swissmedic

Guidance document
Variations TAM

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List of contents

1 Terms, definitions, abbreviations

1.1 Definitions and terms

1.1.1 Variations without assessment

Variations which only have minimal consequences for quality, safety or efficacy of a veterinary medicinal product and must be reported to Swissmedic in writing by the marketing authorisation holder after they have been implemented (*Do and Tell*) do not require assessment. Variations without assessment include all former type IA/IA_{IN} variations and some former Type IB variations. The legal framework is provided by Art. 25a TPO.

Variations without assessment must be reported to Swissmedic within 60 days of their implementation.

1.1.2 Variations with assessment

Variations which may have significant implications for the quality, safety or efficacy of a veterinary medicinal product require assessment. Variations with assessment include all former Type II variations, the majority of former Type IB variations and former extensions. The legal framework is provided by Art. 25b TPO.

The following time limits apply to variations with assessment:

- The former Type IB variations must be reported to Swissmedic in writing before they are implemented (*Tell and Do*). If Swissmedic does not raise any objections within 60 days of receipt of a valid report and the complete documentation, the variation is considered to be approved from the first day after this period elapses (= variation with time limit “Reduced”).
- The former Extensions and the former Type II variations must be approved by Swissmedic before they are implemented (= application with time limit “Standard”).

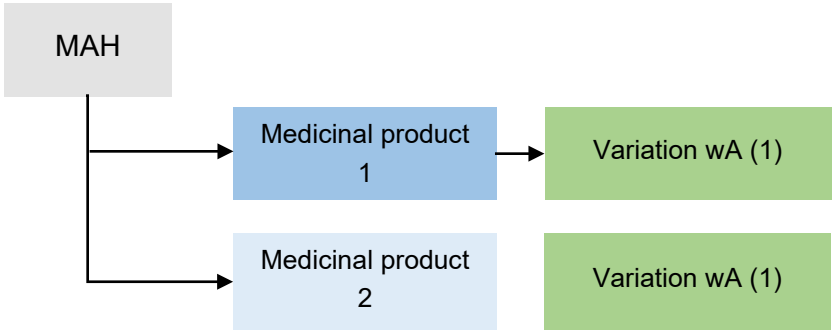
The relevant time limits (“Reduced” or “Standard”) applicable to specific variations for all variations with assessment are listed in the form *Variations VMP*.

1.1.3 Collective application

The same variation for several veterinary medicinal products (identical variation code) can be submitted jointly as a collective application, provided that identical documentation is submitted for all the veterinary medicinal products concerned.

Collective applications which involve changes to the Information for healthcare professionals in sections 4 to 6 or the sections with the corresponding information in the package leaflet are permitted only if these involve collective texts.

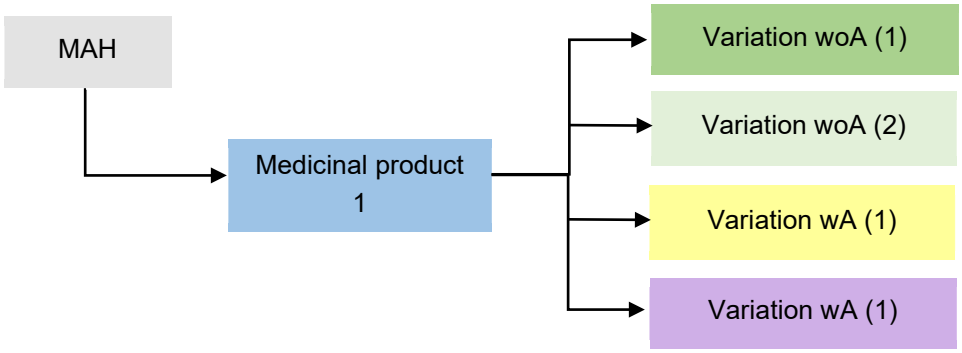
Collective texts are texts for which collective Information for healthcare professionals and/or a collective package leaflet is available for several pharmaceutical forms of the same active substance. The legal framework is provided by Art. 22b, para. 1–4 TPLRO.



1.1.4 Multiple application

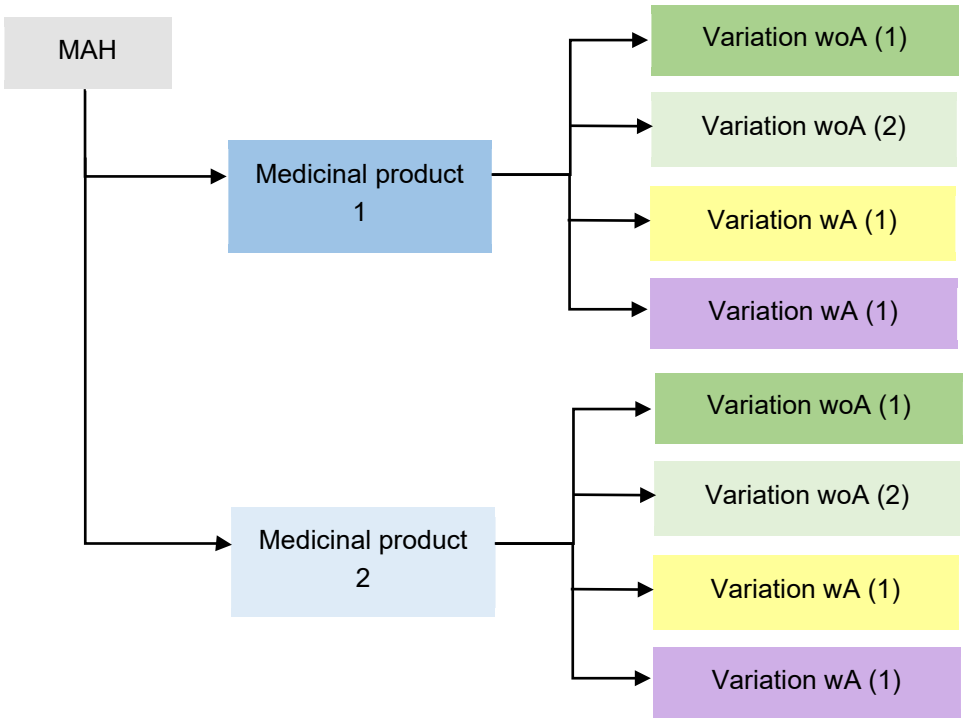
Differing variations can be submitted jointly as a multiple application, provided all the variations involve the same medicinal product. The processing of multiple applications is based on the application with the longest time limit. All variations will be assessed and completed at the same time.

Safety-related changes to the veterinary medicinal product information cannot be part of multiple applications. The legal framework is provided by Art. 22c TPLRO.



1.1.5 Collective-multiple application

This is a combination of a collective and a multiple application and exists, for example, if a marketing authorisation holder submits identical variations for two of its products. In such cases, the requirements for collective and multiple applications stated above remain unchanged.



1.2 Abbreviations

Auth.no.	Authorisation number
CD	Calendar Day(s)
FeeO-Swissmedic	Ordinance on the Fees charged by the Swiss Agency for Therapeutic Products of 14 September 2018 (SR 812.214.5)
i.m.	intramuscular
i.v.	intravenous
MAH	Marketing authorisation holder
s.c.	subcutaneous
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
Var	Variation
Var wA	Variation with assessment
Var woA	Variation without assessment

2 Introduction

This guidance document explains the requirements pertaining to variations for veterinary medicinal products. Annex 7a TPLRO (List of variations as per Articles 25a and 25b TPO) provides a list of variations that are relevant for Switzerland and for which Swissmedic is responsible. Variations “without assessment” are explicitly stated. All other variations are variations “with assessment”. The structure is as follows:

A. Administrative variations that do not require assessment

B. Quality variations that do not require assessment
C. Variations concerning safety, efficacy and pharmacovigilance that do not require assessment
D. Changes to the vaccine antigen master file (VAMF) part of the dossier
E. Administrative variations requiring assessment
F. Quality variations requiring assessment
G. Variations concerning safety, efficacy and pharmacovigilance requiring assessment
I. Variation of the active substance, dosage strength, pharmaceutical form, administration route or non-food-producing target species
Y. Variations relating to complementary and herbal medicines (reduced dossier)

Switzerland has largely taken over the variation numbers (e.g. B.I.a.2) and the corresponding requirements from the *Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council* and the *Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations* and adapted to Swiss laws and requirements. Variations that are not relevant to Switzerland are not listed. The numbering is therefore not continuous in some instances.

The conditions to be fulfilled for the individual variations and the documentation to be submitted are listed. If, for the variations taken over from the European Variation Guideline, certain conditions and/or documentation requirements do not apply in Switzerland, these are either not listed or are shown as "not applicable in Switzerland".

Switzerland-specific variations under A, E and G start with 100 numbers (e.g. E.100 Change in the product information and/or packaging texts without the submission of scientific data).

2.1 Legal framework

Art. 25a to 25c TPO, Art. 22a to 22c and Annex 7a TPLRO and FeeO-Swissmedic (particularly Annex 1).

3 Objective

As this is a guidance document aimed at administrative bodies, it does not directly specify the rights and obligations of private individuals. Swissmedic uses this guidance document first and foremost as a resource for applying the legal provisions on authorisation in a uniform and equitable manner. For applicants, the document is intended to make clear the specific requirements that must be fulfilled so that corresponding applications can be processed by Swissmedic as quickly and efficiently as possible.

4 Scope

This guidance document applies to the Authorisation, Licensing and Market Surveillance divisions of Swissmedic for applications for variation to veterinary medicinal products received by Swissmedic from the effective date of the revised TPLRO.

5 Other valid documents

- *Variations VMP (form)*
- *Formal requirements*
- *Authorisation for veterinary medicinal products*
- *Document protection*

6 Description

6.1 Requirements

Switzerland recognises the following application types for veterinary medicinal products, depending on the possible implications for quality, safety and efficacy:

- Variations not requiring assessment (variations without assessment)
- Variations requiring assessment (variation with assessment) with time limit “Standard” or «Reduced»

The categorisation of the variations can be found in Annex 7a TPLRO (List of variations as per Articles 25a and 25b TPO).

If a variation does not appear in the list or does not meet all conditions, it can be submitted as an "Other variation". An "Other variation" is classed by default as a variation requiring assessment with a time limit «Reduced». If a more extensive variation is involved, both Swissmedic and the marketing authorisation holder can upgrade this to a variation requiring assessment with time limit “Standard”. The templates for “Other variation requiring assessment” can be found in the form *Variations VMP* under the relevant individual variations (e.g. F.I.a.1.) and at the end of sections E, F and G as “z Variations”.

When categorising as-yet unlisted variations, Swissmedic also takes into account the CMDv/EMA recommendations and the classification of variation applications already approved in the EU. The list of variations is regularly compared with the der *Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council* and the *Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations*. Variations can lead to the issuing of new authorisation numbers, dosage strength numbers or packaging codes (see section 9).

6.1.1 Formal requirements

The requirements stated in Annex 7a TPLRO, the form *Variations VMP* and Guidance document *Formal requirements* apply.

6.1.2 Requirements applicable to conditions to be fulfilled and documentation to be submitted

6.1.2.1 Variations without assessment

The applicable conditions must be fulfilled for type variations without assessment, and the appropriate documentation must be submitted. By ticking the checkbox in the form *Variations VMP*, the marketing authorisation holder confirms that the conditions are fulfilled and that the documentation has been submitted. If one or more of the conditions are not met and the variation is not specifically listed as variation with assessment, it should be submitted as a "z" variation with assessment.

For variations without assessment, the implementation date must be provided in the appropriate field in the form *Variations VMP*[1]*,* unless the variation is part of a collective application that also includes variations with assessment. *HMV4*[2]*,* unless the variation is part of a collective application that also includes variations with assessment.
The implementation date must be at least 60 days in the past. If the time that has elapsed between the implementation date and the date the variation was submitted is more than 60 days, a variation with assessment should be submitted.

6.1.2.2 Variations with assessment

a) Variations with assessment and time limit «Reduced»
The appropriate documentation must be submitted. By ticking the checkbox in the form *Variations VMP*, the marketing authorisation holder confirms that the documentation has been submitted. Confirmation that the conditions are met is also required in a very few cases of Swiss-specific variations.

b) Variations with assessment and time limit "Standard"
As a rule, the documentation to be submitted is not defined, as the volume of such documentation can vary depending on the nature of the variation.

Approval of certain variations with assessment and time limit "Standard", such as the variation "*Change to therapeutic indication"* (G.I.7) or the variation "*Modification or addition of a food-producing target species (livestock)*" may be associated with a requirement to submit PSURs.

Elements that are not currently approved in Switzerland – affecting in particular variations with assessment in section I of the form *Variations VMP* (the former extensions) – must be documented in accordance with Art. 3, 4 and 5 TPLRO.

If a variation with assessment according to section I is being requested for a preparation, proof must be provided that the findings on preclinical and clinical efficacy, safety and tolerability that provided the basis for authorisation of the preparation can be transferred to the variation being applied for.

The nature or extent of the proof required depends on the physical, chemical and pharmacological properties of the active substance, the dosage strength, pharmaceutical form and administration route. The marketing authorisation holder must provide a summary evaluation and scientific

[1] Exception: Not date is necessary if the type IA/IA$_{IN}$ variation is part of a collective application that includes type IB or II variations or extensions.
[2] Exception: Not date is necessary if the type IA/IA$_{IN}$ variation is part of a collective application that includes type IB or II variations or extensions.

substantiation of the proof of transferability it has chosen. The cover letter should briefly explain that earlier data has been used for certain elements and point out the sections of the relevant documents.

The following documents must be submitted for variations with assessment in accordance with section I of the form *Variations VMP* (see also the Guidance document *Authorisation for veterinary medicinal products*):

6.1.2.3 Change in the active substance 1a), 1b), 1c), 1e), 1f)

Quality requirements:
- Complete documentation
- CEPs or DMFs are acceptable

Preclinical requirements:
- Complete documentation

Clinical requirements:
- The documentation to be submitted depends on the type of variation.

6.1.2.3.1 Change in the active substance 1d)

Quality requirements:
- Complete documentation
- CEPs or DMFs are acceptable
- Applicants may also want to consult guideline *EMEA/CHMP/BMWP/101695/2006 (comparability)*.

Preclinical requirements:
- Complete preclinical documentation: Sections 2.4, 2.6 and Module 4.

Clinical requirements:
- Complete documentation

6.1.2.3.2 Modification or addition of dosage strength 2c)

Quality requirements:
- Complete documentation

GMP compliance requirement:
- Full documentation according to document ZL000_00_036_WL GMP compliance by foreign manufacturers

Preclinical requirements:
- Safety-critical points should be listed in the expert reports on Part III and a risk/benefit analysis for the new dosage strength should be prepared.

Clinical requirements:
- Substantiation of the new dosage strength plus proof that it is appropriate and the clinical results obtained with the existing dosage strengths can be transferred to the new dosage strength.

6.1.2.3.3 Modification or addition of pharmaceutical form 2d)

Quality requirements:
- Complete documentation

GMP compliance requirement:

- Full documentation according to document ZL000_00_036_WL GMP compliance by foreign manufacturers

Preclinical requirements:

- Experimental studies on formulation.
- For topical preparations, care must be taken to ensure that the local tolerance (e.g. eye and skin irritation studies, investigation of the sensitising and phototoxic potential) and systemic exposure have been experimentally tested with the preparation submitted for authorisation. If there are indications that systemic exposure is significantly higher for the new pharmaceutical form, appropriate animal studies should be submitted.

Clinical requirements:

- Substantiation of the new pharmaceutical form plus proof that it is appropriate and the clinical results obtained with the existing pharmaceutical forms can be transferred to the new pharmaceutical form.
- Bioequivalence studies comparing the new and existing pharmaceutical form
- If the new pharmaceutical form is not bioequivalent to the existing pharmaceutical form, complete pharmacokinetic data must be submitted (possibly including a food-effect bioavailability study).

6.1.2.3.4 Modification or addition of administration route 2e)

Quality requirements:

- If necessary, updated sections along with an index of changes and tabular comparison.

Preclinical requirements:

- Experimental studies on the new administration route (new studies with the new administration route or bridging studies).
- For topical forms: experimental studies of the local tolerance (e.g. eye and skin irritation studies, investigation of the sensitising and phototoxic potential) of the preparation submitted for authorisation (final formulation).

Clinical requirements:

- Substantiation of the new administration route plus proof that it is appropriate and the clinical results obtained with the existing administration routes can be transferred to the new administration route.
- Pharmacokinetic studies, particularly bioavailability studies
- If the pharmaceutical form has not changed (e.g. formerly subcutaneous, now to be intramuscular or vice versa, but same solution for injection) a pharmacokinetic bridging study may be adequate.
- If the new administration route involves a new pharmaceutical form (or other variations such as a new dose, delayed release, etc.), safety and efficacy studies must be submitted.

6.1.2.3.5 Modification or addition of a food-producing target species (livestock) 3)

Requirements for Part III (Documentation on safety and residues):

- Studies of pharmacodynamics / pharmacokinetics in the intended new target species (possibly the same as the studies in Part IV).
- Documents on tolerability / toxicity when used in the new target species.
- Studies relevant to the evaluation of the safety of the veterinary medicine when used in the intended new target species.
- Information on user safety and ecotoxicity when used in the new target species.
- Information on the maximum residue concentrations and residue studies for the intended new target species and proposal for withdrawal periods.

Requirements for Part IV (Documentation on preclinical and clinical data):

- Studies of pharmacodynamics / pharmacokinetics in the intended new target species.
- Current documentation on the emergence and spread of resistance when used in the intended new target species.
- Results of all clinical trials conducted in the new target species.

6.2 Process

6.2.1 Time limits

The processing times stated in the Guidance document *Time limits for authorisation applications* apply, with the proviso described in Chapter 1.1.5 that all the variations submitted in a collective application will be subject to the time limit for the application with the longest time requirement.

6.2.2 Confirmation of receipt

The date of confirmation of receipt is considered to be the starting point for processing.

An electronic confirmation of receipt (*Acceptance of delivery*) is generated for all applications successfully received via the Swissmedic portal. Non-portal users receive an acceptance of delivery for variations without assessment and variations with assessment and time limit “Reduced” . No acceptance of delivery is sent for variations with assessment and time limit “Standard” .

6.2.3 Variations without assessment

The marketing authorisation holder can consider its report of an implemented variation to be accepted if Swissmedic does not send a message to the contrary by 30 CD at the latest after confirmed receipt of the report, or if the approval of the report is already visible in advance in the Swissmedic portal. The date and the decision can be viewed on the Swissmedic portal. In the event of an approval, no official decision is sent for variations without assessment.

If the form or content of the report is the subject of any objections, Swissmedic sends an interim official decision by 30 CD at the latest after the confirmed receipt of the report. Missing documentation must be submitted within the specified deadline, or the correct variation type must be submitted as a new application or new report. If the correct variation type and/or documentation to be submitted are not received by the deadline, Swissmedic will reject the application. The marketing authorisation holder can consider the corrected variation report to be accepted if Swissmedic does not send a message to the contrary by 30 CD at the latest after confirmed receipt of the corrected variation report, or if the approval of the report is already visible in advance in the Swissmedic portal. In the event of a rejection, a corresponding official decision will be sent and the variation must be cancelled.

If product information and/or packaging texts have to be revised in connection with variations without assessment, these are merely acknowledged by Swissmedic and not returned to the marketing authorisation holder as approved by means of an official decision letter. The authorisation holder is responsible for always publishing the latest versions of these texts.

6.2.4 Variations with assessment time limit “Reduced”

The marketing authorisation holder can consider the report to be accepted and implement the variation if Swissmedic does not send a message to the contrary by 60 CD at the latest after receipt of

a valid report and the complete documentation (i.e. after a successful formal control[3]), or if the approval of the report is already visible in advance in the Swissmedic portal. The date and the decision can be viewed on the Swissmedic portal. In the event of an approval, no official decision is sent for variations with assessment and time limit «Reduced» unless the approval is made subject to conditions (e.g. later submission of stability data) or a new packaging code is issued.

A variation relating to safety, efficacy and pharmacovigilance G.I.2 z) for reporting the inclusion of a new indication, administration route, pharmaceutical form, dosage strength or dosage recommendation for the reference medicinal product in the product information of an essentially identical medicinal product as per Art. 12 TPA must not be submitted until at least one day after the document protection has expired for this indication, administration route, pharmaceutical form, dosage strength or dosage recommendation.

If Swissmedic has an objection to the form of the report, it will send an interim official decision by 10 CD at the latest after the confirmed receipt of the report. Missing documentation must be submitted within 30 CD, or the correct variation type must be submitted as a new application. If the correct variation type and/or documentation to be submitted are not received within the specified deadline, Swissmedic will dismiss the application.

If Swissmedic has an objection to the content of the report, it will send an interim official decision by 60 CD at the latest after the report has undergone a successful formal check. The missing documentation must be submitted within 30 CD of the applicant receiving the interim decision. If the requested documentation is not received within the specified deadline, Swissmedic will reject the application.

The marketing authorisation holder can consider the corrected content of the variation report to be accepted if Swissmedic does not send a message to the contrary by 60 CD at the latest after confirmed receipt of the corrected variation report, or if the approval of the report is already visible in advance in the Swissmedic portal. In the event of rejection, a corresponding official decision will be sent.

If product information and/or packaging texts have to be revised in connection with variations with assessment and time limit «Reduced», these are merely acknowledged by Swissmedic and not returned to the marketing authorisation holder as approved by means of an official decision letter. The marketing authorisation holder is responsible for always publishing the latest texts.

6.2.5 Variations with assessment time limit “Standard”

If an application passes the formal control, this is indicated in the portal as the milestone *Formal control completed*. Non-portal users can assume that the formal check was successful if Swissmedic has not sent them a message to the contrary by 30 CD at the latest after receipt of the application (date of postmark).

Variations with assessment and time limit “Standard” are always concluded with a corresponding official decision letter (approval, rejection or partial rejection).

[3] Can be viewed on the Swissmedic portal by 10 CD at the latest after confirmed receipt of the report. Non-portal users can assume that the formal control was successful if Swissmedic has not sent them an interim official decision by 10 CD at the latest after receipt of the interim official decision.

6.2.6 Implementation of variations

Before the report (variation without assessment), after the end of the waiting period if Swissmedic has no objections (variation with assessment and time limit «Reduced»), or after approval (variation with assessment and time limit “Standard”), the variation of the product is considered to be approved. Under the Therapeutic Products Act, only the modified product can be marketed as of this point in time. Swissmedic grants a transitional period for implementation for variations:

- Preparations that the marketing authorisation holder had already supplied to wholesalers or retailers at the time the variation was approved may be sold in the form they were supplied.
- For all other products, implementation must begin with production of the next batch or the next print-run of packaging elements, but at all events within one year following approval. Goods already released onto the market are an exception to this.
- Safety-related variations for which, in line with its general practice to date, Swissmedic orders more rapid implementation are excluded from this practice.
- In specially requested and sufficiently justified exceptional cases, Swissmedic can approve delayed implementation time limits for variations that must be implemented simultaneously worldwide (*replacement changes*, particularly quality variations such as a different active substance manufacturer, replacement method or exchange of columns).

The marketing authorisation holder is responsible for always publishing the latest product information texts in the required languages. The texts should be uploaded to the Compendium of veterinary medicines as soon as possible after the end of the waiting period or after approval.

6.3 Document protection

The requirements of the Guidance document *Document protection* apply.

6.4 Fees

The fees stated in FeeO-Swissmedic apply.

6.5 Issuing of new authorisation and dosage strength numbers and packaging codes

6.5.1 Issuing of a new authorisation number

Swissmedic reserves the right to issue a new authorisation number for variations which may have significant implications for the quality, safety or efficacy of a veterinary medicinal product.

6.5.2 Issuing of a new dosage strength number

Swissmedic issues a new number at least for new dosage strengths. This also always entails a modification of the packaging code.

6.5.3 Issuing of a new dosage packaging code

Swissmedic issues new packaging codes in each case for changed or additional pack sizes. Other changes to the packaging codes by Swissmedic are only made in exceptional cases or in response to a justified request from the marketing authorisation holder.

Change history

Version	Change	sig
4.0	Section 6.1.2.3.2 / 6.1.2.3.3 – Addition re. required documentation/GMP evidence (complete evidence that GMP compliance of foreign manufacturers has been verified) Section 6.2.6 – Introduction of delayed implementation time limits for replacement changes that have been specially requested and sufficiently justified HMV4 suffix removed	fg, stb, ps
3.1	New layout, no content adjustments to the previous version.	dei
3.0	Section 6.4: Editorial change.	ps, fg
2.0	Sections 1 and 6.1.2.1: Variations without assessment: The reporting deadline after implementation is now 60 rather than 30 days. Section 2: “D: Changes to the vaccine antigen master file part (VAMF) of the dossier” inserted.	ps
1.0	New guidance document due to new structure of the variations for VMP (prerevision of the VMP regulations)	ps, fg