Contents

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Change history

Version	Valid and binding as of	Description, comments (by author)	Author's initials
5.1	01.08.2021	Clarification (P1.) and new point (P12.) regarding issuing of new packaging codes in section 9 and changes to department names	stb
5.0	01.06.2021	Inclusion in section 9.1 (Z10) of rules on issuing new authorisation numbers for the adaptation of Covid-19 vaccines to new SARS-CoV-2 variants.	stb
4.1	01.03.2021	Formal adjustments to the header and footer No content adjustments to the previous version.	dei
4.0	01.09.2020	Addition / explanation in section 9.1 under Z5.	stb
3.0	01.12.2019	Addition to section 6.4 – details regarding document protection.	stb, ze
2.0	09.05.2019	Inclusion of an additional case for issuing a new authorisation number (section 9.1), further details in section 5 (incl. in respect of the CMDh list with unforeseen variations) and section 6.6 (changes to the PMF can be submitted together with the Annual Update of the PMF as a multiple application).	stb, wer
1.0	01.01.2019	Implementation of TPO4	stb, wer

1 Definitions, terms, abbreviations

1.1 Definitions and terms

1.1.1 Minor variations to be reported subsequently, type IA/IA$_{IN}$

These are minor variations which only have minimal consequences for quality, safety or efficacy. They must be reported to Swissmedic in writing by the marketing authorisation holder after they have been implemented (*Do and Tell*). These are known as type IA/IA$_{IN}$ variations. The legal framework is provided by Art. 21 TPO.

Type IA variations must be reported to Swissmedic within twelve months of their implementation. Type IA$_{IN}$ variations (IN stands for *Immediate Notification*) must be reported to Swissmedic immediately after they have been implemented.

1.1.2 Minor variations to be reported in advance, type IB

These are minor variations which are neither a minor variation of type IA/IA$_{IN}$, nor a major variation of type II nor a marketing extension. These are known as type IB variations. The legal framework is provided by Art. 22 TPO.

Type IB variations must be reported to Swissmedic in writing before they are implemented. 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. If Swissmedic does raise objections within this period, the marketing authorisation holder can submit

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documentation within 30 days to resolve the objections, or submit a modified report that takes account of Swissmedic's objections.

1.1.3 Major variations, type II

These are variations which may have significant implications for the quality, safety or efficacy of the medicinal product and which do not involve an extension. These are known as type II variations. The legal framework is provided by Art. 23 TPO.

Type II variations must be approved by Swissmedic before they are implemented.

1.1.4 Extensions

Extensions are variations that have to be approved by Swissmedic in a new authorisation procedure before they are implemented. The legal framework is provided by Art. 24 TPO.

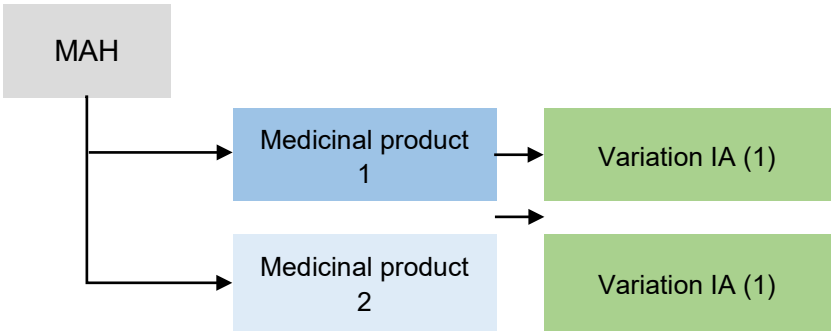
1.1.5 Collective application

Variations of types IA/IA_{IN}, IB or II can be submitted jointly as a collective application, provided they involve the same variation for several medicinal products and the identical documentation is submitted for all the medicinal products concerned.

Extensions cannot be submitted as a collective application.

Identical variations for a human and a veterinary medicinal product cannot be submitted as a collective application.

Collective applications which also involve changes to the product information in sections 4 to 16 (HMP) or 4 to 6 (VMP) or the sections with the corresponding information in the patient information or veterinary medicinal product package leaflet are permitted only if these involve collective texts. The legal framework is provided by Art. 22b TPLRO.



1.1.6 Collective text

A collective text applies when a marketing authorisation holder submits a collective product information text for several pharmaceutical forms of the same active substance or, if an information for healthcare professionals does not exist, a collective patient information or a collective veterinary medicinal product package leaflet. The legal framework is provided by Art. 22b, para. 4 TPLRO.

1.1.7 Multiple application

Differing variations of the same type (e.g. several extensions) or of differing types (IA, IB, II and extension) can be submitted jointly as a multiple application, provided all the variations involve the same medicinal product. The processing of all the variations submitted in a multiple application is based on the variation type in the multiple application with the longest time limit. All variations will be assessed and completed at the same time.

Safety-related changes to the product information or patient information or the veterinary medicinal product information, and variation applications processed in the fast-track procedure (FTP) or the

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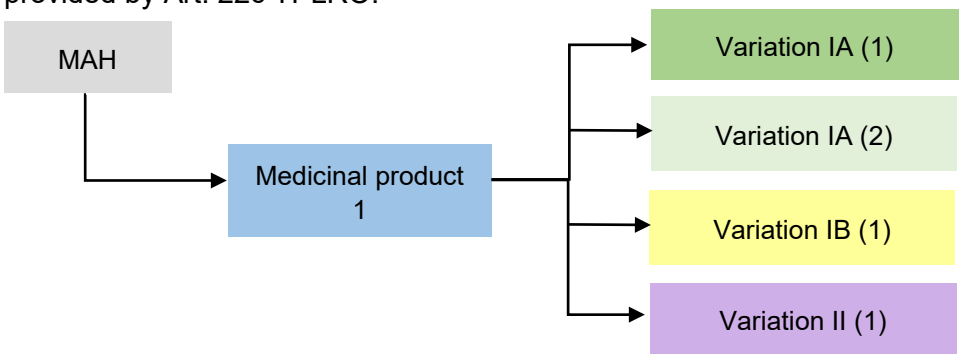
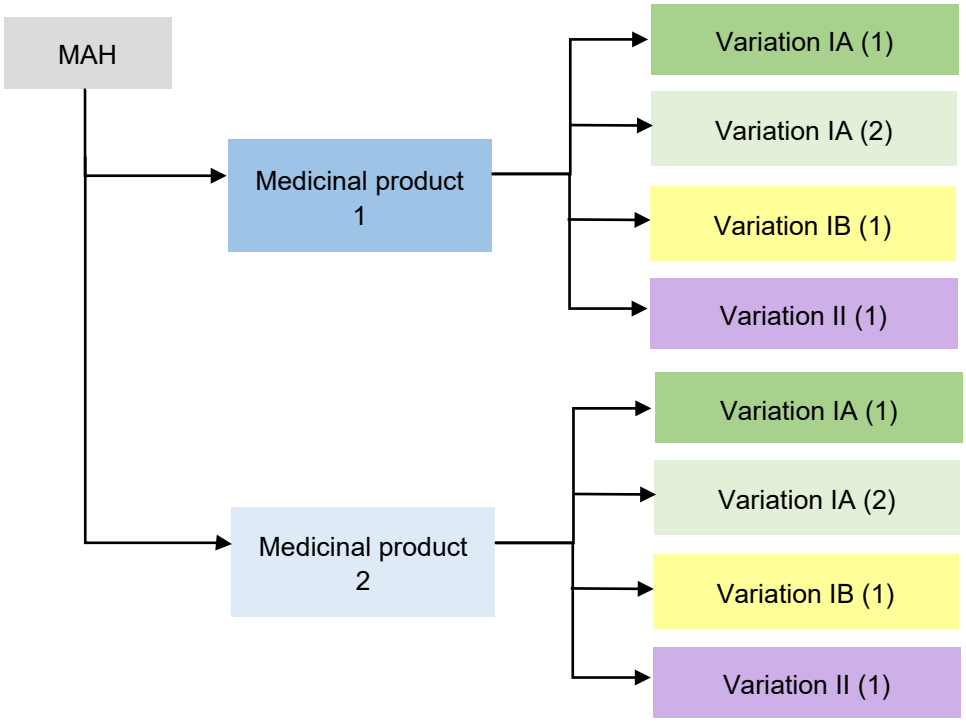
procedure with prior notification (PPN) cannot be part of multiple applications. The legal framework is provided by Art. 22c TPLRO.



1.1.8 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

AD	Authorisation Document
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)
FTP	Fast-Track authorisation Procedure
IA	Minor variation to be reported subsequently, reporting within a maximum of twelve months after implementation
IA_{IN}	Minor variation to be reported subsequently, reporting immediately after implementation, IN stands for *Immediate Notification*
IB	Minor variation to be reported in advance
II	Major variation
i.m.	intramuscular

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INN	International Nonproprietary Name
i.v.	intravenous
KPTPO	Ordinance of 7 September 2018 of the Swiss Agency for Therapeutic Products on the Simplified Licensing of Complementary and Phytotherapeutic Products (SR 812.212.24)
PMF	Plasma Master File
PPN	Procedure with Prior Notification
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)

2 Introduction and objective

This guidance document explains the requirements pertaining to variations and extensions for human and veterinary medicinal products. Annex 7 TPLRO (List of variations as per Arts. 21–24 TPO) provides a list of all variations of types IA/IA_{IN}, IB and II and the extensions that are relevant for Switzerland and for which Swissmedic is responsible. The annex is structured as follows:

A. Regulatory changes
B. Quality changes
C. Safety, efficacy and pharmacovigilance changes
X. Changes to Plasma Master Files (PMF)
Y. Various changes relating to complementary and herbal medicines
Z. Extensions

The European variation numbers (e.g. B.I.a.2) and the corresponding requirements have largely been taken over from the European Variation Guideline (*Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures*) and adapted to the Swiss laws and requirements.

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 shown as "not applicable in Switzerland" (see e.g. variation B.II.b.2).

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

X and Y refer only to Switzerland-specific variations.

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.

3 Scope

This guidance document applies to the Authorisation, Licensing and Market Surveillance divisions of Swissmedic for applications for a change and/or extension relating to human and veterinary medicinal products received by Swissmedic from the effective date of the revised Therapeutic Products Act (TPA).

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4 Legal framework

Art. 21 to 25 TPO, Art. 22a to 22c and Annex 7 TPLRO and FeeO-Swissmedic (particularly Annex 1).

5 Requirements

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

- Minor variations to be reported subsequently, type IA/IA$_{IN}$
- Minor variations to be reported in advance, type IB
- Major variations, type II
- Extensions

The categorisation of the variations can be found in Annex 7 TPLRO (List of variations as per Articles 21–24 TPO).

If a variation does not appear in the list, it can be submitted as an "Other change". An "Other change" is classed as a minor variation of type IB by default. If a more extensive variation is involved, both Swissmedic and the marketing authorisation holder can upgrade this to a variation of type II. The templates for “Other change” can be found under the individual variations (e.g. B.I.a.1.z) and at the end of section A. Regulatory changes (A.z Other regulatory change), at the end of section B. Quality changes (B.z. Other quality change) or at the end of section C. Safety, efficacy and pharmacovigilance changes (C.I.z Other change relating to safety, efficacy and pharmacovigilance) of the form *Variations and extensions HMV4*.

When categorising an “Other change”, Swissmedic also takes account of the published list “CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008”. An "Other change" can then be submitted as type IA or type IA$_{IN}$ only if it was also classified as such in the published CMDh list. The submission must reference the list "CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008", the corresponding EU variation number and the "Date issued".

Variations and extensions can lead to the issuing of new authorisation numbers, dosage strength numbers or packaging codes (see Chapter 9).

5.1 Formal requirements

The requirements stated in Annex 7 TPLRO, the form *Variations and extensions HMV4*, Guidance document *Formal requirements HMV4* and the associated Directory *Overview of documents to be submitted HMV4* apply.

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

5.2.1 Minor variations to be reported subsequently, type IA/IA$_{IN}$

The applicable conditions must be fulfilled for type IA/IA$_{IN}$ variations, and the appropriate documentation must be submitted. By ticking the checkbox in the form *Variations and extensions HMV4*, the 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 being of type II, a type IB variation should be submitted.

For type IA/IA$_{IN}$ variations, the implementation date must be provided in the appropriate field in the form *Variations and extensions HMV4*[1]. This date must be in the past. If the time that has elapsed between the implementation date and the date the variation was submitted is more than 12 months (type IA) or more than one month (type IA$_{IN}$), a type IB variation should be submitted.

[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.

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5.2.2 Minor variations to be reported in advance, type IB

The appropriate documentation must be submitted for type IB variations. By ticking the checkbox in the form *Variations and extensions HMV4*, the authorisation holder confirms that the documentation has been submitted.

5.2.3 Type II variations

For type II variations, it is usual not to define the documentation to be submitted, as the volume of such documentation can vary depending on the nature of the variation. There have, however, been some cases of type II variations where the documentation to be submitted has been defined (e.g. as for B.I.e.1).

Approval of certain type II variations – specifically indication extensions (see also C.I.6 *Change to therapeutic indication(s)*) and new dosage recommendations (see also C.I.101 *Change in the product information and/or packaging texts due to new dosage recommendation data*) – may be associated with a requirement to submit PSURs.

5.2.4 Extensions

The new elements of extensions that are not currently approved in Switzerland must be documented in accordance with Art. 3, 4 and 5 TPLRO. Documentation submitted for a previously authorised medicinal product can be used as supporting material for the known elements.

If an extension 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 extension.

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 authorisation holder must provide a summary evaluation and scientific substantiation of the proof of transferability it has chosen in the form of a statement in the Nonclinical and Clinical Overview. The cover letter should briefly explain that earlier data has been used for certain elements and point out the sections containing the substantiation of transferability.

Approval of extensions may be associated with a requirement to submit PSURs.

The following information applies to CTD format. Documentation for veterinary medicinal products must still be submitted in NTA format (see the Guidance document *Authorisation of veterinary medicinal products HMV4*).

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

Quality requirements:
- Complete documentation: Section 2.3 + Module 3.
- CEPs or DMFs are acceptable: reference should be made to them in section 3.2.S.

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

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

5.2.4.2 Change in the active substance 1d)

Quality requirements:
- Complete documentation: Section 2.3 + Module 3.
- CEPs or DMFs are acceptable: reference should be made to them in section 3.2.S.
- 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:

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- Complete clinical documentation: Sections 2.5, 2.7 and Module 5.

5.2.4.3 Change in bioavailability 2a)

Swissmedic recommends advance clarification of the formal requirements in a presubmission meeting.

5.2.4.4 Pharmacokinetic change 2b)

(e.g. change in release rate)
Swissmedic recommends advance clarification of the formal requirements in a presubmission meeting.

5.2.4.5 Modification or addition of dosage strength 2c)

Quality requirements:
- Complete section 3.2.P.

Preclinical requirements:
- Safety-critical points should be listed in section 2.4 and a risk/benefit analysis for the new dosage strength should be prepared, taking special account of the safety margins.

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.
- If the new dosage strength is linked to a new dosage recommendation, see also the requirements for documentation on C.I.101 *Change in the product information and/or packaging texts due to new dosage recommendation data*.

5.2.4.6 Modification or addition of pharmaceutical form 2d)

Quality requirements:
- Complete section 3.2.P.

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 (section 5.3.1.2)
- If the new pharmaceutical form is not bioequivalent to the existing pharmaceutical form, complete pharmacokinetic data (section 5.3.3.1) must be submitted (possibly including a food-effect bioavailability study).

5.2.4.7 Modification or addition of administration route 2e)

Quality requirements:
- If parts of the quality documentation change as a result of the new administration route, an updated section 3.2.P should be submitted, 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).

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- 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 (sections 5.3.1 and 5.3.3), particularly bioavailability studies (sections 5.3.1.1 and 5.3.1.2).
- 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 (section 5.3.5).

5.2.4.8 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.
- Documents on tolerability / toxicity 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 Process

6.1 Time limits

The processing times stated in the Guidance document *Time limits for authorisation applications HMV4* apply, with the proviso described in Chapter 1.1.7 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 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 notifiable variations of types IA, IA_{IN} and IB by post. No acceptance of delivery is sent for type II variations or extensions.

6.3 Minor variations to be reported subsequently, type IA/IA_{IN}

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 type IA/IA_{IN} variations.

If the form or content of the report is the subject of a complaint, Swissmedic sends an interim official decision by 30 CD at the latest after the confirmed receipt of the report. Missing documentation must

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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 on 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 type IA/IA$_{IN}$ variations, 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.

6.4 Minor variations to be reported in advance, type IB

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[2]), 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 of type IB, unless the approval is made subject to conditions (e.g. later submission of stability data) or a new packaging code is issued.

A change relating to safety, efficacy and pharmacovigilance C.I.2 a) (type IB variation) for reporting the inclusion of a new indication, administration route, pharmaceutical form, dosage strength or dosage recommendation for the reference medicinal product/reference preparation 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 type IB variations, 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.

[2] 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.

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6.5 Type II variations and extensions

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).

Type II variations and extensions are always concluded with a corresponding official decision letter (approval, rejection or partial rejection).

6.6 Handling of variations to Plasma Master Files (PMF)

For each PMF, the application is submitted for one or more PMF variations according to the highest category (type II, IB, IA/IA_{IN}) according to the classification in the European Guideline under point "B.V.a.1 PMF / VAMF" or "D. PMF / VAMF" *(Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures*).

Submitting an annual PMF update is regarded as fulfilment of a condition of authorisation and not as an application for a variation. Annual Updates of the PMF can be submitted together with changes to the PMF as a multiple application (see section X. Changes to the PMF in the *Variations and extensions HMV4* form).

6.7 Implementation of variations and extensions

Before the report (variations of types IA and IA_{IN}), after the end of the waiting period if Swissmedic has no objections (variations of type IB), or after approval (variations of type II and extensions), 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 and extensions:

- Preparations that the 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.
- Excluded from this practice are safety-related variations for which, in line with its general practice to date, Swissmedic orders immediate implementation.

The marketing authorisation holder is responsible for always publishing the latest product information texts in the required languages.

7 Document protection

The requirements of the guidance document *Document protection TPO4* apply.

8 Fees

The fees stated in FeeO-Swissmedic and the further information in the Management Principle *Regulation on levying of fees* apply.

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

9.1 Issuing of a new authorisation number

A **new authorisation number** is issued for the following extensions or variations:

Characteristic features	Examples (with no claim to completeness)	Remarks
Z1. New or additional pharmaceutical form	Solution – tablets – ointment.	-
Z2. New composition:	Change from bovine to human albumin.	Exception: Does not apply to the Annual Update of seasonal influenza vaccines (see D2.).
Z2.1 Change in the active substance, salt, ester		Exception: Does not apply to minor chemical changes to the active substance molecule (e.g. switch from monohydrate to dihydrate), for which, by agreement with the specialist departments QA and CA, bioequivalence does not need to be demonstrated (also see P12.).
Z2.2 New formulation with the aim of modifying the pharmacokinetics	Modified release: Slow Release, Extended Release, etc.	
Z2.3 Same product with/without sugar	Cough preparations.	
Z2.4 Same product with/without preservative	Eye drops, nose drops, anaesthetics.	
Z3. New indication / new application – but same active substance **and** new name of the medicinal product	Parkinson's vs. restless legs syndrome. Erectile dysfunction vs. pulmonary arterial hypertension.	This can be contrasted with an indication extension.
Z4. New administration route	Parenteral – oral.	Exception: Extension of the administration route: i.v. and additionally i.m. and/or s.c. In these cases, no change to the auth. number, dosage strength number (formerly sequence) or packaging code is required. Also applies to the same pharmaceutical form (see Standard Terms EMA 4.1.).
Z5. New primary container for parenterals or poss. new administration system. Evaluation according to the Standard Terms EMA 4.1., e.g. new administration system	Biotechnologicals/biologicals in the mg and µg scale, e.g. growth factors, interleukins, interferon Contrast media in prefilled syringes, ampoules, etc. Immunoglobulins, insulin, vaccines, etc.: previously in	Reason: differing adsorption of the active substances on the surface of the immediate packaging, traceability[3] must be ensured. Change to the administration system only if relevant for users. New pharmaceutical form.

[3] The traceability at the marketing authorisation holder is not identical to the traceability at Swissmedic (Swissmedic receives a signal and must be able to state what product was involved in each case)

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Characteristic features	Examples (with no claim to completeness)	Remarks
	vial, now additionally as prefilled syringe.	No new auth. no. for a change in the form of a primary container.
Z6. Additional primary container with measuring device for semi-solid forms	Tube and newly additional press dispenser.	If the first immediate packaging is abandoned within 6 months, the same authorisation number can be retained. Need for the issuing of a new dosage strength number with new packaging code. In addition, a note on the change must be added on the folding box.
Z7. Additional administration system (inhaler) for inhaled products	New medical device with additional "eFeatures" for inhalation of the authorised medicinal product if combination packs with medicinal products and medical devices are to be authorised.	In accordance with the practice whereby a new authorisation no. is issued if there are administration differences that are relevant to the user (by analogy with Z5/Z6).
Z8. Additional primary container for ophthalmic products	Eye drops in multi-dose containers and, newly, eye drops in single-dose containers.	If the first immediate packaging is abandoned within 6 months, the same authorisation number can be retained. Need for the issuing of a new dosage strength number with new packaging code. In addition, a note on the change must be added on the folding box.
Z9. Additional preparation with new administration route for self-administration by patients	Parenteral dosage form with new administration route (e.g. s.c. instead of i.v.), which are now administered by the patients themselves (instead of by healthcare professionals as was formerly the case).	Patient information required.
Z10. Additional Covid-19 vaccine with changed active substance for new SARS-CoV-2 variants, including exchange or addition of a serotype, a strain, an antigen or a coded region – or a combination of serotypes, strains, antigens or coded regions		

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9.2 Issuing of a new dosage strength number

A **new dosage strength number** is issued for the following extensions or variations: This also always entails a modification of the packaging code:

Characteristic features	Examples (with no claim to completeness)	Remarks
D1. New dosage strength for solid and semi-solid forms	Tablets 5 mg and newly / additionally 10 mg Cream, e.g. 2% and newly 1%	
D2. New composition of seasonal influenza vaccines	Annual update: annual modification of the virus strains based on the WHO recommendations.	
D3. Solutions		
D3.1 New concentration		
D3.2 New pack size / dosage strength for solutions for injection as a single dose (i.e. same concentration but differing volumes and the total dose is administered as a single dose)		Specification of the concentration on multi-dose containers = "only" new packaging code
D3.3 New quantity of active substance in the dry powder or lyophilisate for dissolving		Also corresponds to D3.1 *New concentration*
D4. New / additional flavour		
D5. New / additional colouring agent		
D6. Lyophilisate with / without solvent		
D7. With / without fragrance		Fragrance is declared under "Aromatics". Therefore, as regards compulsory declaration comparable with flavouring agents (not with preservatives).

9.3 Issuing of a new dosage packaging code

Characteristic features	Examples (with no claim to completeness)	Remarks
P1. Medicinal product given new name by new or same marketing authorisation holder	If new marketing authorisation holder: INN-company A ⇨ INN-company B If same marketing authorisation holder: INN-invented company A ⇨ INN-invented company B	Exception: No new packaging code is issued if the addition “New formula”, “New formulation” etc., which was added due to reformulation of the active substances for a period of at least 5 years, is removed.
P2. Primary container		
P2.1 Replacement or additional new primary	Can ⇨ blister Alu tube ⇨ plastic tube	

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Characteristic features	Examples (with no claim to completeness)	Remarks
container (for solid, semi-solid and liquid forms)		
P2.2 New immediate packaging, old one still remains (for solid forms)	Blister ⇨ plastic container	Applies until further notice for semi-solid forms: see Z6.
P2.3 Additional or new ampoule size with unchanged quantity of powder	e.g. 40mg in 25ml ampoule, newly or additionally 40mg in 50ml ampoule	Case 1: The new ampoule size replaces the existing ampoule -> new packaging code Case 2: The new ampoule size is additionally authorised -> additional packaging code and addition on the folding box and in the information for healthcare professionals (powder for solution for infusion in 25 ml ampoules). No additional pack size application is necessary if a variation was submitted for the primary container.
P3. New pack size for solid and semi-solid forms	30 tablets ⇨ 100 tablets 30g ointment ⇨ 100g ointment	
P4. Solutions		
P4.1 New volume (identical concentration) for multi-dose containers		Blood products and e.g. Metoject (0.15 to 0.6 ml), see also new dosage strength number = new pack size or dosage strength
P4.2 New primary containers for basic solutions for infusion		Applies until further notice; only for infusions with e.g. glucose, NaCl, bicarbonate, glucosaline, etc. N.B.: new dosage strength number for new dosage strength / concentrations vs. various immediate packaging materials (bag, bottle, etc.).
P5. Change from export licence to main authorisation		
P6. Change to a medical device	New prefilled syringe guard (e.g. new needle guard or new, finer needle).	The change has a substantial impact on the dispensing, administration, safety or shelf-life of the finished product.
P7. New target animal species		
P8 New excipients / change in the excipient composition or quantity of the individual excipients		Exceptions: New packaging codes are not issued for the following minor variations in excipient composition: - new or modified ink colours (B.II.a.1 a)) - addition, deletion or exchange of flavouring or colouring

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Characteristic features	Examples (with no claim to completeness)	Remarks
		agents (B.II.a.3 a) 1. and 2., B.II.a.3 b) 1.) - change in weight of coating of solid oral pharmaceutical forms or change in weight of capsule shells (B.II.a.4 a))
P9 Change in the dispensing category		
P10 Change, subject to compulsory declaration, in the specification of a herbal product	Change in the drug-extract ratio (DER)	
P11 Change in pack contents	Deletion of the solvent container or dilution container	
P12. Reclassification of active substance to excipient or deletion of active substance (authorisation extension 4. Other authorisation extension)		

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