Contents

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Change history

Version	Valid and binding as of	Description, comments (by author)	Author's initials
7.0	01.07.2021	Clarification of process/procedure AAA	fg/gf/ru/zsa
6.0	01.04.2021	Accelerated Application Hearing replaces FTP application	fg/gf/ru/zsa
5.0	01.11.2020	Inclusion of a decision tree and criteria for distinguishing between FTP and temporary authorisation in Annexes 9.3 and 9.4	stb
4.0	23.09.2019	SMC position on tissue-agnostic indications	ru
3.0	01.08.2019	Section 5.7: For FTP applications for medicinal products with ODS, no flat fee will be charged in light of the status; however, the FTP supplement will be invoiced.	fg
2.0	12.06.2019	Section 4.2: Explanation regarding formal requirements Section 5.3: Addition regarding time windows for submitting answers to the List of Questions Sections 5.5/5.6: Explanation regarding sample testing	fr/rc
1.2	08.01.2019	Modification of the Time limits for the authorisation applications submitted subsequently (Flowchart)	fg/rc
1.1	01.01.2019	Explanation re planning the submission after approval of the application Explanation re fast-track authorisation criteria	fba/fg/rc
1.0	01.01.2019	Implementation of HMV4	fg

1 Definitions, terms, abbreviations

1.1 Abbreviations

AAA	Accelerated Application Hearing
AE	Adverse event
temp.auth.	Temporary authorisation
FTP	Fast-track authorisation procedure
FeeO-Swissmedic	Ordinance on the Fees charged by the Swiss Agency for Therapeutic Products of 14 September 2018 (SR 812.214.5)
LoQ	List of Questions
NAS	New Active Substance
ODS	Orphan Drug Status
PPN	Procedure with prior notification
SAE	Serious Adverse Event
ST	Standard Treatment
TEAE	Treatment-Emergent Adverse Event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (Therapeutic Products Ordinance, TPO) (SR 812.212.21)

2 Introduction and Purpose

A fast-track procedure (FTP) is possible for the authorisation of a medicinal product, provided that the criteria stated in Art. 7 TPO are fulfilled. An FTP application must include the same scientific documentation as an application in an "ordinary" procedure and is reviewed according to the same criteria. However, this faster review procedure is possible thanks to the targeted advance planning of

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resources. Therefore, in contrast with the "ordinary" authorisation procedure, an FTP application must be submitted to Swissmedic beforehand in connection with an Accelerated Application Hearing (AAA), and the implementation of an FTP authorisation procedure must be approved by Swissmedic.

Section 5 of this guidance document describes the conditions and criteria that must be met before an application for an FTP authorisation procedure can be approved, and specifies the detailed procedure for the meeting with the applicant (AAA) scheduled for the processing of this application (see section 9 for the detailed procedure for the AAA). **Section 6** describes the formal and content requirements for an **application** for authorisation of a medicinal product through an FTP, as well as the review procedure itself.

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 applications for authorisation of human medicinal products at Swissmedic.

4 Legal basis

The fast-track authorisation procedure is regulated in Art. 7 TPO.

5 Preconditions for the implementation of a fast-track authorisation procedure and procedural issues

5.1 Material preconditions

The following criteria **must all be met** in accordance with Art. 7 of the TPO for a human medicinal product, or any variations thereto, to be evaluated by means of a fast-track authorisation procedure:

a. *It is promising prevention against, or treatment for, a severe, disabling or life-threatening disease.*
   This criterion is fulfilled if it can be assumed that the respective prevention or treatment of the disease will reduce the risk of disability or loss of life. This must be demonstrated in clinical trials with one or more primary endpoints (see criterion c).

b. *Treatment using currently authorised medicinal products is either unavailable or unsatisfactory.*
   - Lack of treatment options:
     Applies only to diseases for which no treatment options with authorised medicinal products exist, or where non-medicinal treatments (such as surgery) are not curative.
   - Unsatisfactory treatment options:
     The available treatment options with authorised medicinal products may be unsatisfactory in several ways, such as insufficient effect, unsatisfactory safety, or no established standard treatment (ST) with authorised medicinal products. The proposed new treatment should significantly improve the treatment options based on new evidence (see also point c).

c. *A high therapeutic benefit is expected from using this new medicinal product.*
   - High therapeutic benefit:
     The therapeutic benefit is clinically superior to the benefit of the existing authorised treatment/standard treatment (comparative basis). This should be demonstrated as probable on the basis of the submitted clinical documentation, even without a detailed data evaluation. The evaluation of the clinical data considers not just the control arm of the clinical trial as a basis for comparison, but also all treatments with authorised medicinal products (used as monotherapy or in combination) that are available in Switzerland at the time of submission of the application for an AAA for the proposed indication(s). In a tabular overview, the company must compare the study results on efficacy (endpoints accepted from the regulatory standpoint) and safety (in addition to TEAEs, a table of grade 3-5 TEAEs; SAEs and TEAEs

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that resulted in death) with the existing treatments with authorised medicinal products that are available in Switzerland. This applies particularly if the submitted clinical trial does not have a control arm. An ST is considered to be the treatment with the ordinarily or temporarily authorised medicinal products that are available in Switzerland for the corresponding indication. The AAA application submission date is considered to be the key date for the evaluation of the high therapeutic benefit. If the ST changes between the implementation of the study and the time of submission of the application for an AAA, the applicant must demonstrate that the medicinal product proposed for the FTP offers a higher therapeutic benefit than the new (current) ST.

- Clinical relevance of the trial:
  The high therapeutic benefit in clinical trials must be demonstrated by means of one or more primary endpoints.
  The following three aspects must be fulfilled in this respect:
  1. The selected trial endpoints must be *clinically relevant*.
  2. The events attributed to the trial endpoints must occur with sufficient frequency to permit an assessment of the effect size.
  3. There must be a clear causal link between the treatment and the clinical effect.

  The assessment of the clinical relevance depends on the individual clinical presentation and the associated clinical and scientific practice. The target population according to the requested indication should include patients with the corresponding established and clearly defined disease entity. Only in cases where clinical hard endpoints such as overall survival cannot be investigated at reasonable expense may surrogate parameters that are clinically established, scientifically validated and recognised by international guidelines be appropriate in order to demonstrate clinical relevance. In the relevant clinical context, such surrogate parameters can include, for example, functional capacity in daily life, or the progression of a disease.

  In the context of an application for the implementation of an AAA for a planned FTP authorisation procedure, biomarkers on their own are generally not suitable for defining an established clinical condition, with the exception of clearly delimited subgroups, e.g. tumour subgroups of an entity with specific mutations. Swissmedic acknowledges the growing clinical significance of molecular diagnostics, particularly in oncology, and is continually reviewing its regulatory processes. Please refer to Annex 9.2 for information on the issue of applications involving tissue-independent or tumour-agnostic indications.

In any case, a positive evaluation for the application for an FTP authorisation procedure is possible only if the applicant can demonstrate, separately for each proposed indication, that the criteria a and b (Description/evaluation of the medical environment) and c (Description/evaluation of the FTP candidate compared to authorised treatments/ST) are all fulfilled.

5.2 Formal preconditions for the implementation of an AAA

An AAA is generally mandatory before an FTP authorisation procedure can be accepted. The application for an AAA should be submitted between 2 and 12 months before the authorisation application so that planning and procedural certainty can be guaranteed. The application for an AAA must be submitted to Swissmedic in writing by the applicant or its legal representative. The application must be substantiated scientifically and backed up by the required documentation. The following documents should be submitted:

a) Cover letter describing the indication(s) scheduled for Switzerland as precisely as possible. The wording of the scheduled indication(s) should be based on the investigated study population and substantiated by study results. If applicable, the covering letter must also refer to authorisation applications or the existence of questions or decisions from other authorities.
b) Rationale stating the extent to which the medicinal product to be notified for authorisation satisfies all the criteria for an FTP. Specific position statements on all criteria specified in Art. 7 let. a to c TPO should be provided (see point 5.1). The rationale should be substantiated by existing data and by references (e.g. summary of the pivotal study) and should not usually exceed 15 pages.

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c) If several indications are proposed for the medicinal product, the applicant must demonstrate that the criteria specified in Art. 7 let. a to c TPO are all fulfilled for each individual indication.
d) Relevant top-line results (still no complete study or interim reports according to ICH-E3) of ongoing studies, if available, should also be submitted (see also criterion c under section 5.1).
e) An overview of the data scheduled for the future authorisation application: tabular listing with a brief description of the pivotal studies, number of patients for efficacy and safety results, and stating whether interim or final study reports are involved. The table from CTD module 5.1 "Table of All Clinical Studies" can be used as a template for this listing. In this case, the pivotal studies should be presented in the ICH E3 format when the authorisation application is submitted.
f) Draft version of the Information for healthcare professionals or the Summary of Product Characteristics.

5.3 Processing the application for an AAA

The applicant will receive confirmation of receipt of the application for an AAA, and the documentation will then be formally checked. Swissmedic will decide within 30 days of completion of the formal checks of the application whether the criteria for an AAA are met. The applicant will be informed of the decision on an AAA with, if applicable, confirmation of the date no later than 10 days before the meeting is due to take place. The AAA is conducted on Swissmedic premises or, if applicable, in the form of a teleconference.
If, after receiving the applicant's application, Swissmedic unconditionally agrees to review its authorisation application in the context of an FTP, and if the evaluation of the submitted documentation does not reveal any aspects requiring clarification, Swissmedic can dispense with the implementation of an AAA. In this case, Swissmedic will directly issue an official decision to approve the application for an FTP authorisation procedure. The approval will be recorded in the decision minutes. These will be included as an integral part of the official decision.

5.4 Procedure for the AAA (see annex for detailed procedure)

During the AAA, Swissmedic discusses with the applicant whether on the basis of the submitted documents the preconditions of Art. 7 let. a to c TPO are satisfied and an FTP is possible. The applicant can issue a position statement on Swissmedic's line of reasoning and, if applicable, present counterarguments that justify the implementation of an FTP.

Based on the provisional result of the review of the documents submitted with the application for an AAA and the supplementary reasons presented to the applicant during the hearing, Swissmedic will reach a binding decision during the AAA on whether an FTP authorisation procedure can be accepted or not.

The decision taken by Swissmedic is recorded in writing in the minutes with, if necessary, the appropriate legal justification. The applicant signs (electronically if applicable) the decision minutes to confirm that it has been informed of all the reasons for Swissmedic's decision during the AAA. The applicant confirms that it has orally presented its position statement on the intended decision and has therefore been granted a fair hearing in accordance with the law. The decision minutes are signed both by Swissmedic and the applicant. Swissmedic therefore assumes that at least one authorised signatory with decision-making powers will represent the applicant at the AAA.

Following the AAA, the applicant will receive the decision in writing in the form of an official order. The signed decision minutes (= rationale for the decision) produced at the AAA and signed by Swissmedic and the applicant will be enclosed as an appendix and as an integral part of the official order concerning the application for an FTP authorisation procedure.

5.5 Combination of application for an AAA with request for PPN

A request for a PPN procedure can be submitted at the same time as an application for an AAA for a fast-track authorisation procedure (FTP) under the terms of Art. 7 TPO. To this end, all the required information and documentation for the application for an AAA for an FTP and the request for a PPN must be submitted concurrently.

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If Swissmedic rejects the procedure for an FTP during the AAA, then in the event of their FTP application being rejected the applicant does not have to submit a request for a PPN afterwards.

In the event of an official rejection decision for the application for an FTP, Swissmedic requires the applicant to confirm, within seven days of receipt of the negative decision, that they are continuing with the requested PPN procedure.

If the request for an FTP is rejected at the AAA, the applicant can also submit a request for a PPN following the AAA. The information in the guidance document *Request for a procedure with prior notification HMV4* also applies.

5.6 Fee for the AAA

Swissmedic invoices the applicant for its costs associated with the AAA. The fee is based on the administrative and scientific work involved. The fee is calculated on the basis of Art. 4 FeeO-Swissmedic.

5.7 Submission of the authorisation application following the approval of the application for an FTP

If the submission of an authorisation application in the FTP is approved, the authorisation application can be submitted at the earliest two months and must be submitted at the latest twelve months following the official decision to approve the application. Applicants must notify Swissmedic in writing of a date (exact date) on which they intend to submit the authorisation application as soon as possible, but at least one month before submitting the authorisation application. At the same time, applicants must indicate whether documentation on quality and preclinical aspects (ERA and/or modules 2.4/2.6/4) and an RMP are being submitted so that Swissmedic can recruit all the necessary specialist reviewers for assessing the application. Swissmedic will check whether the required staff resources are available in the review period and confirm the date or, if applicable, propose an alternative date.

The applicant may, if required, apply for a preliminary discussion of the dossier with Swissmedic at a pre-submission meeting. The aim of this Presubmission Meeting is to ensure that the authorisation application is complete upon submission and will not lead to any formal objections (see guidance document *Meeting for applicants held with the Authorisation sector HMV4*).

6 Application in the fast-track procedure

6.1 Formal aspects and the documentation to be submitted

In the FTP, the applicant must submit the authorisation application together with all documentation required according to the application type to Swissmedic by the agreed date. If it is planned to make the submission in eCTD format, it is recommended that applicants with limited or no experience with eCTD submit a test sequence in good time (at least 3 weeks before submitting the application), in order to avoid exceeding the time limits as a result of technical problems.

6.2 Review phases

The application is reviewed according to the processes described in the guidance document *Authorisation of human medicinal product with new active substance HMV4* or the guidance document *Variations and extensions HMV4*.

6.3 Review time limits

The time limits are those stipulated in the guidance document *Time limits for authorisation applications HMV4*. Answers to the LoQ must be submitted within the time windows published on the Swissmedic website. To ensure that applications are processed promptly, the applicant must also notify Swissmedic in advance of the date on which the responses to the preliminary decision will be submitted.

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6.4 Labelling phase between preliminary decision and official authorisation decision

The applicant accepts the texts in the product information and on the packaging texts following revision and/or correction by Swissmedic. Discussions regarding the corrections to the medicinal product information texts made by Swissmedic can lead to a delay in the authorisation process.

6.5 Sample testing

Experimental sample testing by Swissmedic does not take place in this phase. In the preliminary decision, however, the applicant is informed of the specific samples and documents that may need to be submitted after authorisation for investigation by Swissmedic.

6.6 Phase after fast-track authorisation

Where appropriate, the applicant shall spontaneously provide Swissmedic with samples from the first batch placed on the market after authorisation of the medicinal product in the original packaging (= first commercial batch) and all substances required for performing the analysis, as well as certificates of analysis according to the list received with the preliminary decision.
Swissmedic will analyse the samples and inform the authorisation holder of the result.
The authorisation holder must fulfil the conditions stated in the official decision within the time limit specified.

7 Time limits

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

8 Fees

The fees specified FeeO-Swissmedic apply.

In the case of new authorisations of medicinal products with Orphan Drug Status (ODS), the supplement is payable, but no flat fee is charged.

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9 Annex 1

9.1 Instruction Accelerated Application Hearing (AAA) procedure

Before the AAA

- The hearing takes place 6-8 weeks following receipt of the application for an AAA. The AAA lasts up to 2 hours, including two time-outs. Confirmation of the date on which the AAA will be held is sent to the applicant in writing at least 10 days before the Hearing takes place. Swissmedic provides the applicant with instructions on applying for access to the SharePoint platform.

- The applicant's line of reasoning to substantiate fulfilment of the criteria set out in Art. 7 let. a to c TPO for the planned FTP must be presented on slides. The presentation slides are uploaded to the SharePoint platform by the applicant at least 5 days before the AAA.

- Shortly before the AAA begins, Swissmedic makes the draft decision minutes available in Word format on the SharePoint platform so that the applicant can work on them during the AAA.

During the AAA

- During the Hearing, the person authorised by the applicant to manage the application presents the prepared presentation of the application for an FTP.

- If Swissmedic has asked for any clarification regarding the data submitted, the applicant must provide this information on a differentiated basis during the AAA. However, no additional or new data are accepted during the AAA.

- Swissmedic informs the applicant whether the preconditions of Art. 7 let. a to c TPO are satisfied on the basis of its provisional review result, and whether the FTP requested by the applicant can be accepted.

- The applicant can issue a position statement on Swissmedic's line of reasoning and, if applicable, present counterarguments that justify the requested implementation of an FTP.

- During the AAA the applicant documents its opinion and relevant points for discussion in the decision minutes on the SharePoint.

- Before the AAA ends, Swissmedic reaches a binding decision on the basis of the provisional result of the documentation review and the supplementary line of reasoning presented by the applicant at the Hearing. Swissmedic will allow itself a 15-minute time-out for decision-making after discussing the data with the applicant.

- After the time-out, Swissmedic will present its decision to the applicant verbally. The decision will be recorded in the decision minutes. If the application for an FTP is rejected, Swissmedic can recommend the applicant to submit an application for authorisation via an alternative procedure (e.g. temporary authorisation, temp.auth).

- Once Swissmedic has communicated its decision, the applicant is granted a 15-minute time-out. The applicant then has the chance to discuss the decision and, where required, to discuss the proposal for the submission of another authorisation procedure without Swissmedic being present.

- The decision to switch to a temp.auth. procedure may be taken by the applicant during the AAA. If the applicant does not wish to take the decision to switch to a temp.auth. during the AAA, a new application may be submitted at a later date to request an AAA for a temp.auth. procedure.

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Equally, if the request for an FTP is rejected at the AAA, the applicant may subsequently submit an application for a procedure with prior notification (PPN).

- The decision minutes written up by the applicant during the AAA are read and supplemented as necessary by Swissmedic. The final decision minutes are signed by the applicant and Swissmedic before the AAA ends.

After the AAA

- After the AAA, Swissmedic informs the applicant of the binding decision taken at the AAA in the form of a written official order. The decision minutes produced and signed at the AAA are enclosed as an appendix and as an integral part of the official order concerning the application for an FTP authorisation procedure.

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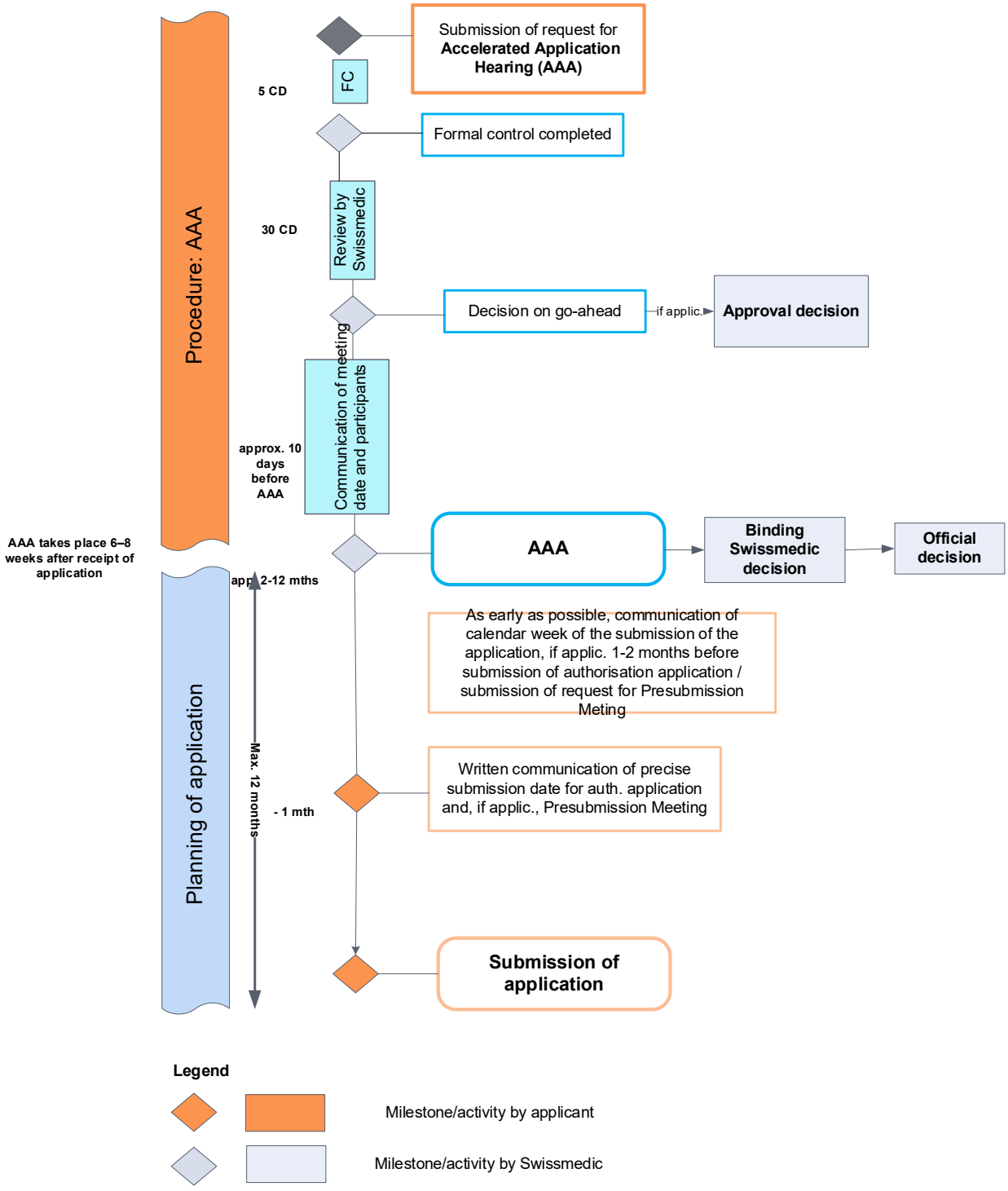
10 Annex 2

10.1 Procedure for an AAA / FTP application



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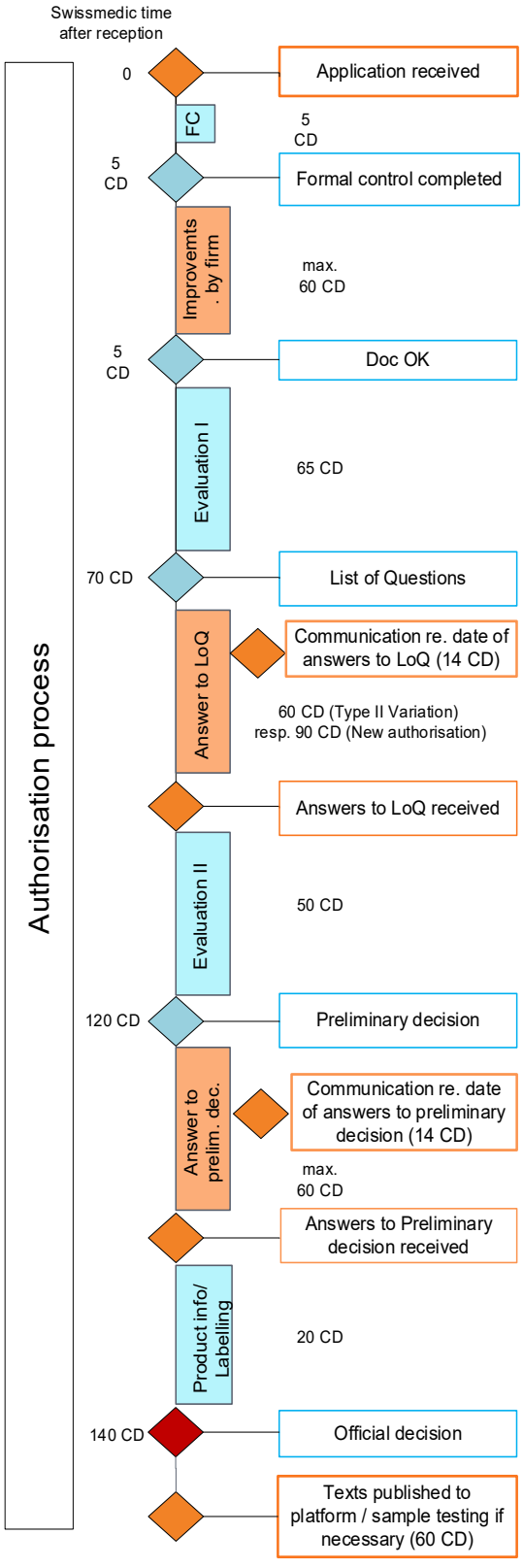
After reception of application



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10.2 Annex on tissue-independent or tissue-agnostic indications

Definition
A tissue-independent or tumour-agnostic indication is characterised by the fact that its wording describes a patient population with a particular molecular abnormality that is not restricted to a localised, tissue-specific tumour entity, but that extends to all tumour entities regardless of their location (e.g.: “medicinal product A is indicated for all patients whose tumours display genetic abnormality xyz”).

Application
Although an FTP involving a tumour-agnostic indication is not excluded in principle, it is subject to a thorough case-by-case review for compliance with criteria of Art. 7 let. a to c TPO (see Guidance below).

Guidance on the fulfilment of the criteria of Art. 7 let. a to c TPO
A disease or a subgroup of a disease may be deemed “recognised” or “established” in the context of a “tissue-agnostic” indication if it can be unequivocally distinguished from other subgroups by virtue of its prognosis, treatment and course, and by the fact that the medicinal product demonstrates general efficacy. It is incumbent on the applicant to present appropriate evidence. The relevant specialist guidelines should be consulted for this purpose.

The validity of a tissue-independent or tumour-agnostic indication wording in terms of compliance with criteria a to c is reviewed on a case-by-case basis using the evidence base submitted. Evidence demonstrating unequivocal efficacy in the form of a clinical response resulting predominantly from the medicinal product’s mechanism of action on the molecular aberration, regardless of tumour type, must have been obtained from an adequate number of patients with tumours in peripheral and central nervous system locations and from different tissues of origin (sarcomas, carcinomas, or haematologic tumours if appropriate).

Since the aim of the FTP – in contrast to temporary authorisation (temp.auth., see WL *Temporary authorisation for human medicinal products HMV4*, Annex 12.4) – is the granting of an ordinary authorisation, the data submitted to demonstrate efficacy will be reviewed in detail to ensure that they are complete, i.e. that they represent an adequate number of patients with tumours in the appropriate location and in different tissues of origin.

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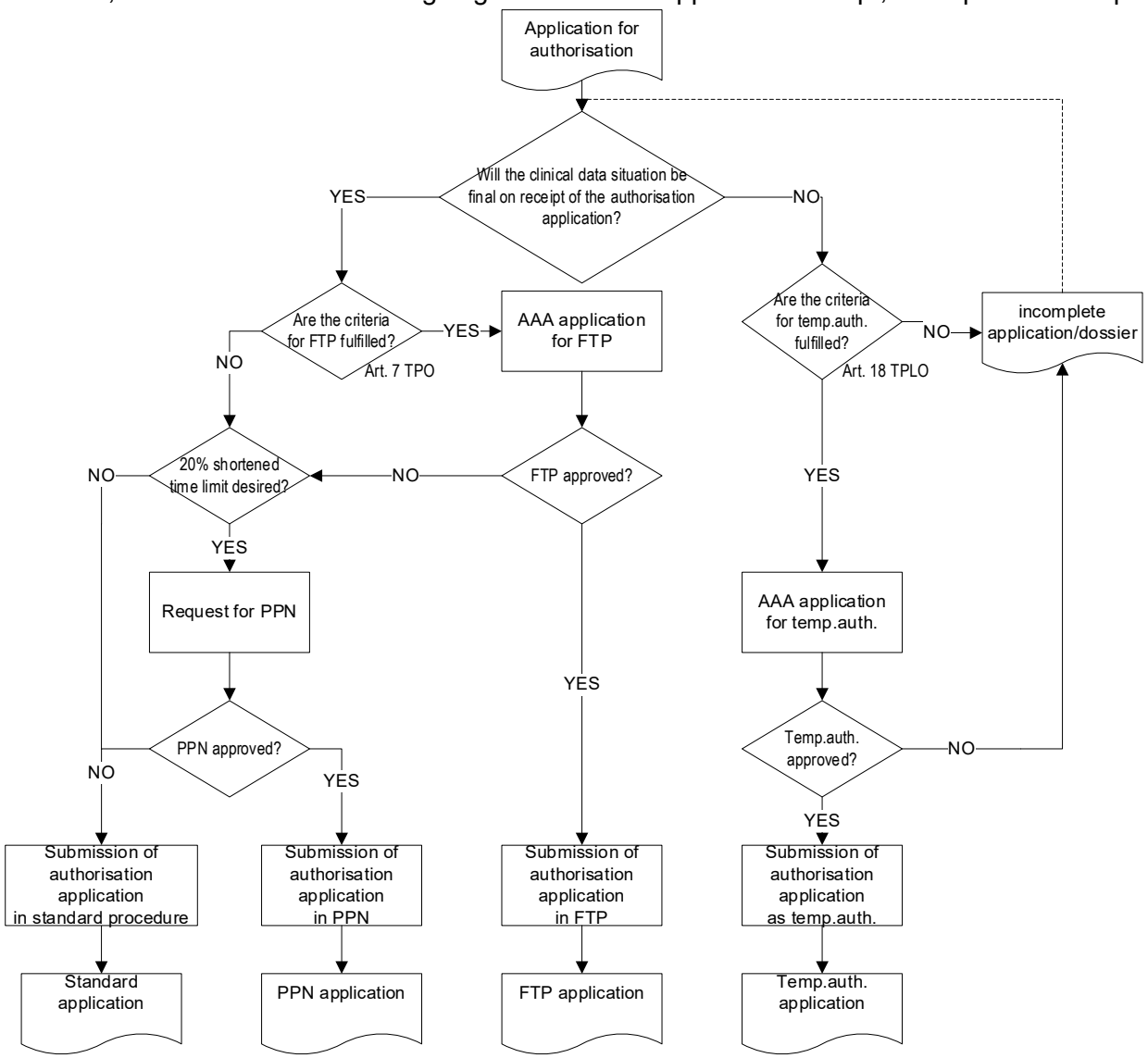
10.3 Decision tree

The key criterion for demarcating between FTP and temp.auth. is the **degree of finalisation of the clinical data package** on receipt of the authorisation application. If the pivotal clinical trials have been completed and evaluated (incl. CSR) at the time of application submission, then an FTP is possible. However, if clinical trials are still ongoing at the time of application receipt, a temp.auth. is required.



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10.4 Interpretation in respect of the criterion of Art. 7 let. c TPO when applying for fast-track authorisation in connection with an AAA

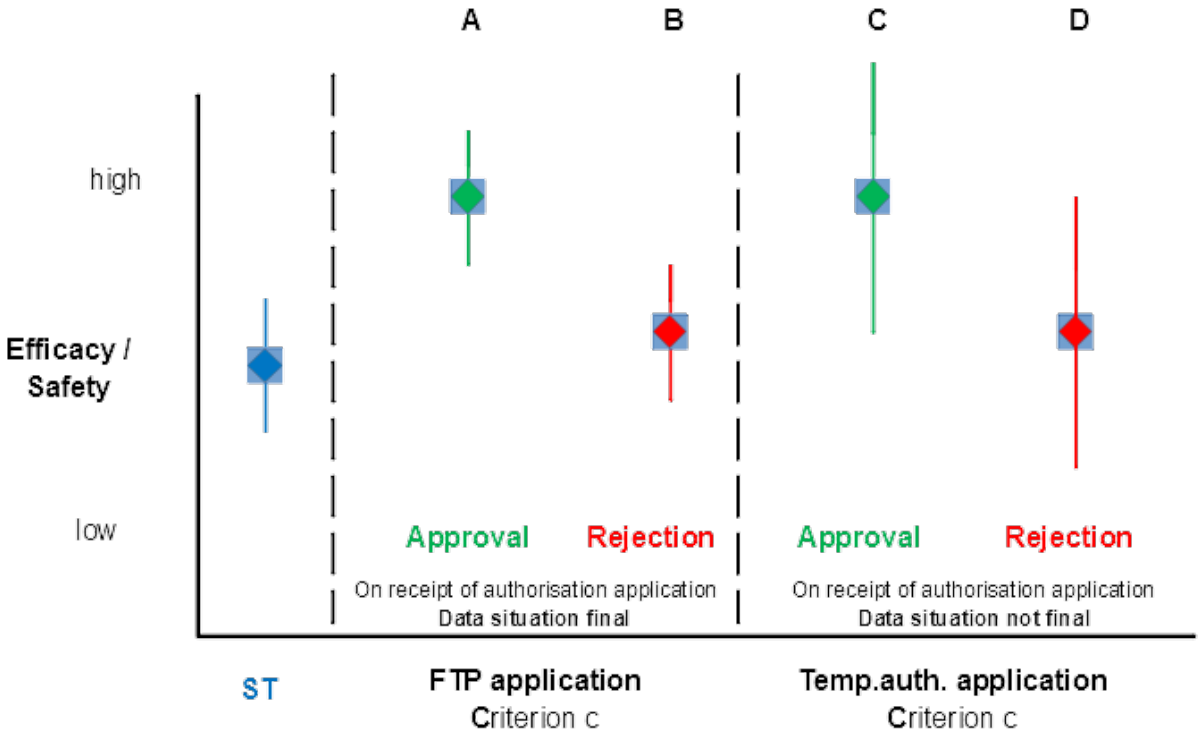
Due to the differing degree of finalisation of the clinical data package on receipt of an FTP application compared to a temp.auth application (see section 9.3), the requirement pertaining to the **point estimate** in respect of efficacy and safety and its **variation** (usually the 95% confidence interval) also differs.

A. An **approval of the application for an FTP** is likely if the point estimate is appreciably higher than that for the ST and the confidence intervals **do not overlap**.
B. A **rejection of the application for an FTP** is likely if the point estimate is higher but the confidence intervals **overlap**.
C. An **approval of the application for a temp.auth.** is likely if the point estimate for safety and efficacy is appreciably higher than that for the ST. However, the confidence intervals (ST – temp.auth.) may overlap in this case.
D. A **rejection of the application for a temp.auth.** is likely if the point estimate is only slightly higher and the confidence intervals overlap appreciably with those for the ST.

The efficacy and safety of the latest ST always form the basis for comparison in demonstrating the high therapeutic benefit (criterion c). The effect size for the FTP candidate must be higher, to a clinically relevant extent, than that for the ST for an application in connection with an AAA to be approved. The confidence intervals (ST – FTP) must not overlap.

The required difference in effect sizes (ST vs. proposed medicinal product in the FTP) in terms of safety and efficacy depend on the clinical situation, the currently marketed medicinal products for the respective indication and the prevalence and incidence of the illness. For an FTP application in connection with an AAA and the final study situation on receipt of the application, the high therapeutic benefit must be clearly assessable at the time of high-level data submission.

Basically, statistically verified effects are expected at the time of the final data situation (FTP), whereas a conclusive statistical assessment, particularly from studies that are still in progress, might still be outstanding at the time of the prefinal data situation (temp.auth.).



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