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 HMV4*, guidance document *Formal requirements HMV4* (particularly section 3.11), and the form *Variations and extensions HMV4* 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.

1.5. Must type IA or IA$_{IN}$ 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 HMV4*.

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 HMV4* 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".

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?

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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 HMV4*.

It is important to note that any requirements in the guidance document *Product information for human medicinal products HMV4* (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 HMV4*.

It is important to note that any requirements in the guidance document (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 HMV4*?

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.

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

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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 HMV4* 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 HMV4* 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 HMV4* (1.2.1 ch-foapplvar-VAR.pdf)? What applies regarding the form *New authorisation of human medicinal products HMV4*?

Both for the form *Variations and extensions HMV4* and the form *New authorisations of human medicinal products HMV4* 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 HMV4*, 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 HMV4* 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.

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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.

2.7. With the regulatory change A.7 (type IA), can several manufacturing sites be deleted from the following sections in the *Manufacturer information HMV4* form: "Manufacture of finished

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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 HMV4* form as an A.7 variation (type IA).

The wording (singular or plural) of a variation in the *Variations and extensions HMV4* 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 IA_{IN} 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 HMV4* 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 HMV4* 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 HMV4* form.

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?

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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

C.I.2 a) (type IA_{IN} or IB).

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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 2019

The wording (singular or plural) of a variation in the Variations and extensions HMV4 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.

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., 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?

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 HMV4*, 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). What variation do we need to use to notify this to Swissmedic?

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

3.7. According to HMV4, does a name change for a supplier of primary packaging need to be notified or not? According to the *Variations and extensions HMV4* form, only the deletion of a supplier or the replacement/addition of a supplier needs to be notified under B.II.e.7.

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

3.8. We would like to delete the notification of a manufacturer for batch release and notify a

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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, according to HMV4, in the submission of an application for a new MCB/WCB (Master Cell Bank/Working Cell Bank) for a biotechnological product?

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 an approved protocol is followed): type IB, B.I.a.2.a)

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, IA_{IN}, 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".

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?

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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 CMDh, 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 (CMDh/CMDv: Q&A - List for the submission of variations according to Commission Regulation (EC) 1234/2008, Question 3.4). Does Swissmedic accept this practice too? New from July 2019

No. A single type II variation for all changes in Module 3.2.S does not cover the workload that Swissmedic has. For this reason, the Agency does not accept this type of classification. The specifications should continue to be listed in the appropriate templates for variations (B.I.a.1 (active substance manufacturer); B.I.a.2 (active substance manufacturing process); B.I.a.3 (active substance batch size); B.I.a.4 (active substance in-process controls); B.I.b.1 (active substance specifications); etc.) and submitted as a multiple application.

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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 HMV4* 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 HMV4* form now specifies what information has to be provided for a variation to medicinal product information texts for the relevant applications.

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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 HMV4* 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 HMV4* 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 HMV4* 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 HMV4*, 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 HMV4, 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.

6.4. Is an application for an extension with reference to Art. 13 TPA possible for e.g. adding a pharmaceutical form for medicinal products with new active substances?

Yes, this is possible provided that the medicinal product with the new active substance has Orphan Drug Status.

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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 HMV4*.

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?

Yes, it is true that "only" the process-controlling variation application is currently displayed in the Swissmedic portal for multiple applications without any mention of that fact that a multiple application is involved.

Swissmedic is currently checking whether an upgrade is possible to enable multiple applications to be displayed in the portal.

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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.

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