are qualitatively the same. The change in the amount (or concentration) of each excipient is within ±10% of the amount (or concentration) of each excipient in the originally registered product.

**Documentation required**

1) P.1) Description and composition of the VPP.
2) (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of APS and excipients, preservative effectiveness, suitability studies on the packaging system for the changed product).
3) (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
4) (P.4) Control of excipients, if new excipients are proposed.
5) (P.5) Copies of VPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot or production scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the VPP.
6) (P.8.1) Results of stability testing generated on at least two pilot or production scale batches with a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing.
7) (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
8) (R.1) Copies of relevant pages of blank master production documents with changes highlighted, as well as relevant pages of the executed production document for one batch and confirmation that there are no changes to the production documents other than those highlighted.
9) Two (2) commercial samples of the product

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 25 | *Addition or replacement of a manufacturing site for part or all of the manufacturing process for a VPP involving* | | | |
| 25a | Secondary packaging of all types of VPPs | 2-3, 5 | 1 | IN |
| 25b | primary packaging site of: | | | |
| 25b.1 | solution liquid VPPs | 2-3, 5 | 1,6 | IN |
| 25b.2 | other liquid VPPs (emulsions) | 2-5 | 1,6 | IN |
| 25c | all other manufacturing operations except batch control/release testing | 1-5 | 1-7 | Vmin |

**Conditions to be fulfilled**

1) No change in the batch formula, description of manufacturing process and process controls, equipment class and process controls, controls of critical steps and intermediates, or VPP specifications.
2) Satisfactory joint inspection in the last three years by The Authority.
3) Site appropriately authorized by an NPRA (to manufacture the pesticide form and the product concerned).
4) Validation protocol is available or validation of the manufacturing process at the new site has been successfully carried out on at least three production scale batches in accordance with the current protocol.
5) The current/previous manufacturing site has a valid NPRAs GMP certificate.

**Documentation required**

1) Evidence that the proposed site is appropriately authorized in the last 3 years, for the pesticide form and the product concerned:
    a. a copy of the current manufacturing authorization, a GMP certificate or equivalent issued by the NPRA
    b. a GMP certificate issued by NPRAs
    c. date of the last satisfactory inspection concerning the packaging facilities by Authority
2) Date and scope of the last satisfactory inspection.
3) (P.2) Where applicable, for semisolid and liquid formulations in which the APS is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
4) (P.5.1) Copies of VPP release and shelf-life specifications from the proposed manufacturing site.
5) (P.5.4) Batch analysis data on one production scale batch from the proposed site and comparative data on the last three batches from the previous site.
6) (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of the VPP produced at the new site, into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
7) (R.1)Executed production documents for one batch of the VPP manufactured at the new site.

**Note:**
Two (2) commercial samples of the product should be submitted where the manufacturing site appears on the product label.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 26 | *Replacement or addition of a site involving batch control testing* | 1-2 | 1-3 | AN |

**Conditions to be fulfilled**

1) Site is appropriately authorized by The Authority and should be GMP compliant
2) Transfer of methods from the current testing site to the proposed testing site has been successfully completed.

**Documentation required**

1) Clear identification of the currently accepted and proposed quality control sites on the letter accompanying the application.
2) Documented evidence that the site is appropriately authorized by The Authority and satisfactorily inspected by The Authority.
3) Documented evidence of successful transfer of analytical procedures from the current to the proposed site.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 27 | *Change in the batch size of the VPP involving* | | | |
| 27a | up to and including a factor of ten (10) compared to the biobatch | 1-4 | 1, 4-5 | IN |
| 27b | downscaling | 1-4 | 1,5 | AN |
| 27c | other situations | 1-~~4~~ | 1-5 | Vmin |

**Conditions to be fulfilled**

1) The change does not affect the reproducibility and/or consistency of the product.
2) Changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch size e.g. use of different size equipment.
3) A validation protocol is available or validation of the manufacture of three production scale batches has been successfully undertaken in accordance with the current validation protocol.
~~4)~~ The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

**Documentation required**

1) (P.3.5) Process validation reports for three batches of the proposed batch size or validation protocol (scheme).
2) (P.5.1) Copies of release and shelf-life specifications.
3) (P.5.4) Batch analysis data (in a comparative tabular format) on a minimum of one production scale batch manufactured to both the currently accepted and the proposed batch sizes. Batch data on the next two (2) full production scale batches should be available on request and should be reported immediately if outside specifications (with proposed remedial action).

4) (P.8.2) Updated post-acceptance stability protocol (approved by authorized personnel) and stability commitment to place the first production scale batch of each strength at the proposed scale into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
5) (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch (if manufactured as required by documentation 3) and confirmation that there are no changes to the production documents other than those highlighted.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| *28a* | *Change in the manufacturing process of the VPP* | *1-7* | *1-2, 4-5* | *AN* |
| 28b | | 1-3, 5-7 | 1-5 | Vmin |

**Conditions to be fulfilled**

1) The change does not require supporting in vivo data.
2) No change in qualitative and quantitative impurity profile or in physico-chemical properties; dissolution profiles are similar with those of the biobatch.
3) The manufacturing processes for the currently accepted and proposed products use the same principles (e.g. a change from wet to dry granulation, from direct compression to wet/dry granulation or vice versa would be considered a change in manufacturing principle), same processing intermediates and there are no changes to any manufacturing solvent used in the process.
4) The same classes of equipment, operating procedures, in-process controls (no widening or deleting of limits) are used for the currently accepted and proposed products; no change in critical process parameters.
5) No change in the specifications of the intermediates or the VPP.
6) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
7) The change does not involve packaging or labeling where the primary packaging provides a metering and/or delivery function.

**Documentation required**

1) (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
2) (P.5) Specification(s), certificate of analysis for one production scale batch each manufactured according to the currently accepted and the proposed processes.
3) P.8.1) Results of stability testing generated on at least two pilot batches (for uncomplicated products one pilot batch, the other one can be smaller) with a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing.
4) P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of the proposed product into the long-term stability programme.
5) (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as executed production documentation for one batch and confirmation that there are no changes to the currently accepted production documents other than those highlighted.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 29 | *Change to in-process tests or limits applied during the manufacture of the VPP or intermediate involving:* | | | |
| 29a | tightening of in-process limits | 1-2,5 | 1 | AN |
| 29b | deletion of a test | 2,4 | 1, 5 | AN |
| 29c | addition of new tests and limits | 2-3 | 1-5 | Minor variation (zero rated) |
| 29d | revision or replacement of a test | 2-3 | 1-5 | Minor variation |

**Conditions to be fulfilled**

1) The change is within the range of acceptance limits.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any new test does not concern a novel, non-standard technique or a standard technique used in a novel way.
4) The deleted test has been demonstrated to be redundant with respect to the remaining analytical procedures (e.g. colour) and does not affect the critical quality attributes of the product (e.g. blend uniformity, weight variation).
5) No change in the analytical procedure.

**Documentation required**

1) (P.5.1) Copy of the proposed in-process specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2) (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4) (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot scale) and comparative summary of results, in tabular format, for one batch using current and proposed methods, if new analytical procedures are implemented.
5) (P.5.6) Justification for the addition/deletion of the tests and limits.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 30 | *Change in the specifications or analytical procedures of an excipient involving:* | | | |
| 30a | deletion of a non-significant in-house parameter | 2 | 1-3 | AN |
| 30b | addition of a new test parameter or analytical procedure | 2-3 | 1-2 | AN |
| 30c | tightening of specification limits | 1-2,4 | 1-2 | AN |
| 30d | change or replacement of an analytical procedure | 2-3 | 1-2 | Vmin |

**Conditions to be fulfilled**

1) The change is within the range of currently accepted limits.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4) No change in the analytical procedure.

**Documentation required**

1) Justification for the change.
2) (P.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications and details of procedure and summary of validation of any new analytical procedure (if applicable).
3) Justification to demonstrate that the parameter is not critical.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 31 | *Change in the specifications of the VPP involving test parameters and acceptance criteria:* | | | |
| 31a | deletion of a test parameter | 4 | 1,5 | AN |
| 31b | addition of a test parameter | 2-3, 6 | 1-5 | AN |
| 31c | tightening of an acceptance criterion | 1-2 | 1,5 | AN |
| 31d | relaxation of an acceptance criterion | 2,3,4-5 | 1,4-5 | IN |
| 31e | replacement of a test parameter | 2-3,4-5 | 1-5 | IN |

**Conditions to be fulfilled**

1) The change is within the range of currently accepted limits.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4) The deleted test has been demonstrated to be redundant with respect to the remaining tests.
5) The change to the specifications does not affect the stability and the performance of the product.
6) The change does not concern sterility testing.

**Documentation required**

1) (P.5.1) Copy of the proposed VPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2) (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4) (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed procedures, if new analytical procedures are implemented.

5) (P.5.6) Justification for the proposed VPP specifications.

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 32 | *Change in the analytical procedures for the VPP involving:* | | | |
| 32a | deletion of an analytical procedure | 3 | 1,5 | AN |
| 32b | addition of an analytical procedure | 2,4-5 | 1-4 | AN |
| 32c.1 | modification or replacement of an analytical procedure | 1-2, 4-5 | 1-4 | AN |
| 32c.2 | | 4-5 | 1-4 | Vmin |

**Conditions to be fulfilled**

1) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected.
2) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
3) The deleted analytical procedure is an alternate method and is equivalent to another currently accepted analytical procedure.
4) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
5) No new impurities have been detected.

**Documentation required**

1) (P.5.1) A copy of the proposed VPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2) (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (P.5.3) Copies or summaries of validation reports, including verification data for assay or purity methods, if new analytical procedures are used.
4) (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed analytical procedures.
5) Justification for the deletion of the analytical procedure, with supporting data.

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 33a | *Replacement or addition of a primary packaging type* | 1 | 1-2,3-5 | Vmin |
| 33b | | None | 1-5 | Vmaj |

**Conditions to be fulfilled**

1) None

**Documentation required**

1) Two (2) commercial samples of the product as packaged in the new container-closure system.
2) (P.2) Data on the suitability of the container closure system (e.g. extractable/leachable testing, permeation testing, light transmission) demonstrating equivalent or superior protection compared to the current packaging system. For changes to functional packaging, data to demonstrate the functioning of the new packaging.
3) (P.7) Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications, results of transportation studies, if appropriate).
4) (P.8.1) Stability summary and conclusions, results for a minimum of two (2) batches of pilot or production scale, of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing and where applicable, results of photo stability studies.
5) (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of the proposed product into the long-term stability programme, unless data was provided in documentation 5.

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 34 | *Change in the package size involving:* | | | |
| 34a | Change in the fill weight/fill volume of multidose products | 1-2 | 1-3 | Vmin |

**Conditions to be fulfilled**

1) The change is consistent with the posology and treatment duration accepted in the SmPC.
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 SmPC.
2) (P.8.2) A written commitment that stability studies will be conducted in accordance with NPRAs guidelines for products where stability parameters could be affected.
3) Two (2) commercial samples of the product.

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 35 | *Change in the shape or dimensions of the container or closure for:* | | | |
| 35 a | All delivery forms of VPPs | 1-2 | 1-2 | Vmin |

**Conditions to be fulfilled**

1) No change in the qualitative or quantitative composition of the container and/or closure.
2) The change does not concern a fundamental part of the packaging material, which could affect the delivery, use, safety or stability of the VPP.

**Documentation required**

1) Two (2) commercial samples of the product.
2) (P.7) Information on the proposed container-closure system (e.g. description, materials of construction, specifications etc.)

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 36 | *Change in qualitative and/or quantitative composition of the immediate packaging material for:* | | | |
| 36a | liquid VPPs | 1 | 1-3 | Vmin |

**Conditions to be fulfilled**

1) The relevant properties of the proposed packaging are at least equivalent to those of the currently accepted material.

**Documentation required**

1) (P.2) Data demonstrating the suitability of the proposed packaging material (e.g. extractable/leachable testing, light transmission, permeation testing for oxygen, carbon dioxide, moisture etc.).
2) (P.7) Information on the proposed packaging material (e.g. description, materials of construction, specifications etc.).
3) (P.8.1) Stability summary and conclusions, results for a minimum of two batches of pilot or production scale, of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing and where applicable, results of photo stability studies.

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 37 | *Change in the specifications of the immediate packaging involving:* | | | |
| 37a | tightening of specification limits | 1-2 | 1 | AN |
| 37b | addition of a test parameter | 2-3 | 1-2 | AN |
| 37c | deletion of a non-critical parameter | 2 | 1,3 | AN |

**Conditions to be fulfilled**

1) The change is within the range of currently accepted limits.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

**Documentation required**

1) (P.7) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2) (P.7) Description of the analytical procedure and summary of validation of the new analytical procedure.
3) Documentation to demonstrate that the parameter is not critical.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 38 | *Change to an analytical procedure on the immediate packaging involving:* | | | |
| 38a | minor change to an analytical procedure | 1-3 | 1 | AN |
| 38b | other changes to an analytical procedure including addition or replacement of an analytical procedure | 2-4 | 1 | AN |
| 38c | deletion of an analytical procedure | 5 | 2 | AN |

**Conditions to be fulfilled**

1) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method).
2) Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.
3) Comparative studies indicate the new analytical procedure to be at least equivalent to the former procedure.
4) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5) The deleted analytical procedure is an alternate method and is equivalent to a currently accepted method.

**Documentation required**

1) (P.7) Description of the method and comparative validation results demonstrating that the currently accepted and proposed methods are at least equivalent.
2) Documentation demonstrating that condition #5 is met.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 39 | *Change in any part of the (primary) packaging material not in contact with the VPP formulation (e.g. colour of caps, and change of secondary pack).* | | | |
| 39a | Change in any part of the (primary) packaging material not in contact with the finished pesticide product formulation (e.g. colour of caps) | 1 | 1-2 | IN |
| 39b.1 | Change of secondary packaging components | 2 | 2-3 | IN |
| 39b.2 | | None | 1-4 | Vmin |

**Conditions to be fulfilled**

1) The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the VPP.
2) The registered and proposed secondary packaging components are non-functional

**Documentation required**

1) (P.7) Information on the proposed packaging material (e.g. description, materials of construction, specifications etc.).
2) Two (2) commercial samples of the product.
3) Brief description of the secondary packaging components
4) Discussion on suitability with respect to, for example, protection from moisture and light, and provide supportive data e.g. moisture permeability, photo-degradation, stability studies.

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 40 | *Change to an administration or measuring device that is not an integral part of the primary packaging:* | | | |
| 40a | addition or replacement | 1,2 | 1-2 | IN |
| 40b | deletion | 3 | 3 | IN |
| **Conditions to be fulfilled** | | | | |
| 1) The proposed measuring device is designed to accurately deliver the required dose for the product concerned, in line with the posology and results of such studies are available.<br>2) The proposed device is compatible with the VPP.<br>3) The VPP can be accurately delivered in the absence of the device. | | | | |
| **Documentation required** | | | | |
| 1) (P.2) Data to demonstrate accuracy, precision and compatibility of the device.<br>2) Two (2) samples of the device.<br>3) Justification for the deletion of the device. | | | | |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 41 | *Change in the shelf-life of the VPP (as packaged for sale) involving:* | | | |
| 41a | reduction | 3 | 1-4 | Vmin |
| 41b | extension | 1-2 | 1-4 | Vmaj |
| **Conditions to be fulfilled** | | | | |
| 1) No change to the primary packaging type in direct contact with the VPP and to the recommended condition of storage.<br>2) Stability data was generated in accordance with the currently accepted stability protocol.<br>3) The change is not necessitated by unexpected events arising during manufacture or because of stability concerns. | | | | |
| **Documentation required** | | | | |
| 1) (P.5.1) Copy of the currently accepted shelf-life specifications.<br>2) (P 8.1) Proposed shelf-life, summary of long-term stability testing according to currently accepted protocol and test results for a minimum of two pilot or production scale batches.<br>3) (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.<br>4) Two (2) commercial samples of the product | | | | |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 42 | *Change in the in-use period of the VPP (after first opening):* | | | |
| 42a | Reduction | 1 | 1-3 | IN |
| 42b | Extension | None | 1-3 | 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) (P 8) Proposed in-use period, test results and justification of change.<br>2) (P5.1) Copy of currently accepted end of shelf-life VPP specifications and where applicable, specifications after dilution.<br>3) Two (2) commercial samples of the product | | | | |

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 43 | *Change in the labelled storage conditions of the VPP (as packaged for sale), the product during the in-use period* | 1 | 1-3 | 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) (P.8.1) If applicable, stability and/or compatibility test results to support the change to the storage conditions.<br>2) (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.<br>3) Two (2) commercial samples of the product | | | | |

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 44 | Change in the Summary of product Characteristics, Labelling or Package Leaflet of a generic pesticide product following assessment of the same change for the reference (innovator) product | | | |
| 44a | Implementation of change(s) for which no new additional data are submitted by the MAH | None | 1 | Vmin |
| 44b | Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability) | | 1,2 | Vmaj |
| **Documentation required** | | | | |
| 1) Revised product information<br>2) Applicable additional data | | | | |

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 45 | *Implementation of change(s) requested by The Authority following assessment of an Urgent safety restriction, class labelling or periodic safety update report* | | | |
| 45a | Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH | | 1,2 | Vmin |
| 45b | Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH | | | Vmaj |
| **Documentation required** | | | | |
| 1) The Authority's request with attached relevant assessment report<br>2) Revised product information. | | | | |

| Description of change | | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|---|
| 46 | *Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or monitoring data* | | | |
| 46a | Change to the hazard of the Pesticide Product | 1, 2 | 1 or 2 | Vmaj |
| **Conditions to be fulfilled** | | | | |
| 1) Reference to the established or updated hazard classification or Risk assessment for the APSs<br>2) For generic products the same change should have been approved for a reference/innovator product | | | | |
| **Documentation required** | | | | |

| |
|---|
| 1) A report of WHO Rotterdam and other relevant hazard classification bodies to justify the change.<br>**2)** Relevant numbers of commercial samples of the product |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 47 | *Change(s) to indication(s)* | | | |
| 47a | Addition of a new indication or modification of an approved one | | | Vmaj |
| 47b | Deletion of indication | | | Vmin |
| **Note:** Where the addition or modification of indication takes place in the context of the implementation of changes to the product information of a generic/hybrid/biosimilar product following assessment of the same change for the reference (innovator) product, variations 46 applies. Could be due to re-classification. | | | | |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 48 | Variations concerning a change to or addition of a non-food producing target species | | | |
| | | | 1-3 | Vmaj |
| **Documentation required** | | | | |
| 1) Copies of reports for dose-response studies performed in the new target species<br>2) Where the addition or change of the target species takes place in the generic product following assessment of the same change for the reference (innovator) product, evidence of approval of the change by the Stringent Regulatory Authorities<br>3) Revised product information including the SmPC, product leaflet and label. | | | | |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 49 | Deletion of a food producing or non-food producing target species | | | |
| 49a | Deletion as a result of a safety issue | | | Vmaj |
| 49b | Deletion not resulting from a safety issue | | 1,2 | Vmin |
| **Documentation required** | | | | |
| 1) Justification for the deletion of the target species<br>2) Revised product information | | | | |

| **Description of change** | | **Conditions to be fulfilled** | **Documentation required** | **Reporting type** |
|---|---|---|---|---|
| 50 | Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics including; | | | |
| | • Change in colour of the packaging.<br>• Change in the layout of information /pictures without altering the meaning.<br>• Addition/deletion/replacement of pictures, diagrams, bar code, logos. | | 1,2,3,4 | Vmin |
| **Documentation required** | | | | |
| | 1) Current approved product labeling.<br>2) Proposed product labeling, a clean and annotated version highlighting the changes made.<br>3) Letter of declaration from the marketing authorization holder stating that no other changes on the label/package leaflet except for the intended change.<br>4) Relevant document/reference to support the changes (where applicable). | | | |

## Appendix 1: Examples of Changes That Make a New Application Necessary

| Description of change | Conditions to be fulfilled | Documentation required | Reporting type |
|---|---|---|---|
| 1. Change of the APS to a different APS<br><br>2. Inclusion of an additional APS to a multicomponent product<br><br>3. Removal of one APS from a multicomponent product<br><br>4. Change in the dose/strength of one or more APSs<br><br>6. Change in dosage form<br><br>7. Changes in the route of administration | None | 1 | New application |
| **Conditions to be fulfilled** | | | |
| None | | | |
| **Documentation required** | | | |
| Documents in fulfillment of the requirements outlined in National Pesticide Regulatory Agencies Guidelines on Submission of Documentation for Marketing Authorization of a Registered Pesticide Product. | | | |

## Appendix 2: Changes to Excipients

| Excipient | Percent excipient (w/w) out of total target dosage form core weight |
|---|---|
| Filler | ±5.0 |
| Disintegrant<br>• Starch<br>• Other | <br>±3.0<br>±1.0 |
| Binder | ±0.5 |
| Lubricant<br>• Ca or Mg Stearate<br>• Other | <br>±0.25<br>±1.0 |
| Glidant<br>• Talc<br>• Other | <br>±1.0<br>±0.1 |

(a) These percentages are based on the assumption that the APS in the VPP is formulated to 100.0% of label/potency. The total additive effect of all excipient changes should be not more than 5.0% relative to the target dosage form weight (e.g. in a product consisting of APS, lactose, microcrystalline cellulose and magnesium stearate, the lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%).

(b) If an excipient serves multiple functions (e.g. microcrystalline cellulose as filler and as a disintegrant), then the most conservative recommended range should be applied (e.g. ±1.0% for microcrystalline cellulose should be applied in this example). If a wider range is proposed, scientific justification and supporting data should be provided to demonstrate that the wider range will not affect the other function of the excipient.

## LITERATURE REFERENCES


(a) Guideline to a registered pharmaceutical Product-Code PSS/1/1/21/104): https://www.eac.int/documents/category/livestock

(b) European Commission's Guidelines. https://www.ema.europa.eu/en/veterinary-regulatory/post-authorisation