1 Formal requirements

1.1 Where can I find information that will help me submit a variation to Swissmedic correctly?

The most important information can be found in the guidance document *Variations VMP*, guidance document *Formal requirements* (particularly section 3.12), and the form *Variations VMP* on the Swissmedic website.

1.2 What is the procedure if variations without assessment ("do and tell") cannot be approved or fit the criteria for a variation with assessment? Do applicants have to cancel the variation that has already been implemented?

If an applicant has submitted the incorrect variation type, it will be notified in the interim decision. It will then have to revise its notification of variation so that the correct type is submitted. If a variation cannot be accepted or approved, it may be necessary to demand cancellation of the implemented variation. This rarely happens, however.

1.3 Deleted in September 2023

1.4 What happens if I submit a variation without assessment more than 60 days after implementation? Revised in September 2023

In such cases, an interim official decision is issued and the notification will have to be submitted as a variation with assessment ("shortened" time limit). If the applicant notices that the time limit has passed before submitting the corresponding variation without assessment, the application should be submitted as a variation with assessment ("shortened" time limit) from the outset. Both the time limit and fee requirements for variations with assessment ("shortened" time limit) will be applied.

1.5 Do variations without assessment have to have been implemented at the time of submission?

Yes. According to Art. 25a TPO, variations without assessment have to be reported to Swissmedic in writing **after they have been implemented**. The implementation date must therefore be in the past and must be stated on the *Variations VMP* form.
An **exception** exists if the variations without assessment are part of a multiple application that includes variations with assessment. In these cases, the variations can be implemented after the variations in the multiple application have been approved, and an implementation date does not need to be stated. However, if the variation without assessment has already been implemented as part of the multiple application, Swissmedic also requires an implementation date.
Any deviations from the requirement to state the implementation date on the *Variations VMP* form will be specified on the form.

1.6 How is the implementation date defined (manufacture, release)?

Swissmedic follows the definition stated by the EMA in its Q&A.
Implementation of a quality change without assessment: Date on which the company makes the change in its own quality system. For Switzerland, the Switzerland-specific quality system is relevant in this context.
Implementation of a variation without assessment for product information and/or packaging texts: Date of internal release by the company / approval of the revised product information and/or packaging texts. Here too, the Switzerland-specific release is relevant for Switzerland. The implementation date should be stated in the format "DD.MM.YYYY".

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1.7 Can I submit a multiple application for administrative variations (sections A and E), quality variations (sections B and F) and variations relating to safety, efficacy and pharmacovigilance (sections C and G) mixed together?

Although this type of submission for a multiple application is possible in principle, it does raise the question of the usefulness of submitting a multiple application. Swissmedic therefore recommends that such applications be submitted together as a multiple application only if their subject matter is related.

1.8 Variations without assessment have to be implemented in advance. How should the date of revision of the product information texts be adjusted when it changes?

For variations without assessment that involve a change in the product information texts, the date of revision should be modified to match the implementation date (see explanations in the *Information for healthcare professionals* and *Veterinary medicinal product package leaflet* documents).

1.9 For variations with assessment, "shortened" time limit, I do not receive any approved product information texts after the variation has been approved. How should the date of revision of these texts be adjusted?

For variations with assessment, "shortened" time limit, that involve a change in the product information texts, the date of revision should match the date the application was submitted (see explanations in the *Information for healthcare professionals* and *Veterinary medicinal product package leaflet* templates).

1.10 Can an extension of the time limit be granted for the reply to an interim decision/preliminary decision for variations without assessment and variations with assessment, "shortened" time limit?

No extension of the time limit for corrective actions is granted for companies, either for variations without assessment or variations with assessment, "shortened" time limit. For both variation types, a maximum of 30 calendar days is granted for corrective actions.

1.11 Collective application: What must be submitted in respect of the form *Variations VMP*?

A form consisting of the administrative part (sections 1–7) plus the proposed variation (e.g. F.I.a.1.a) "new active substance manufacturer with DMF"). In the administrative part, the table under section 1 (Basic information) must be reproduced and completed according to the number of authorisation numbers/medicinal products concerned.

1.12 Do variation applications submitted to Swissmedic using the form *Variations VMP* also require a covering letter?

Swissmedic does not require covering letters for applications for variations without assessment and variations with assessment, "shortened" time limit, provided no further information or explanations in addition to those in the form *Variations VMP* are required.

1.13 Are the time limits for adapting the product information and/or packaging texts for co-marketing products to the revised TPLRO (Full declaration) based on the time limits for the basic product? Since the variations for co-marketing products are submitted with an application for adaptation to the basic product, the variations would be easier to implement.

Yes. Co-marketing products must make the adaptations to the revised TPLRO (Full declaration) only after these have been implemented for the basic product.

1.14 For a multiple application, can I submit the form *Variations VMP* in several PDF files?

No. For a multiple application, all the information and proposed variations should be submitted in one PDF file.

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1.15 For variations, do I have to submit one form for each medicinal product dosage strength or one form for each medicinal product/authorisation number?

As before – and as also applies with other applications (e.g. renewal) – you submit one form for each medicinal product/authorisation number, not one form for each medicinal product dosage strength.

1.16 Can E.106 *Implementation of new requirements in accordance with the revised TPLRO (version of 1 January 2019)* be submitted as collective or collective-multiple applications?

No. E.106 cannot be submitted as collective or collective-multiple applications because they do not meet the requirements of Art. 22b TPLRO.

1.17 Can applications for variations be submitted while the authorisation procedure for a new veterinary medicinal product is in progress?

Applications for variations that are submitted as part of ongoing new authorisation applications are not recorded as separate applications, but are included in the ongoing review of the new authorisation. Submitting additional documentation while an application is being processed or submitting a variation for an ongoing new authorisation procedure may result in Swissmedic taking additional time or charging additional fees (see Chapter 1.1 “Additional time” of guidance document *Time limits for authorisation applications*)

1.18 What happens to multiple applications comprising variations without assessment if one variation requires improvement? Will all applications be delayed by the amount of time it takes to make the improvements?

All variations in a multiple application will be completed together. This means that if an individual variation within a multiple application has to be improved, the total processing time for all the variations will increase.

1.19 A.101 Adaptation of a co-marketing medicinal product to ensure alignment with the basic product (for example in the event of a change in the product information and/or packaging texts or a change of quality): In which cases does an updated *Manufacturer information* form need to be submitted?

For this application type, the *Manufacturer information* form only needs to be submitted if the secondary packer has changed.

1.20 Why does the form *Variations VMP* not include changes in the name and/or address of the authorisation holder?

The form *Variations VMP* does not include changes in the name and/or address of the authorisation holder because these do not require a separate application. The variation is initiated by Swissmedic when the application for a change in establishment licence is received (see guidance document *Change name or domicile of the authorisation holder* link).

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2 Administrative changes

2.1 When a variation E.106 is submitted (Implementation of new requirements in accordance with the revised TPLRO, as at 1.1.2019), can additional variations (e.g. safety-related changes) also be submitted at the same time?

No. E.106 only applies to the implementation of new requirements according to the revised TPLRO. In connection with a multiple application, in addition to E.106 you can also submit other pooled variations for the specific medicinal product. However, safety-related variations cannot form part of multiple applications.

2.2 Should the full declaration for co-marketing medicinal products be implemented as an A.101 variation (Adaptation of a co-marketing medicinal product to ensure alignment with the basic product) or separately (independently of the basic product) as an E.106 variation?

The full declaration for co-marketing medicinal products should be implemented with A.101, not separately.

2.3 Can the design of the label for the primary packaging (logo change) be adapted to the new product manufacturer without notifying Swissmedic, as soon as the corresponding name change of the product manufacturer has been approved?

There is no need to submit an A.100. A.1 is sufficient.

2.4 What variation does Swissmedic require for the conformation (change in the product information and/or packaging texts) of a medicinal product with a known active substance without innovation once document protection for the reference medicinal product has expired?

A variation without assessment C.3.

2.5 Can the procedure under Art. 13 TPA be requested for variations without assessment and variations with assessment, “shortened” time limit?

Yes, provided these specific variations are processed in an Assessment Report (AR) by the reference authority. For multiple applications, all variations within the same multiple application must be processed in the same Assessment Report.

2.6 How do I submit an editorial change to the Information for healthcare professionals, package leaflet or other packaging elements (formerly a variation A.z)?

As a variation without assessment C.9 if the changes cannot be submitted as part of another application.

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3 Changes in quality

3.1 With variation B.3 a), can several manufacturing sites be deleted from the following sections in the Manufacturer information form: "Manufacture of finished product", "Medicinal product packaging", "Quality control of medicinal products" and "Batch release"?

Yes. You can submit the deletion of a manufacturer that involves several sections of the *Manufacturer information* form as a variation without assessment B.3 a).
Apart from that, the wording (singular or plural) of the variation in the form *Variations VMP* should be followed.

3.2 Can several Ph. Eur. certificates of suitability be deleted with variation B.3 t) and u)

Yes. Apart from that, the wording (singular or plural) of the variation in the form *Variations VMP* should be followed.

3.3 For a variation B.44, does Swissmedic accept just one CEP per variation number or are several CEPs allowed?

One variation per CEP has to be submitted when presenting new or updated Ph. Eur. certificates of suitability.

3.4 We would also like to notify a manufacturer for the primary and secondary packaging. Does that involve two submissions?

An additional manufacturing site for the primary and secondary packaging has to be submitted as two variations: B.20 (for non-sterile finished products) or F.II.B.1 d) (for sterile medicinal products) and B.21).

3.5 Can various substantial changes to an updated DMF be submitted as one variation?

Yes. As a variation with assessment, “standard” time limit F.I.f.1. All changes have to be set out in detail in the “Previously approved” / "Applied for” list.
Swissmedic will also accept the submission of several variations involving the same variation template for section F. Quality variations with assessment as one variation on template F.z b) “standard” time limit. In this case, the scope / justification section must list the number of the variation template to which the variations refer and all change parameters must be set out in detail in the “Previously approved” / "Applied for” list. (See section 3.12 of guidance document *Formal requirements*).

Example:

F.z Other quality change that requires assessment

F.z	Other quality change that requires assessment	Documentation to be submitted	Time limit	SAP no.
☐ a)			Shortened	5727
☐ b)			Standard	5734

Scope / justification for the change
F.II.b.3. Change in the manufacturing process for the finished product, including an intermediate used in the manufacture of the finished product a) 1x minor change in the manufacturing process b) 1x introduction of active substance overage c) 1x change in bulk hold time

Previously approved	Applied for
a) Stirring time 1 h	a) Stirring time 30 min

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b) No active substance overage c) Bulk hold time: 1 week	b) 2% active substance overage c) Bulk hold time before filling: 2 weeks

3.6 How can editorial changes be submitted if the updated part 2 consists solely of editorial changes and no changes are expected in the foreseeable future?

Editorial changes to part 2 can be submitted as a variation without assessment B.43. “Editorial changes to part 2 of the dossier if it is not possible to incorporate them into part 2 of a pending procedure” (see also section 3.12 of guidance document *Formal requirements*).

3.7 Can one or more approved suppliers/manufacturers of rubber closures for a parenteral dosage form be deleted from the quality documentation by way of a variation without assessment B.3 s) and can the name of the supplier(s)/manufacturer(s) be omitted as a result?

In the case of rubber closures for parenterals, the manufacturer and/or the precise, manufacturer-specific designation for the closure as well as the specifications for the closure must be stated in section II.C.3 of the quality documentation. Closures may exhibit the following differences, which can influence the finished product quality:

- surface treatment (e.g. silicon or Teflon coating);
- type of rubber closure (e.g. halobutyl type), i.e. exhibiting a different qualitative and quantitative composition;
- dimensions (even minor deviations can impair the impermeability of the closed vial).

Moreover, Ph. Eur. section 3.2.9, “Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders”, states the following: “The manufacturer of the preparation must obtain from the supplier an assurance that the composition of the closure does not vary and that it is identical to that of the closure used during compatibility testing.”

Thus, the manufacturers of rubber closures for a parenteral dosage form may only be deleted from section II.C.3 by way of an application for a variation without assessment B.3.s) if it is explicitly stated in this section that only alternative closures with the same quantitative and qualitative composition and identical specifications may be used.

3.8 We want to notify a new site for an active substance manufacturer by means of a variation without assessment B.45 because the manufacturer has a Ph. Eur. certificate of suitability (CEP). The CEP does not specify a retest period, but we have stability data that document it. Can we tick all the conditions and include the stability in the variation without assessment B.45?

No. A variation without assessment is a simple and fast procedure intended for minor variations with no data assessment. It is therefore a condition of B.45 variations that no further data is required. In the case described, however, the stability data have to be assessed. This means that a variation without assessment B.45 and a variation with assessment F.I.d.1.c are required. In its F.I.d.1 variation, the applicant should confirm that the stability studies of the active substance were conducted in the packaging material specified in the CEP dossier submitted to the EDQM. Where CEPs were issued before 1 September 2011 and do not specify packaging material, the applicant should also submit details of the packaging materials used in the stability studies.

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3.9 Which variation should be submitted for a change in the supplier of sterilised primary containers used in the aseptic manufacture of medicinal products and what additional information should be submitted?

Terminal sterilisation of primary packaging components that are subsequently used in the aseptic manufacture of medicinal products is a critical process and the sterility of the primary container is a crucial quality factor in guaranteeing medicinal product sterility. For this reason, a variation with assessment F.II.b.1.e should be submitted for pre-filled syringes and other types of sterilised primary container that are filled in an aseptic process (e.g. ophthalmic preparations) and which do not undergo any further sterilisation process after they have been filled and their primary packaging has been closed. The application should contain documents on the site's GMP conformity and information on the sterilisation method. If a Ph. Eur. method is not used for sterilisation, validation data should be submitted too (see also EMA/CHMP/CVMP/QWP/850374/2015).

3.10 What changes can be submitted under a single F.II.b.1 variation (replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product)? New from January 2024

A single F.II.b.1 variation for a new manufacturing site of a finished product may include the following changes that are directly related to the change in the manufacturing site: changes in the manufacturing process, batch size and in-process controls to adapt to the conditions at the new manufacturing site.
All changes directly related to the change in the manufacturing site that are applied for as part of a single F.II.b.1 variation must be listed in the *Variations VMP* form and compared in the "Present / Proposed" table.
Changes that affect the finished product and are not directly related to the new manufacturing site applied for, such as changes to the excipients, the specification parameters/limit values for the finished product or the container closure system, including the suppliers, must be submitted as additional variations.

3.11 How can changes submitted in the EU as F.V.b.1 a), b) and c) changes (harmonisation part II) be submitted in Switzerland? New from February 2024

As changes under F.V.b.1 are EU-specific changes that are not listed in the Swiss form, these can be submitted in Switzerland (including as part of a multiple application) as a type F.z b) change (Other quality change that requires assessment, "standard" time limit). It should be noted under "Scope / justification" that the application has been submitted in the EU as a type F.V.b.1 a), b) or c) change, and all changes must be listed in the table "Present / Proposed".

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4 Safety, efficacy and pharmacovigilance changes

4.1 Document protection applies to the reference medicinal product. Can I submit the implementation via a variation with assessment G.I.2 according to Art. 12 para. 2 TPA two years earlier as well?

No, an application for implementation following the expiry of document protection for the reference medicinal product may only be submitted once the document protection has expired.

4.2 Can I make editorial changes in addition to changes referencing studies/literature as part of a variation with assessment G.I.4 or do these need to be applied for separately using a variation without assessment C.9?

Additional editorial changes may be made as part of a variation with assessment G.I.4. It is not necessary to apply for an additional variation without assessment C.9 for this purpose.

4.3 A medicinal product was authorised as a KAS without innovation but its reference product is no longer authorised. Is it possible, in compliance with Art. 28 TPO, to adapt the product information texts to another KAS without innovation for which more recent texts exist? And if so, what type of variation should be submitted for the adaptation?

If the reference product is no longer authorised, it is basically the responsibility of every holder of authorisation for a KAS without innovation that is still authorised to keep its product information texts up to date and in line with the state of the art. However, it is also possible to adapt the product information texts to another KAS without innovation if more recent texts are available for the latter. This first-time implementation should be submitted as a variation with “shortened” time limit G.I.2 z). If the text should then be consistently adapted to the same KAS without innovation, the following applications can be submitted as a variation without assessment C.3, provided that the conditions according to the *Variations VMP* form are met.

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5 Variation of the active substance, dosage strength, pharmaceutical form, administration route or non-food-producing target species

5.1 For an existing authorised solution for injection, any additional (higher) dosage strength, including corresponding clinical data, should be notified. All other things unchanged, we assume that this would represent an extension of the authorisation and the new dosage strength could be marketed under the same trade name (provided the strength – generally in mg/mL – is stated in the veterinary medicinal product name to avoid confusion).

a) Is that correct

b) Would the new strength be assigned a new authorisation number or just a different packaging code?

c) What would the situation be if two excipients were to be exchanged in the solution for injection? Would this still be a line extension with retention of the veterinary medicinal product name (with the above-mentioned addition of the strength)? Would this result in a new authorisation number?

a) Yes, that is correct. An additional (higher) dosage strength corresponds to a variation I.II.1 c) and may be marketed under the same trade name with the addition of the dosage strength (generally in mg / mL).

b) A new dosage strength number will be issued for the new dosage strength, with corresponding new packaging codes for the new packs (see section 9.2 of guidance document *Variations VMP*).

c) As a general rule, a new authorisation number will only be issued if the variation has substantial implications for quality, safety or efficacy (see section 9.2 of guidance document *Variations VMP*). In individual cases, Swissmedic will consider the submitted documentation when making its decision.

5.2 Is it – for example – permissible to submit an application for an additional pharmaceutical form if the first authorisation procedure (first pharmaceutical form) is not yet concluded? Do we have to wait for the official decision on authorisation or the preliminary decision?

Any application that would normally entail a new authorisation number, such as a new dosage form, can be submitted at any time.

Variations that do not require a new authorisation number (normally a new dosage strength for solid and semi-solid forms) can be submitted as part of the ongoing first authorisation procedure (submission of additional documents with possible delay in the first authorisation). Alternatively, the application can be submitted after the conclusion of the first authorisation procedure.

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6 Other questions

6.1 Switzerland now largely follows the EU's classification system for variations involving veterinary medicinal products. Do the Q&A published by the EU also apply to Switzerland?

No. When categorising variations and considering the modalities of their submission, Swissmedic is guided by the relevant directives, specifically Regulation (EC) no. 2019/6 and Implementing Regulation (EU) 2021/17 (variations not requiring assessment) issued under this Regulation, and guidance document EMA/CMDv/7381/2021 (variations requiring assessment) (cf. Art. 25c para. 1 of the Therapeutic Products Ordinance [TPO; SR 812.212.21]).

6.2 In the context of the new ordinances, how will the transfer from an existing authorisation to a new authorisation holder be handled (variation type)? Will the future authorisation holder still have to apply for the transfer? Will the time limit of 30 days now also apply, as in the EU? What costs are involved?

As in the EU, the transfers of authorisations are also not classified as variations in Switzerland, but as "Übrige/Other" applications. These applications will continue to be requested by the future authorisation holder. The application must be submitted to Swissmedic at least three months before the planned transfer date. Further details can be found in the guidance document *Transferring an authorisation*.

6.3 We would like to apply for a new pharmaceutical form for a previously authorised medicinal product. The currently authorised form consists of tablets with various dosage strengths, and we would now like to notify a solution for injection with two new dosage strengths. What do I need to submit exactly?

In this example, one variation I.II.1.d) "Change or addition of a pharmaceutical form" should be submitted. The new dosage strengths and administration route are subsumed into the new pharmaceutical form 2.d).

6.4 Does a cost cap equal to the cost of authorising the product apply to variations? Revised in March 2023

Yes, a cost cap does apply and the maximum amount is CHF 5,000.

6.5 What do I have to submit if I want to discontinue a medicinal product that shares a collective medicinal product information text with other, still authorised medicinal products?

In addition to the discontinuation, a variation without assessment B.3 v) "Deletion of a pharmaceutical form or dosage strength" has to be submitted for the remaining medicinal products so that the collective medicinal product information can be updated.
Please note that "Discontinue preparation" applications are not variations in accordance with the *Variations VMP* form and cannot therefore be submitted in a multiple application.

6.6 What do I have to submit if I want to discontinue a dosage strength of a medicinal product?

Regardless of whether or not a collective medicinal product information text that includes additional medicinal products exists, discontinuation of a dosage strength must be submitted as a variation without assessment B.3 v "Deletion of a pharmaceutical form or dosage strength.

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6.7 A medicinal product was authorised with a particular dosage strength. We would now like to apply for a new dosage strength for it. We would also like to apply for a new indication for both the new and the already approved dosage strength. What do I need to submit exactly?

A variation G.I.7 a) “Addition of a new, or a variation to, an approved therapeutic indication” should be submitted in addition to an application I.II.1.c) “Modification or addition of a dosage strength”.

6.8 Application types “Variations with assessment” and “Variations without assessment” are not available when we come to upload variations for veterinary medicinal products to the portal. What submission type should we use instead?

You can use the “new application / variation” submission type for variations with and without assessment.

6.9 Why does variation E.106 still appear as A.109 on the portal and when will this change?

The number of the variation “Alignment of veterinary medicinal product information / packaging with EU format incl. full declaration in accordance with Annex 6 TPLRO” was overlooked when the new variation structure was rolled out on 1 January 2022. It is scheduled for updating when the next major product portfolio update takes place in early 2023.

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