Contents

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Change history

Version	Valid and binding as of	Description, comments (by author)	Author's initials
2.2	01.02.2022	Section 5.1: Explanation of PIP obligation (no new requirements in terms of content)	bic/dts
2.1	01.03.2021	Formal adjustments to the header and footer No content adjustments to the previous version.	dei
2.0	08.04.2019	Further details in chapters 5.4, 6.2.2 and 6.3	dts
1.0	01.01.2019	Implementation of TPO4	dts

1 Definitions, terms, abbreviations

1.1 Definitions and terms

1.1.1 Paediatric investigation plan (PIP)

A PIP is a drug development plan that supports the authorisation of a medicinal product for children and adolescents. It ensures that the required paediatric study data are obtained only when this is appropriate and the children and adolescents are not exposed to any unnecessary risks.

1.1.2 Deferral

Deferred studies of the quality, safety and efficacy of a medicinal product, or other measures initiated or concluded at a later date.

1.1.3 Waiver

A waiver is the complete or partial waiving of the obligation to carry out studies of the quality, safety and efficacy of a medicinal product for use in children.

1.2 Abbreviations

Art.	Article
CH-PIP	A paediatric investigation plan newly produced for Switzerland
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FeeO-Swissmedic	Ordinance of 14 September on the Fees charged by the Swiss Agency for Therapeutic Products (SR 812.241.5)
HMP	Human Medicinal Products
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IIP	Federal Institute of Intellectual Property
Let.	Letter
Para.	Paragraph
PatA	Federal Act of 25 June 1954 on Patents for Inventions (SR 232.14)
PIP	Paediatric Investigation Plan
SPC	Supplementary protection certificate
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPLO	Ordinance of the Swiss Agency for Therapeutic Products of 22 June 2006 on the Simplified Licensing of Therapeutic Products and the Authorisation of Therapeutic Products by the Notification Procedure (SR 812.212.23)

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TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Introduction and objective

The revision of the TPA involved the introduction, in a form adapted to Swiss circumstances, of the system employed in the EU since the entry into force of the Paediatric Regulation[1] of obligations and incentives designed to encourage the pharmaceutical industry to develop paediatric medicinal products.

The obligation to develop and submit a paediatric investigation plan and to carry out studies for paediatric use is implemented by Swissmedic on the basis of the EU Regulation (see Regulation (EC) no. 1901/2006).

Applicants can either submit to Swissmedic a PIP that has already been approved by a foreign medicines agency with comparable medicinal product control or develop their own PIP (CH-PIP). PIPs that have already been approved by a foreign medicines agency with comparable medicinal product control are accepted by Swissmedic without a separate review.

This guidance document describes the Swiss requirements pertaining to the application documentation, the review of the PIP in connection with a marketing authorisation application and the complete fulfilment of the PIP after authorisation.

Swissmedic uses this guidance document first and foremost as a resource for applying the legal provisions in a uniform and equitable manner. For applicants, the document is intended to make clear the specific requirements that must be fulfilled so that corresponding applications can be processed by Swissmedic as quickly and efficiently as possible.

3 Scope

This guidance document applies to human medicinal products.

Aspects related to patent law, for example the procedure for requesting a paediatric supplementary protection certificate (SPC) or the extension of an SPC from the Federal Institute of Intellectual Property (IIP) do not fall within the remit of Swissmedic and are not covered in this guidance document.

4 Legal framework

TPA

- Art. 11 para. 2 a, no. 6 Authorisation application
- Art. 54a Paediatric investigation plan

TPO

- Art. 5 Paediatric investigation plan
- Art. 9 para. 5 Authorisation
- Art. 84 Paediatric investigation plan

TPLRO

- Art. 13 para. 2 Information for healthcare professionals

5 Basic requirements

5.1 Obligation to submit a PIP

Paediatric patients (0 - 18 years) must be considered during the development of new medicinal products. In the context of the PIP, Swissmedic must be presented with a research and development

[1] Regulation (EC) no. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) no. 1768/92, Directives 2001/20/EC and 2001/83/EC and Regulation (EC) no. 726/2004, OJ L 378 of 27.12.2006, p. 1

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programme that generates data that can be used to assess the relevant medicinal product for paediatric use. Details of the timing and the measures proposed to demonstrate the quality, safety and efficacy of the medicinal product in paediatric patients should be presented in detail in the PIP and submitted to Swissmedic (Art. 54a TPA).

The obligation to submit a PPK applies to applications:

1. for the new authorisation of medicinal products containing at least one new active substance in the ordinary procedure in accordance with Art. 11 TPA, if the relevant application was filed on or after 1 January 2019 (Art. 5 para. 2 let. A TPO);
2. for the new authorisation of important medicinal products for rare diseases (orphan drugs) containing at least one new active substance, if the relevant application was filed on or after 1 January 2019 (Art. 5, para. 2 let. b TPO);
3. for the authorisation of a new indication, new dosage form or new administration route for a medicinal product (Art. 5 para. 2 let. c TPO)

    a) according to points 1 and 2 above
    b) for which a PIP was voluntarily submitted after 1 January 2019 with an earlier application for new authorisation or variation;
    c) applied for before 1 January 2019 and for which Swissmedic has issued a confirmation in accordance with Art. 9 para 5 TPO or for which a PIP was submitted to Swissmedic for approval (Art. 84 TPO).

The applicant can voluntarily submit a PIP with applications received after 1 January for the new authorisation of medicinal products with known active substances in accordance with Art. 14 para. 1 let. a TPA, including known active substances in accordance with Art. 12 para 5 TPLO. If a voluntary PIP is submitted for such new authorisations, subsequent applications for variation in accordance with Art. 5 para. 2 let. c VAM will also require submission of a PIP. This rule concerning the ongoing PIP obligation also applies to medicinal products for which an application for authorisation was submitted prior to 1 January 2019 but for which a PIP was voluntarily submitted to Swissmedic with an application for variation in accordance with Art. 5 para. 2 let. c VAM. In this case too, submission of a PIP is also mandatory for all subsequent applications for variation in accordance with Art. 5 para. 2 let. c VAM (i.e. if a PIP is submitted once, a PIP must always be submitted).

Waiver of the obligation to implement measures:

Swissmedic can, on request or ex officio, grant a specific waiver of the obligation to produce a paediatric investigation plan or carry out studies for individual paediatric indications or development stages (partial waiver) if:

- there is evidence that the medicinal product is likely to be ineffective in the paediatric population, or its use appears questionable for safety reasons;
- the disease to be treated by the medicinal product occurs only in adults;
- the medicinal product is not expected to offer any significant therapeutic benefit over existing paediatric treatments.

Swissmedic accepts “Class Waivers” according to the list published by the EMA. Reference can be made to this list.

5.2 Deferral of measures

In certain cases, the initiation or completion of some or all of the measures set out in the paediatric investigation plan can be deferred. This is designed to ensure that studies are conducted only if they are safe and ethically acceptable, and that the (planned) studies with paediatric patients do not delay the authorisation of medicinal products for other population groups.

Applicants must request a deferral, providing appropriate justification for the request. Ensuring public health and scientific or technical arguments are possible grounds for deferral.

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5.3 Formal requirements

The formal requirements are based on the guidance document *Formal requirements HMV4* and the associated directory of *Documents to be submitted HMV4.*

A fundamental distinction is made between two cases:

1st Submission of a PIP recently approved by a foreign authority with comparable medicinal product control and most recently approved PIPs, including applications for waiver and/or deferral. See chapter “PIP approved by a foreign authority” and Overview of documents to be submitted HMV4.

2nd Submission of a PIP newly produced for Swissmedic (CH-PIP), including any applications for waivers and deferrals. See section: “PIP newly produced for Switzerland”.

5.4 Requirements for the information for healthcare professionals

Relevant results from studies/investigations conducted in accordance with the approved PIP must be continually updated in suitable form in the information for healthcare professionals, irrespective of whether or not the relevant paediatric indications have been approved by Swissmedic (Art. 28 TPO in conjunction with Art. 13 para. 2 TPLRO).

Basic information on the requirements for product information can be found in the *Guidance document on product information for human medicinal products HMV4*.

5.5 Document protection

The requirements specified in Art. 11a and 11b TPA apply to all types of application.
For medicinal products authorised specifically and exclusively for paediatric use, document protection according to Art.. 11*b* para. 3 TPA is granted only if the submitted studies/investigations correspond with the approved paediatric investigation plan according to article 54*a* TPA and provided document protection does not exist for another medicinal product with the same active substance authorised by the Agency for the same specific paediatric use.
Further information on documentation protection is provided in the guidance document *Document protection HMV4*.

5.6 Time limits

The time limits are based on the guidance document *Time limits for authorisation applications HMV4*.

5.7 Fees

The fees specified in the Ordinance on Fees Levied by the Swiss Agency for Therapeutic Products (FeeO-Swissmedic) apply.

6 Process

6.1 Scientific Advice for Swiss PIPs

If no PIP approved by a foreign authority with comparable medicinal product control exists, a separate paediatric investigation plan, including any waivers and deferrals, must be produced for Switzerland (CH-PIP). The applicant is advised to clarify any critical points concerning the Swiss PIP, particularly relating to any waivers and/or deferrals, in the early development phase of the medicinal product with Swissmedic in connection with a Scientific Advice Meeting. The procedure is based on the *Guidance document Company meetings in Authorisation HMV4*.

6.2 Content and initial assessment of the PIP

6.2.1 PIP newly produced for Switzerland

A CH-PIP is fundamentally geared to the requirements of the EU (Regulation (EC) No 1901/2006). By way of deviation from the EU process, CH-PIPs, including any applications for waiver or deferral of measures, are usually assessed as part of the regular review process for the authorisation

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application. An advance assessment of the CH-PIP can also take place before the authorisation application as part of an extended Scientific Advice[2].

The EMA “Template for scientific document (part B-F)” should be used for producing a Swiss PIP. The information must cover the following aspects:

- Overview of the disease, its diagnosis and treatment. Any differences between children and adults should be highlighted.
- Overview of the available data on the medicinal product, including:
  - Chemical information about the current formulation
  - Non-clinical and clinical study data
- Proposed strategy, including some or all of the following:
  - Plans for a paediatric formulation (if required), including measures for adapting the formulation of the medicinal product to make its use more acceptable in children, for example the use of a liquid formulation instead of tablets
  - Description of additional non-clinical studies
- A description of planned clinical trials or modelling/simulation for predicting the efficacy of the medicinal product in children, including:
  - Details of the timeline of the studies with children compared to the development plan for adults
  - If the paediatric studies cannot be conducted parallel to adult studies, a deferral of these studies must be requested (see section: “Deferral of measures”).

Modelling/simulation are intended to optimise trial design and restrict the number of patients involved in trials to an appropriate minimum. Only in exceptional cases can a model replace the actual clinical trial.

For CH-PIPs, the corresponding ICH Guidelines relating to paediatrics should also be taken into account.

6.2.2 PIP approved by a foreign authority

The applicant can submit a PIP approved by the EMA or a PSP approved by the FDA (incl. approved waivers and/or deferrals). If a PIP approved by a foreign authority with comparable medicinal product other than the EMA or FDA exists, the applicant should, before submitting an application, check with Swissmedic whether the foreign PIP is considered by Swissmedic to be equivalent.

The latest version of the PIP/PSP should be submitted. The decisions of foreign authorities are accepted by Swissmedic, provided that the medicinal products are comparable (e.g. same indications, same dosage recommendation or same pharmaceutical form). Swissmedic reserves the right to ask questions about the foreign PIPs.

Documentation is to be supplied in accordance with the *Overview of documents to be submitted HMV4.* Further documents may be requested in specific cases.

Approved subsequent amendments to the PIPs approved by foreign authorities should not be submitted to Swissmedic. Amendments approved by the foreign authority, including for example changes to the time limits for fulfilling individual PIP measures, are accepted by Swissmedic unseen, without the need for the applicant to keep Swissmedic updated.

6.3 Fulfilment of the PIP conditions after authorisation and supplementation of the information for healthcare professional

For a CH-PIP, the applicant is obliged to submit to Swissmedic the results of the measures ordered as conditions at the latest within 60 calendar days of the existence of the final study report.

[2] Scientific Advice in the context of a formal request for approval of a PIP before submitting the application for authorisation (Art. 5 para.6 TPO)

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For PIPs approved by foreign authorities with comparable medicinal product control, the measures according to the foreign PIP are ordered cumulatively in a single condition. If all measures according to the PIP are completed, the corresponding documentation on the fulfilment of the conditions should be submitted to Swissmedic.

The applicant is obliged to keep the product information constantly updated based on the study results according to the PIP (Art. 28 TPO in conjunction with Art. 13 TPLRO). To this end, applications to modify the product information should be submitted accordingly. Both positive and negative study results should be included in the product information.

Example for a positive result from a PIP study
When new knowledge has been acquired, the marketing authorisation holder accordingly submits an application for an additional indication for a corresponding paediatric age group.

Example for a negative result from a PIP study
The marketing authorisation holder submits a clinical study report in order to fulfil a PIP condition. A lack of efficacy or a serious side effect was observed in the study.

The clinical study report is approved and the status of the measure is recorded as completed. The results must be reflected in the information for healthcare professionals and the patient information.

If a paediatric pharmaceutical form has been developed as part of fulfilment of the foreign PIP measures, the corresponding change request must also be submitted Swissmedic promptly.

6.4 Confirmation of the fulfilment of all PIP conditions and supplementation of the information for healthcare professionals

If all the conditions set out in the PIP are fulfilled and if the knowledge obtained on paediatric use is fully incorporated in the information for healthcare professionals in the appropriate form, Swissmedic will order the issuing of a corresponding written confirmation on request (Art. 9 para. 5 TPO). On receipt of this confirmation from Swissmedic, the applicant can apply to the IIP for a 6-month extension of an existing supplementary protection certificate (SPC) or for a new paediatric SPC, provided the preconditions, including requirements relating to time limits according to the Patents Act (PatA), are fulfilled (see in particular, Art. 140n and 140o PatA).

The marketing authorisation holder obtains the confirmation from Swissmedic by submitting a summary table of fulfilment of the conditions after the last PIP condition has been fulfilled (see form: *Paediatric investigation plan HMV4*, Part C); this table must include the following information:

- All measures listed in the PIP
- Abbreviated results of studies
- Swissmedic official decision (date and application ID) on the fulfilment of the measures
- If applicable, list of changes, in keywords, in the information for healthcare professionals and patient information, incl. mention of negative study results

After it has been checked by Swissmedic, the summary table is included in the annex to the official decision, by which Swissmedic confirms that the PIP is completely fulfilled and that the newly acquired information on paediatric use has been included in the product information in the appropriate form.

If a PIP for a medicinal product is considered by a foreign authority with comparable medicinal product control to be completely fulfilled, and if an application for authorisation was submitted to Swissmedic before 1 January 2019, an application for confirmation of the complete fulfilment of the PIP can likewise be submitted to Swissmedic. Swissmedic checks whether the medicinal products are sufficiently comparable and whether the results from the paediatric studies according to the PIP have been included in the Swiss product information in the appropriate form.

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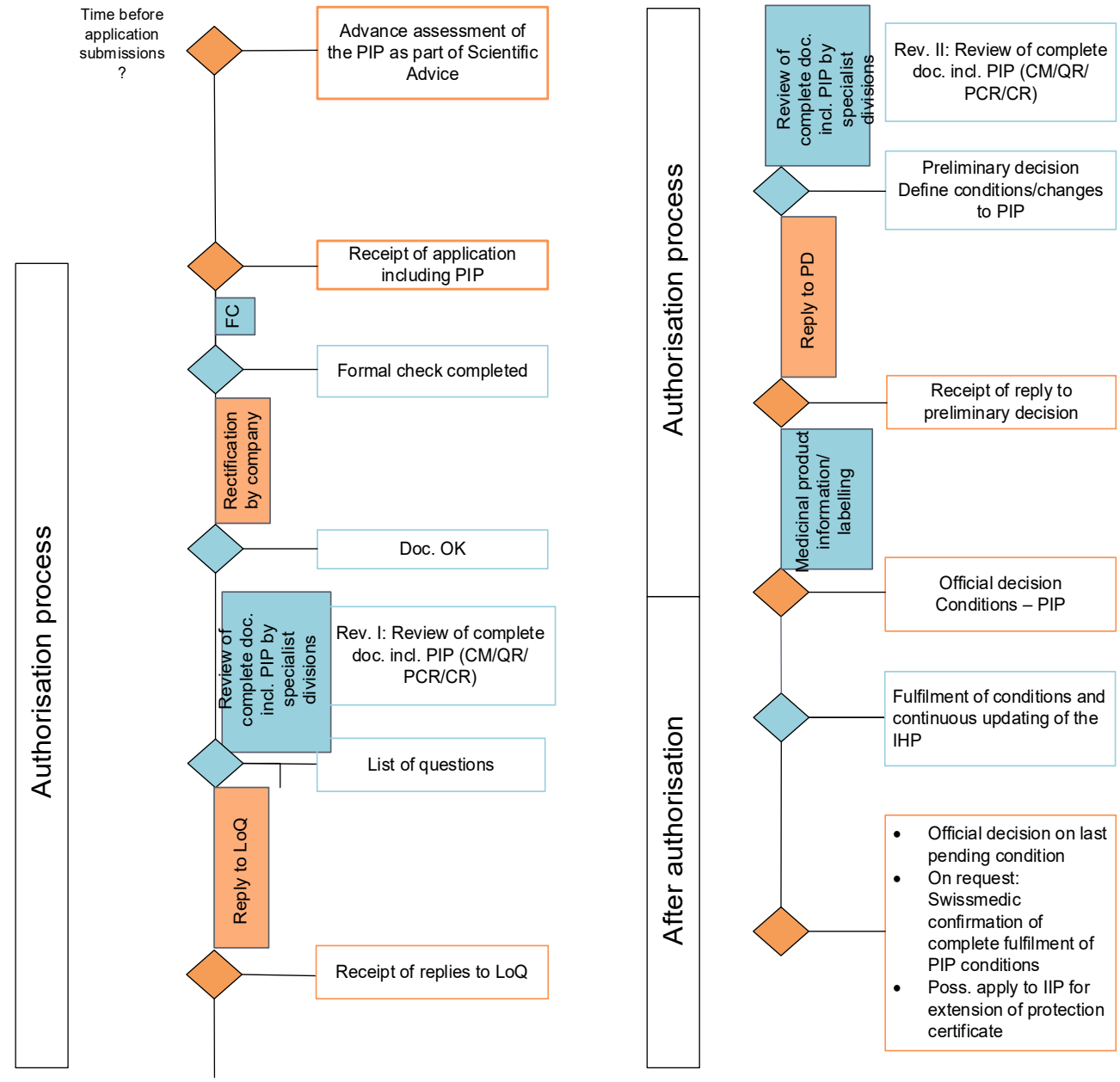
7 Annex



Key:

Milestone/activity by applicant

Milestone/activity by Swissmedic

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