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 and extensions*, guidance document *Formal requirements* (particularly section 3.12), and the form *Variations and extensions* on the Swissmedic website.

1.2 What is the procedure if type IA/IA$_{IN}$ variations (*Do and Tell*) cannot be approved or fit a different variation type (type IB or II)? 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 Type IA$_{IN}$ variations have to be notified to Swissmedic immediately after implementation. What does Swissmedic understand by "immediately" ("*Immediate" notification*)?

Type IA$_{IN}$ variations must be notified to Swissmedic no later than one month after implementation.

1.4 What happens if I am too late in submitting a type IA or IA$_{IN}$ variation (i.e. I submit it more than 12 months/one month after implementation)?

In these cases an interim decision will be issued and the notification will then have to be submitted as a type IB variation. If the applicant notices that the deadline has passed before submitting the corresponding type IA or type IA$_{IN}$ variation, the application should be submitted as a type IB variation from the outset. Both the deadline and fee requirements for type IB variations will be applied.

1.5 Must type IA or IAIN variations already have been implemented at the time of submission?

Yes. The definition for type IA/IA$_{IN}$ is "Minor variation to be reported subsequently" (TPO Art. 21). These variations must already have been implemented at the time of submission; the implementation date must be in the past and must be stated on the form *Variations and extensions*.

An exception applies if the type IA or IA$_{IN}$ variations form part of a multiple application that also contains other types of variations (type IB, type II or extensions). 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 type IA-/IA$_{IN}$ variation has already been implemented as part of the multiple application, we would then also require an implementation date.

Any deviations from the requirement to state the implementation date (e.g. not necessary for A.101, PMF) are mentioned in the *Variations and extensions* 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 an IA/IA$_{IN}$ quality change: 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 IA/IA$_{IN}$ variation 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 variations consisting of A. Regulatory changes, B. Quality changes and C. Safety, efficacy and pharmacovigilance changes mixed together?

Although this type of submission for a multiple application is possible in principle, it does raise the question of the usefulness of 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 Can I collect all type IA variations for a medicinal product during a year and submit these as a multiple application?

Yes, it is possible to collect type IA variations for a product and submit them as a multiple application provided the conditions are fulfilled.

However, Swissmedic would advise the authorisation holder to consider a staggered submission in order to preserve an ideal overview of type IA variations for a medicinal product.

1.9 Type IA and IA_{IN} variations must be implemented beforehand. How should the date of revision of the product information texts be adjusted when these change?

For variations of type IA, IA_{IN} involving a change to the product information texts, the date of revision (month/year) should, if applicable, be adjusted to match the implementation date, taking account of the requirements stated in section 2.20 and Annex 1 of the guidance document *Product information for human medicinal products*.

It is important to note that any requirements in the guidance document *Product information for human medicinal products* (section 2.20 and Annex 1) may override this requirement (e.g. the requirement that the date of revision should not be adjusted).

1.10 For type IB variations, 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 of type IB involving a change to the product information texts, the date of revision in the form month/year should, if applicable, be adjusted to match the date of application submission, taking account of the requirements stated in section 2.20 and Annex 1 of the guidance document *Product information for human medicinal products*.

It is important to note that any requirements in the guidance document *Product information for human medicinal products* (section 2.20 and Annex 1) may override this requirement (e.g. the requirement that the date of revision should not be adjusted).

1.11 Can an extension of the time limit be granted for the reply to an interim decision/preliminary decision for variations of types IA, IA_{IN} or IB?

No extension of the time limit for corrective actions is granted for companies, either for type IA/IA_{IN} or type IB variations. For both variation types, a maximum of 30 calendar days is granted for corrective actions.

1.12 In the EU, an "Annual Report" is possible for type IA. Does this also apply in Switzerland?

While Switzerland does not recognise "Annual Report" as a concept, the authorisation holder can collect all type IA variations for a medicinal product and submit these once a year. It is important that the implementation date for the "oldest" type IA variation should not be more than 12 months before the reporting date (see also Q&A 1.8).

1.13 Collective application: What must be submitted in respect of the form Variations and extensions?

A form consisting of the administrative part (sections 1-7) plus the requested variation (e.g. B.II.b.1.a "Secondary packaging site"). 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.

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1.14 The CMDh group has published recommendations for classifying unforeseen variations. Do these also apply to Swissmedic? Revised in July 2019

When categorising an "Other change", Swissmedic takes account of the published list "*CMDh Recommendations for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008*".

1.15 Do variation applications submitted to Swissmedic using form Variations and extensions also require a covering letter?

Swissmedic does not require covering letters for applications for variations of types IA, IA_{IN} and IB, provided no further information or explanations in addition to those in the form *Variations and extensions* are required.

1.16 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.

1.17 What is the correct eCTD file name for the form *Variations and extensions* (1.2.1 ch-foapplvar-VAR.pdf)? What applies regarding the form *New authorisation of human medicinal products*?

Both for the form *Variations and extensions* and the form *New authorisations of human medicinal products* the eCTD file name starts with 1.2.1 ch-foapplvar-. In the variable part it is then up to the applicant to generate an appropriate file name, provided it is not too long.

1.18 If I receive an interim decision for a type IB variation and this was answered within 30 days, do I have to wait 60 or 70 days from the date of confirmed receipt before I can assume that the variation is approved?

If you receive an interim decision as a result of shortcomings in form or content and these have been answered within 30 days, you must wait for 60 days from the date of confirmation of receipt / *Acceptance of delivery* (for Portal users) of the replies before you can assume that the variation has been accepted/approved.

1.19 According to the guidance document *Formal requirements*, section 2.5.5 Curriculum vitae of experts, a curriculum vitae must accompany the submission of *Overviews* (2.3, 2.4 and 2.5). What about type IA/IA_{IN} variations? A Module 2 is not normally submitted for these variations in the EU (to our knowledge). However, in Switzerland we often submit "2.3 *Introduction*" with a brief description of the variation. Does 1.4.1 also have to be submitted for this purpose?

The curriculum vitae of experts is not necessary for type IA/IA_{IN} variations.

1.20 Does Module 2 (*Quality Overall Summary*) have to be submitted for a type IB variation? If it is not required, can Module 1.4.1 (*Information about the expert*) also be omitted?

If the content of the existing Module 2 does not change as a result of the type IB variation, then Module 2 and Module 1.4.1 do not need to be submitted.

1.21 For a multiple application, can I submit the form *Variations and extensions* in several pdf files?

No, for a multiple application all the information and proposed variations should be requested in one pdf file.

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1.22 For variations and/or extensions, 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.

1.23 Can A.109 *Implementation of new requirements in accordance with the revised TPLRO (version of 1 January 2019*) be submitted as collective or collective-multiple applications? New from July 2019

No. A.109 cannot be submitted as collective or collective-multiple applications because they do not meet the requirements of Art. 22b TPLRO.

1.24 Will it be possible to perform do and tell or submit other variations during registration of a new product? New from November 2019

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”)

1.25 What happens to multiple applications comprising type IA/IA$_{IN}$ variations if one variation requires improvement? Will all applications be delayed by the amount of time it takes to make the improvements? New from November 2019

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.

1.26 Can multiple applications be processed under an FTP or PPN? New from November 2019

No, applications for variations that are processed under an FTP or PPN cannot form part of a multiple application.

1.27 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? New from May 2020

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

1.28 For a sterile biological/immunological medicinal product that is already authorised in vials, can the inclusion of a new container (pre-filled syringe) be submitted as a B.II.e.1 b) 2. (type II) application? New from September 2020

No. Please see Section 9.1, Z.5 of the guidance document ‘Variations and extensions’. In this case, a Z. 2. d) Modification or addition of a pharmaceutical form authorisation extension must be submitted, as the new container is deemed to be a new pharmaceutical form.

1.29 We would like to submit an application A.106 Conversion of the authorisation of co-marketing medicinal products to independent authorisation (basic product). How should the formal requirement “Submission of a complete identical set of documentation” be interpreted? New from February 2023

Swissmedic understands a complete set of documentation to refer to the entire life cycle of the basic product, i.e. including all submissions in chronological order from application to first authorisation of the basic product.

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As an alternative to submission of the complete set of documentation, if there is a relevant declaration of consent from the authorisation holder of the basic product, only the actually approved documentation (Module 2 to Module 5) and any forms to be amended from Module 1 can be submitted, see section 3.11.2. of the guidance document *Formal requirements*.

1.30 We have a comprehension question regarding application A.106: How should the declaration of consent from the authorisation holder of the basic product mentioned in section 3.11.2 of the guidance document *Formal requirements* be formulated? New from February 2023

The marketing authorisation holder of the basic product must give an appropriately formulated declaration of consent to Swissmedic as the regulatory authority stating that it is making available the scientific documentation on the product. For example: “The marketing authorisation holder of the basic product [...] hereby gives its consent to Swissmedic for its scientific documentation for the basic product [...] being placed on file in the process regarding conversion of the co-marketing medicinal product [...] to a regular authorisation.”

1.31 The ATC code is listed in the WHO provisional list. Can an application for inclusion of the ATC code in the Information for healthcare professionals be submitted already with A.6? New from July 2023

No, variation A.6 should only be submitted when the ATC code has been incorporated in the WHO final index. The application will not be dealt with if it is submitted too early.

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2 Regulatory changes

2.1 Can the application A.109 (Implementation of new requirements in accordance with the revised TPLRO) be submitted, as of 01.01.2019, in connection with an ongoing application for a packaging change according to the old application type?

No, application A.109 should be submitted separately.

2.2 When a variation A.109 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, A.109 only applies to the implementation of new requirements according to the revised TPLRO. In connection with a multiple application, in addition to A.109 you can also submit other pooled variations for the specific medicinal product. However, safety-related variations cannot form part of multiple applications.

2.3 We would like to notify a further pack size for one of our products. At the same time, the whole design is to be changed. The application for a further pack size corresponds to A.102: New and/or modified pack size (type IB). Can we submit all packaging materials with the new design in the same application (A.102)?

No, a modified pack design corresponds to an A.100 variation (Change in the product information and/or packaging texts without the submission of scientific data) and cannot be processed under A.102 since A.102 is only intended for the additional pack size. A multiple application should therefore be submitted (A.100 and A.102).

2.4 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 a A.109 variation?

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

2.5 The following question arises in connection with the regulatory variation A.100 (type IB): The product manufacturer changes its name. For the radiopharmaceuticals concerned, the product manufacturer is not mentioned on the packaging/package leaflet, with one exception. Since radiological protection requires uniform labels to be used for the primary packaging (vials) throughout Europe, the logo of the product manufacturer appears on the vial labels of products for Switzerland - currently A, in future B. What is now the correct procedure for this logo change?

The scenario described above involves a regulatory change A.5: Change in the name and/or address of a manufacturer of the finished product (including batch release and quality control sites) (type IA_{IN}, or IA, depending whether the corresponding manufacturer is responsible or not for batch releases).

If the product information and/or packaging texts are now modified in connection with this change, a separate A.100 variation is not necessary. A.5 changes must be notified for each medicinal product concerned.

2.6 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?

In this case we consider the submission of an A.100 to be unnecessary. A.5 is sufficient.

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2.7 With the regulatory change A.7 (type IA), 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 an A.7 variation (type IA).

The wording (singular or plural) of a variation in the *Variations and extensions* form should be followed in all cases. In this case, the variation reads: "Deletion of sites..." (Plural).

2.8 We would like to submit a type IAIN variation for a co-marketing medicinal product. On the basis of the duty of the authorisation holder of the basic product to notify changes that need to be taken over to the authorisation holder of the co-marketing medicinal product, the latter submits the respective change within 30 days of approval being granted for the basic product. This means that we have to implement all changes to the product information and/or packaging texts for the co-marketing products within this short period.
How can this be implemented? What is meant by "Date of implementation"? For example, we do not implement the product information texts in our quality system. Otherwise, 30 days is a very short period for adapting all artworks. Would you accept "n.a." on the form under "Date of implementation"? Or a date in the future?

The adaptations of a co-marketing medicinal product to its basic product should be notified to Swissmedic via the regulatory change A.101.

If this involves a change in the packaging code, or if not all the conditions are fulfilled, this would be a type IB variation, otherwise a type IA_{IN} variation. In both cases, the changes to the co-marketing medicinal product must be notified to Swissmedic within 30 days of approval of the corresponding changes to the basic product.

Since the implementation of the change(s) to the co-marketing medicinal product must be made at the same time as that for the basic product, and since this rarely occurs within the 30 days described above, Swissmedic does not require an implementation date for A.101 b) (type IA_{IN}).

2.9 What form must now be used for notifying a new sample pack with a promotional section? Must the omission of the discount coupon in the promotional section of an already notified sample pack with promotional section be renotified?

Sample packs should be notified to Swissmedic on the *Variations and extensions* form (regulatory change: A.102).

The promotional section of sample packs is checked only if an advertising permit needs to be obtained (sensitive groups: laxatives, anorectics, analgesics, sedatives and sleeping aids, with the potential for dependence or abuse). Authorisation of the sample pack must be applied for in the normal manner, and the promotional section must satisfy the legal provisions applicable to therapeutic products.

Since Swissmedic does not check the promotional section (apart from the exceptions mentioned above), a variation does not need to be submitted to us unless a product subject to compulsory prior control is involved. The legal provisions applicable to therapeutic products must be satisfied (direct responsibility of the authorisation holder).

2.10 According to the guidance document for changing the domicile of an authorisation holder, a variation application for A.1 should be submitted. However, section A.1 is not included in the *Variations and extensions* form, which starts with A.2. Where can A.1 be found?

Variation A.1 is included in Annex 7 to TPLRO. However, since authorisation holders do not need to notify A.1 separately, but this variation is rather initiated by Swissmedic in connection with a corresponding variation application for the establishment licence (change of name/domicile), A.1 is not included in the *Variations and extensions* form.

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2.11 Can a former notifiable variation no. 4 (Adaptation of the product and patient information for generics to the original product) be submitted as an A.100, type IB variation?

No, the above-mentioned change should be submitted as a C.I.2 a) variation. Regardless of whether the conditions stated in the form can be satisfied or not, the application should be classified as type IA_{IN} or type IB.

2.12 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? New from July 2019

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2.13 For the basic product, an official decision of approval was concluded for a multiple application. Now I need to submit the implementation for our co-marketing medicinal product. Would it be sufficient if I submit only one application? New from November 2019

No, it is not sufficient to submit only one application. For multiple applications of the basic product, all variations (same amount) of the multiple application must be submitted for the co-marketing medicinal product.

2.14 Can the procedure as per Art. 13 TPA be requested for minor variations in line with Art. 21 (types IA and IA_{IN}) and Art. 22 (type IB) TPO? New from May 2020

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.

2.15 As part of the adaptation of the original preparation (C.I.2. a), type IAIN), updated product information texts for the basic product of our co-marketing medicinal product were uploaded to AIPS. This consisted of a multiple application for additional type II and IB variations for approval of the basic product. To date, this multiple application has not yet been approved. Can we nonetheless submit the adaptation of the co-marketing medicinal product for the already published product information texts via an A.101 b), type IA_{IN} variation? New from July 2020

No, the adaptation of a co-marketing medicinal product may only be submitted once the corresponding variation of the basic product has been approved.

2.16 The document protection for a biological medicinal product (reference preparation) has expired for one or more indications. The authorisation holder of the related biosimilar wishes to adopt these indications by way of extrapolation and to adapt the product information texts for the biosimilar accordingly. How exactly should the application for this variation be submitted? New from July 2020

On expiry of the document protection for the reference preparation, the authorisation holder submits a C.I.2 variation for its biosimilar. If this variation entails new, additional data (e.g. data on comparability or clinical trial results), a type II variation – C.I.2 b) – must be submitted. However, if the extrapolation is backed up by a scientific assessment which also specifies explicitly why a biosimilar does not require any additional clinical data, then a type IB variation should be submitted: C.I.2.

2.17 Does notification have to be given in the form of an application for a sample pack that corresponds to the smallest pack size authorised by Swissmedic? New from January 2022

No, if the sample pack corresponds to the smallest authorised pack size, it is the responsibility of the marketing authorisation holder to ensure that the sample pack is correctly labelled.
Swissmedic will not consider the submission of an application A.102 for such a sample pack.

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2.18 How exactly should the description of variation A.102 *New and/or modified pack size* be interpreted? New from July 2022

Application A.102, type IB should be used to submit applications for inclusion of a new pack size or a change in pack size of, for example, 5 to 10 ampoules (i.e. the 10 ampoule pack replaces the 5 ampoule pack). It should be noted that a separate application A.102 must be submitted for each new or modified pack. Several variations can be submitted as a multiple application.

2.19 Is it possible to change only one dosage strength for an export licence and leave the remaining dosage strengths unchanged for the main authorisation on the Swiss market? New from January 2023

Yes, it is possible to change only individual dosage strengths for export. However, it must be ensured that the remaining product presentations for the main authorisation conform to the dosage instructions and treatment duration defined in the Information for healthcare professionals or that the dosage instruction can be met using the remaining dosage strengths.

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3 Changes in quality

3.1 For a B.III.1 variation, does Swissmedic accept just one CEP within the same variation number or are several CEPs allowed? Revised in July 2020

The wording (singular or plural) of a variation in the Variations and extensions form should be followed in all cases. It is necessary to submit one variation per CEP when presenting a new or updated Ph. Eur. certificate of suitability. If deleting Ph. Eur. certificates of suitability, several deletions can be combined in one application.
Exception: In the case of Ph. Eur. certificates of TSE Suitability for an excipient (e.g. gelatine), it is acceptable to submit several CEPs within the same variation number (B.III.1.b.2 or B.III.1.b.3).

3.2 Can several Post Approval Change Management Protocols (PACMPs) be submitted as one variation (B.II.g.2)?

No, each individual PACMP must be submitted with a B.II.g.2 variation, and the variation template for B.II.g.2 must be copied accordingly.

3.3 New packaging codes are not assigned to cartons in the event of the following minor variations in excipient composition: new or modified inks (B.II.a.1.a); addition, deletion or replacement of the flavouring or colouring system (B.II.a.3.a.1., B.II.a.3.a.2.); minor changes to the proportion of other excipients in the quantitative composition of the finished product (B.II.a.3.b.1.); change in coating weight of solid oral pharmaceutical forms or change in weight of capsule shells (B.II.a.4.a). How must I proceed, nevertheless, in order to obtain new packaging codes for cartons? Revised in January 2022

Any applicant who wants a new packaging code for any of the cases outlined above can apply for a type IB variation. The wish to obtain a new packaging code should be mentioned in the covering letter or on the form.

3.4 We would like to notify a new finished product manufacturer for our medicinal product who will be responsible for the manufacture and the primary and secondary packaging. On the Variations and extensions form, can we enter a cross against a) Secondary packaging site, b) Primary packaging site and e) New manufacturing site simultaneously?

No. A separate template B.II.b.1 must be completed for each change (3 copies of template B.II.b.1). The three changes (secondary packaging site (B.II.b.1.a), primary packaging site (B.II.b.1.b), and new manufacturing site for non-sterile medicinal products (B.II.b.1.e)) may not be checked on one template.

3.5 For a B.II.b.3 variation, point 6 under "Documentation" states that a "Copy of approved release and end-of-shelf-life specifications" is required. In the EU, this document is attached as an annex to the form and not inserted in Module 3, since Module 3 does not change in connection with this type of variation. Where in the variation dossier should this copy of the approved specifications be inserted in the eCTD for Switzerland – in Module 1 under "additional data" or in Module 3.2.P.5.1?

We expect the copy of the approved release and end-of-shelf-life specifications to be inserted in Module 1 under "additional data".

3.6 Our medicinal product contains a medical device as an inhaler and this will now be reclassified from Class I to Class IIa (according to the new EU Medical Devices Regulation). The medical device remains unchanged. What variation do we need to use to notify this to Swissmedic? Revised in November 2019

Please submit your described variation as B.IV.1.z. Other variation (type IA).

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3.7 Does a name change for a supplier of primary packaging need to be notified or not? According to the Variations and extensions HAM form, only the deletion of a supplier or the replacement/addition of a supplier needs to be notified under B.II.e.7. Revised in January 2024

A name change for suppliers of primary packaging should be submitted as B.II.e.7.z (type IA).

3.8 We would like to delete the notification of a manufacturer for batch release and notify a new one. Can the deletion and new notification be implemented in a single step?

For the change in batch release c) provides subitems 1, 2 or 3, each of which starts with "Replacement or addition of a manufacturer responsible for batch release…". "Replacement" means that a deletion and new notification can be implemented in the same step.

3.9 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 involves two changes: B.II.b.1.a) and B.II.b.1.b).

3.10 Please can you state what type of variation is involved in the submission of an application for a new MCB/WCB (Master Cell Bank/Working Cell Bank) for a biotechnological product? Revised in November 2019

A distinction should be made between the establishment of a new MCB or a new WCB.

a) Establishment of a new MCB: type II, B.I.a.2.c)
b) Establishment of a new WCB (provided that no approved protocol is followed): type IB, B.I.a.2.a)
c) Establishment of a new WCB (provided that an approved protocol is available in Module 3): no application.
d) Establishment of a new WCB and a protocol: type II, B.I.a.2.c)

3.11 I have a question on the "z variations": In all quality changes (section B), the last of the possible changes is listed as a "z variation". Is our assumption correct that a z variation is involved if all other listed changes (e.g. a-k for the variation B.I.a.1) do not apply? What is the basis for classifying such a "z variation", i.e. when does the type IA, IAIN, IB or type II variation apply?

A variation can be submitted as "Other change" if it is not listed in Annex 7 TPLRO (List of variations according to articles 21-24 TPO). An "Other change" is by default a minor variation of type IB. If a more extensive variation is involved, both Swissmedic and the marketing authorisation holder can upgrade this to a variation of type II.

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".

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3.12 We have the following question concerning a quality change for a vaccine that we have submitted as a variation requiring approval according to the old law. However, this change has not yet been submitted in the EU, but only reported to the OMCL:
Virus seed stock changes (aka working virus stock) is used in Drug Substance manufacturing as the starting point for DS manufacture. As such, it is registered as a starting material under 3.2.S.2.3. Only the production and qualification of stock seeds is mentioned there.
In the EU, replacement of a working virus stock does not require regulatory activity when an approved protocol for qualification of new working virus stocks is in place. So we only notify the OMCL about the change in working virus stock, but not the EMA.
How should we proceed in future in Switzerland? Does such a change have to be submitted to Swissmedic?

The use of a new working virus stock that has been qualified according to an approved protocol does not need to be reported to Swissmedic.

3.13 We would like to submit the Annual Update for our authorised seasonal influenza vaccine. Under what variation type must we submit this, and has anything changed from the former procedure/requirements?

The Annual Update for an authorised seasonal influenza vaccine must be submitted as a B.I.a.5 change: Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against influenza (type II). The corresponding documents should be made available to Swissmedic as soon as possible. The procedure is identical to the former procedure. If possible, the application is processed as a matter of priority.

N.B.: This change may not be part of a multiple application. The Annual Update may only include changes connected with the new strains.

3.14 According to the EMA and CMDh Q&A, in cases where there are substantial changes to an updated DMF/Module 3.2.S, it is possible to submit the individual changes as a type II variation under B.I.z. Does Swissmedic accept this practice too? Revised in March 2023

Yes. An update to a DMF / Module 3.2.S can be submitted with the B.I.z “Other quality change to active ingredient”, type II variation. All updated sections of Module 3.2.S and all changed parameters must be set out in detail in the “Present” / "Proposed” list. This type II variation will be invoiced at a rate of CHF 3,500 for human medicinal products (item 5.4 in Annex 1 of FeeO-Swissmedic). Any additional costs incurred will be invoiced.

3.15 The notified body previously responsible for the CE marking of our medical device (plastic syringe) has been replaced by a new notified body. The new certificate can be found in Chapter 3.2.R (Regional Information). The medical device remains unchanged. How should this variation be submitted? New from November 2019

This variation should be submitted as B.IV.1.z, type IA.

3.16 How can editorial changes be submitted if the updated Module 3 consists solely of editorial changes and no changes are expected in the foreseeable future? New from January 2021

Editorial changes to Module 3 can be submitted as an “Other change” B.z, type IA (also see the guidance document Formal requirements, section 3.12).

3.17 Can one or more approved suppliers/manufacturers of glass ampoules or glass vials for a parenteral dosage form be deleted from section 3.2.P.7 of the quality documentation by way of a type IA application B.II.e.7.a, thus resulting in the name of the supplier(s)/manufacturer(s) being omitted? New from June 2021

Yes, this is possible provided the specifications for the glass container remain unchanged. The application must be accompanied by reasons and/or by a confirmation that there is no risk, with the preparation concerned, of there being an incompatibility between the preparation and the glass

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container such as may arise, for example, with formulations containing phosphate, citrate, gluconate or tartrate salts or complex-forming agents such as EDTA or formulations with alkaline pH values. A confirmation must also be provided stating that, in the event of a future change of supplier/manufacturer, the compatibility of preparation and glass container will be subjected to compatibility testing on a case-to-case basis, as described in the Production Statement in Ph. Eur. section 3.2.1 (Glass containers for pharmaceutical use).

3.18 Can one or more approved suppliers/manufacturers of rubber closures for a parenteral dosage form be deleted from section 3.2.P.7 of the quality documentation by way of a type IA application B.II.e.7.a, thus resulting in the name of the supplier(s)/manufacturer(s) being omitted? New from June 2021

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 3.2.P.7. 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 manufacturer of rubber closures for a parenteral dosage form may only be deleted from section 3.2.P.7 by way of a type IA application B.II.e.7.a if it is explicitly stated in section 3.2.P.7 that only alternative closures with the same quantitative and qualitative composition and identical specifications may be used.

3.19 How should I submit a new reference standard for a biological medicinal product? Revised in January 2023

If a new reference standard is introduced using the limits/conditions as detailed in an approved qualification protocol, then no variation has to be filed. If no qualification protocol has been approved and the old material is still available and comparability test results can be provided using both reference standards, a type IB variation should be filed either under B.I.b.2.e for Active Substance or under B.II.d.2.d for Finished Product. If no qualification protocol has been approved and the old material is not available anymore and therefore no direct comparison new/old material is possible a type II variation should be filed either under B.I.b.2.d for Active Substance or under B.II.d.2.c for Finished Product.
A type II variation B.I.b.2.d or B.II.d.2.c should be submitted for introduction of a qualification protocol for the manufacture of a new reference standard. Following approval of the variation, the future introduction of a new reference standard according to this qualification protocol will be covered by the existing quality assurance system.

3.20 Can an updated CEP for a heparin be submitted as type IA (B.III.1.a.2)? New from August 2022

Submission of an updated CEP for a heparin as type IA (B.III.1.a.2) is only possible in the case of a change of name and/or address of the CEP holder or a manufacturer of the active substance. The manufacturing location and all manufacturing steps must remain unchanged.

In the case of other content changes to the CEP, the following applies:

- Because the starting material for heparins (including low-molecular-weight heparins) is of animal origin, condition 3 is not met. Type IB should therefore be checked for the B.III.1.a.2 variation.
- If an assessment of the risk of potential contamination with adventitious agents is required, a type II variation (B.III.1.b.5) should be submitted.

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4 Safety, efficacy and pharmacovigilance changes

4.1 An authorised antibiotic is used to treat infections involving bacteria A, B and C. Recent studies have shown that the medicinal product is also effective against bacterium D, but has ceased to be effective against bacterium A. How should the company apply for the variation?

The company requests the following variations in connection with a multiple application:
C.I.6.a): Addition of a new, or a variation to, an approved therapeutic indication for bacterium D (type II) and
C.I.6.b): Deletion of a therapeutic indication for bacterium A (type IB)
The maximum amount levied will be that for the new authorisation of a medicinal product.

4.2 In the EU there are new PRAC recommendations and, therefore, new requirements stating how medicinal product information texts should be adapted. Can this be submitted in Switzerland as C.I.z: Other change relating to safety, efficacy or pharmacovigilance? Revised in July 2019

No. Submit a C.I.4 variation (type II) in this case. The PRAC recommendations and corresponding PRAC minutes are adequate documentation. The PRAC assessment report should also be submitted if available.

4.3 For a C.I.4 (type II) application, is a detailed comparison of the 'currently approved' vs. 'proposed' text required in the *Variations and extensions* form? This would make comprehensive applications very confusing. Revised in July 2019 (displaced from chapter 6)

For changes to product information texts, Swissmedic expects the following under “currently approved – proposed”:

- A.100: List of sections that have been changed
- C.I.2: Status of “old” information compared with status of “new” information.
- C.I.4: List of sections that have been changed

The *Variations and extensions* form now specifies what information has to be provided for a variation to medicinal product information texts for the relevant applications.

4.4 Document protection applies to the reference medicinal product/preparation. Can I submit the implementation via application C.I.2 according to Art. 12 para. 2 TPA two years earlier as well? New from November 2019

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

4.5 Can I make editorial changes in addition to changes referencing studies/literature as part of a C.I.4, type II variation, or do these need to be applied for separately using a A.100, type IB variation? New from July 2020

Additional editorial changes may be made as part of a C.I.4, type II variation. It is not necessary to apply for an additional A.100, type IB variation for this purpose.

4.6 New medicinal product information texts have been published for the reference medicinal product relating to my medicinal product with known active substance without innovation, because, for example, A.109 (implementation of the requirements in the revised TPLRO, full declaration) has been implemented. As the changes to the preparation are purely product-specific ones and do not affect my medicinal product, only the date of revision will change for me. Can I implement this myself, or do I have to submit a C.I.2 application? Revised in January 2022

In this case, no application is necessary. The date of revision can be amended independently.

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4.7 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? Revised in September 2021

If the reference product is no longer authorised, it is basically the responsibility of every authorisation holder of 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 adaptation should be submitted as a C.I.2 a), type IB variation
If in the future the text should consistently be adapted to the same KAS without innovation, the following applications can be submitted as type IA_{IN} variations, provided that the conditions according to the *Variations and extensions* form are met.

4.8 Several consecutive variations to the medicinal product information for the original preparation have been made, each with a different text revision date. Can several variations be collated in a single C.I.2 a) application as part of the adaptation of the original preparation? New from January 2022

No. Pursuant to Art. 28 TPO, the marketing authorisation holder is obligated to adapt the medicinal product information on an ongoing basis without being requested to do so and notify Swissmedic of this promptly. A C.I.2 a) application should be submitted per variation of the medicinal product information for the original preparation, i.e. per text revision date. If the variations concerning the original preparation follow in quick succession, a multiple application with several C.I.2 a) variations can be submitted; however, it should be noted that the completion deadline – as of the implementation date for the first Type IA_{IN} application – must not lie more than 1 month ahead.

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5 Changes to Plasma Master File (section X)

5.1 How will PMF annual update submissions be handled under the revised TPA (TPA2/HMV4)? Revised in July 2019

Annual updates to PMFs for authorised medicinal products should be submitted to Swissmedic in a cover letter (no additional form needed) once a year as conditions of authorisation. Changes to PMFs must be notified to Swissmedic using the form *Variations and extensions* or as an application for approval. Annual PMF updates (to fulfil conditions of authorisation) and variations to this PMF can be submitted simultaneously (and will be treated as a multiple application in this case).
To ensure a clear distinction between “simple PMF annual updates” and a combination of “PMF annual update and variation(s) to a PMF”, we would ask companies to specify in their cover letter that:

- The annual update is **not** combined with variations *or*
- The annual update **is combined** with variations to the PMF*

Where a PMF annual update is combined with variation(s) to a PMF, Swissmedic will therefore expect to receive a cover letter containing the appropriate indication (see above), an appropriately completed *Variations and extensions* form and the PMF annual update.
A corresponding publication can be found in the Swissmedic Journal 09/2018 (page 826).
* Marked accordingly in the *Variations and extensions* form

5.2 Swissmedic has stated that the new TPA is intended to bring Swiss variations practice into line with EU variations. To what extent does Swissmedic intend to implement harmonisation for PMF annual updates?

Swissmedic is not intending to harmonise its practice with European requirements.

5.3 Is Switzerland also planning to adopt the special D2-D23 PMF classification?

Indirectly yes, because there will be "grouping" by the highest category taking account of the PMF classifications according to D2-D23 (see Annex 7 TPLRO, section X. Variations to PMFs).
For each PMF, applications for one or more PMF variations are submitted according to the highest category (type II, IB, IA/IA_{IN}) as classified in the EU Guideline (Guideline 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) under "B.V.a.1 PMF / VAMF" or "D. PMF / VAMF".
Example 1: The applicant plans to submit two type IA variations and one type II variation together: All three variations are to be submitted as a type II application.
Example 2: The applicant plans to submit four type IB variations together: All four variations are to be submitted as a type II application.

5.4 Will a PMF be registered centrally?

No, Swissmedic is not involved in the EU’s PMF certification process.

5.5 To what extent will the "second step" be applied?

Not at all. Swissmedic has no access to the PMF registered centrally in the EU.

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6 Extensions

6.1 For an existing authorised solution for injection, any additional (higher) dosage strength, including corresponding clinical data, should be notified. We assume that – if everything else remains the same – this would correspond to an extension and that the new dosage strength could be marketed under the same trade name (stating the strength in mg / mL next to the product name in order to avoid mix-ups).
a) Is that correct?
b) Would the new strength then also receive a new authorisation number, or just another packaging code?
c) What would the situation be if two excipients in the solution for injection were exchanged? Would this always still be a "line extension" with retention of the 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 an extension 2.c) and may be marketed under the same trade name with the addition of the dosage strength in mg / mL
b) A new dosage strength (formerly sequence) will be issued for the new dosage strength, with corresponding new packaging codes for the new packs (see guidance document *Variations and extensions*, sections 9.2).
c) Generally speaking, it can be stated that a new dosage strength (number) is issued within the same authorisation number, provided no effects on efficacy, interactions, absorption etc. are expected. In conclusion however, your question cannot be answered since not enough information is provided.

6.2 Is it permissible to submit an extension (e.g. addition of a pharmaceutical form), if the first authorisation procedure (first pharmaceutical form) is not yet concluded? Does one have to wait for the official decision on authorisation or the preliminary decision?

An extension that requires a new authorisation number (according to the guidance document: Variations and extensions, section 9, e.g. new pharmaceutical form) can be submitted at any time.

Extensions that do not require a new authorisation number (e.g. new dosage strength for solid and semi-solid forms) can be submitted in connection with 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.

6.3 Must an application for an extension be submitted in the same eCTD (with new sequence), or may a new eCTD (with seq. 0000) also be submitted?

A seq. 0000 may be submitted only if a new eCTD lifecycle is started. This is the case if an existing product is switched from eDok/paper (with/without baseline) to eCTD or in the event of new notifications. For extensions, Swissmedic recommends working with the existing lifecycle and e.g. integrating the new pharmaceutical form in the existing lifecycle. If a new lifecycle is to be started for an extension, Case Management or Operational Support Services must always be consulted beforehand.

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7 Other questions

7.1 Switzerland now largely follows the EU classification of CMC Post-Approval Changes. Do the Q&A published by the EU also apply to Switzerland? Revised in July 2019

No. When categorising variations and considering the modalities of their submission, Swissmedic is guided by the relevant directives, specifically Regulation (EC) no. 1234/2008 and the European Commission Guidelines based on this Regulation (cf. Art. 25 para. 1 of the Therapeutic Products Ordinance [TPO; SR 812.212.21]).

7.2 May those medicinal products downgraded from C to D still be distributed to druggists in the old packaging (old vignette) during the transitional periods?

Yes, medicinal products may continue to be supplied to druggists with those old packaging elements (C vignette) during the published transitional periods. This does not apply to medicinal products that must incorporate a warning on the packaging.

7.3 After the submission of applications via the eGov portal, or in the event of updates by Swissmedic, the authorisation holders have hitherto received an automated notification e-mail. Will this still happen or will anything change?

The automated notification via e-mail will still happen.

7.4 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*.

7.5 To increase patient safety, may the package leaflet include the sentence "The latest approved version of this package leaflet can be found at www.swissmedicinfo.ch"?

Your proposed sentence may **not** be included in package leaflets. The reasons for this include the transfer of responsibility for publication from Swissmedic to the "institution in the form of a foundation" (refdata) and the fact that the wording of section 16 of the Patient Information is fixed according to the annex to the TPLRO and that no addition is possible.

7.6 As a result of the revised TPA / HMV4, differing variations of the same or different types (IA, IB, II) can be submitted together as a multiple application. All variations will be assessed and completed at the same time. The processing period is based on the longest time limit in the multiple application. We have now seen, on the Swissmedic portal, that only one application ID is shown for a multiple application, which we basically consider to be a good idea. The application is designated with one of the submitted variation categories. However, we find it rather confusing that the Application Tracking section does not make it clear that a multiple application with differing variation types is involved and not just the named variation. Are there plans to enable a "Collective Application", for example, to be displayed in the portal in future under Application Type? Revised in July 2022

The Swissmedic Portal has been adapted and for multiple applications, all variations of the multiple application can now be seen under *Application Type*.

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7.7 In the EU, we use the option of submitting a binding classification enquiry to ensure that the EMA will accept classifications that diverge from the Guidelines. Can we also submit the change classification accepted by the EMA to Swissmedic? New from July 2019

When categorising variations and considering the modalities of their submission, Swissmedic is guided by the relevant generally accessible directives, specifically Regulation (EC) no. 1234/2008 and the European Commission Guidelines based on this Regulation (cf. Art. 25 para. 1 of the Therapeutic Products Ordinance [TPO; SR 812.212.21]). However, individual agreements that the EMA or a national authority has concluded bilaterally with individual authorisation holders cannot be considered in applications submitted to Swissmedic.

7.8 A product was authorised with a particular dosage strength. We would now like to apply for two further dosage strengths for this product. We would also like to apply for a new indication and a new administration route for these two new dosage strengths. What do I need to submit exactly? New from November 2019

In this example, two applications for extension 2.c) "Change or addition of a dosage strength" should be submitted. The new indication and new administration route should be subsumed into them (see also 7.14).

7.9 We would like to apply for a new pharmaceutical form for a previously authorised 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? New from November 2019

In this example, one application for extension 2.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).

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

Yes, a cost cap does apply and the maximum amount is CHF 30,000.

7.11 Please give an exact definition of/distinction between "authorisation extension" and "indication extension". New from November 2019

Authorisation extensions are extensions in the EU's sense of the term. You can find them in Chapter 1.6 "Extensions" of Annex 7 to the TPLRO. Extension of indications (modification of an indication or new indication) are classified as type II variations.

7.12 What do I have to submit if I want to discontinue a medicinal product that shares a collective Information for healthcare professionals text with other, still authorised medicinal products? New from November 2019

In addition to the discontinuation of the medicinal product, an application for a variation C.I.7 a) "Deletion of a pharmaceutical form", type IB should be submitted for the remaining medicinal products in the collective Information for healthcare professionals text.
Please note that "Discontinue preparation" applications are not variations in accordance with the "Variations and extensions" form and cannot therefore be submitted in a multiple application.

7.13 What do I have to submit if I want to discontinue a dosage strength of a medicinal product? Revised in October 2023

Discontinuation of a dosage strength must be submitted as a variation C.I.7 b), type IB. In grouped Information for healthcare professionals, the C.I.7 b) application should only be submitted for the medicinal product concerned (no collective application required).

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7.14 A product was authorised with a particular dosage strength. We would now like to apply for a new dosage strength for this product. 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? New from September 2021

A type II, C.I.6 a) “Addition of a new, or a variation to, an approved therapeutic indication” variation should be submitted in addition to a 2.c) “Modification or addition of a dosage strength” authorisation extension (see also 7.8).

7.15 Our medicinal product consists of an oral solution with a spoon included in the packaging. A second pack of the same medicinal product (oral solution) will now be placed on the market with a dosing syringe included in the packaging. Which application for variation does Swissmedic require? New from October 2023

This is an application for variation B.IV.1.a): Addition or replacement of a device which is not an integral part of the primary packaging. We also require proof of the CE marking and the confirmation of conformity for the included medical device. This variation involves a substantial change to the medicinal product information and/or packaging text and is therefore a type IB variation. An additional A.102 application is not required. As indicated in the form *Variations and Extensions HMP*, the revised medicinal product information and/or packaging texts must be submitted with the B.IV.1 application and the new packaging code will be issued in connection with this application.

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