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1 Definitions, terms and abbreviations

1.1 Definitions and terms

1.1.1 Medicinal product containing a new active substance

A new active substance (NAS) is understood to be a chemical, biological, biotechnological or radiopharmaceutical¹ active substance that to date has not been included in any medicinal product that is (Art. 11 TPA) or was (Art. 4 para. 1 let. h TPA) authorised by Swissmedic.

In particular, this may concern:

- a new chemical substance, including an isomer, a mixture of isomers, a complex or a derivative of a functional group or a salt of this substance that has already been authorised in Switzerland as a medicinal product, but whose characteristics regarding efficacy and safety differ from those of the originally authorised chemical substance
- a new substance derived from biological starting material² that differs from substances in starting material for manufacturing or the manufacturing process that have already been authorised for medicinal products in Switzerland, and that demonstrates different characteristics with regard to efficacy and safety
- a new biotechnological substance³, that differs from medicinal products already authorized in Switzerland in either its molecular structure (including chemical modifications such as pegylation or glycosylation pattern), in the substances used as starting material for manufacturing (e.g. new plasmids or new cell line) or in its manufacturing process and/or one that demonstrates different characteristics with regard to efficacy and safety

¹ see Guidance document: *Authorisation of radiopharmaceutical HMV4*

² Substance isolated from biological starting materials such as microorganisms, organs or tissues of plant or animal origin, cells or fluids (including urine, blood and plasma) of human or animal origin. The organisms from which the biological starting materials originated occur naturally in the environment (in the sense of Art. 3, para 1, let. f of the Ordinance on the Handling of Organisms in the Environment (Release Ordinance, RO; SR 814.911)

³ A biotechnological substance is understood to be a substance manufactured by means of cell culture and/or genetic technology processes.

1.1.2 Fixed combinations of medicinal products

Medicinal products consisting of several new active substances or those that consist of known and new active substances, and that are used as fixed combinations, are considered to be medicinal product combinations. The relevant requirements are addressed in chapter 5.3 and in chapter 8.1.2. For fixed combinations of medicinal products that consist exclusively of known active substances, see the Guidance document *Authorisation of human medicinal product with known active substance HMV4*.

1.2 Abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical Classification System
CHMP	EMA Committee for Medicinal Products for Human Use
CEP	Certification of Suitability of Monographs of the European Pharmacopoeia
CTD	Common Technical Document for the Registration of Pharmaceuticals for Human Use
DMF	Drug Master File
eCTD	Electronic submission in CTD format
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMO	Genetically modified organism
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Nonproprietary Name
IT	Index Therapeuticus
KAS	Medicine with known active substance
OGLP	Ordinance of 18 May 2005 on Good Laboratory Practice (SR 813.112.1)
MedDRA	Medical Dictionary for Regulatory Activities
NAS	New Active Substance
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PDP	Paediatric Development Plan
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PVP	Pharmacovigilance Plan
RMP	Risk Management Plan
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)
TPLO	Ordinance of the Swiss Agency for Therapeutic Products of 22. June 2006 on the Simplified Licensing of Therapeutic Products and the Licensing of Therapeutic Products by the Notification Procedure (SR 812.212.23)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9. November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22)
TSE	Transmissible Spongiform Encephalopathy
WHO	World Health Organisation

2 Introduction and objective

This guidance document describes the requirements relating to the documentation for the submission and authorisation of human medicinal products with new active substances. Since this guidance

document is aimed at administrative bodies, it does not directly specify the rights and obligations of private individuals. Swissmedic uses this document first and foremost as a resource for applying the legal provisions on authorisation in a uniform and equitable manner. The publication of the guidance document is designed to make it clear to third parties what requirements must be fulfilled according to the practice of Swissmedic. It is also intended as a description of the requirements for having human medicinal products with new active substances authorised in Switzerland.

3 Scope

This guidance document applies to the authorisation of human medicines with new active substances pursuant to Arts. 9, 10 and 11 TPA and for important medicinal products for rare diseases pursuant to Art. 14 para. 1 let. f TPA.

For excipients not previously authorised in Switzerland, these instructions are also valid if applicable. For radiopharmaceuticals, the specifications in Guidance document *Authorisation of Radiopharmaceuticals HMV4* apply in addition.

This Guidance document does **not** apply to medicinal products eligible for simplified authorisation in accordance with Art. 14 TPA, for blood and labile blood products, for authorisation extensions or for product categories regulated by any of the following specific Guidance documents:

- Guidance document: *Authorisation of human medicinal product with known active substance HMV4*
- Guidance document *Variations and extensions HMV4*
- Guidance document *Authorisation of antidote HMV4*
- Guidance document *Authorisation of allergen product HMV4*
- Guidance document *Authorisation of antivenin HMV4*
- Guidance document *Authorisation of herbal medicinal products HMV4*
- Guidance document *Authorisation of medicinal gas HMV4*
- Guidance document *Authorisation of biosimilar HMV4*
- Information sheet *Requirements relating to authorisation documentation for TpP/GT/GVO*

4 Legal framework

The procedure for the authorisation of medicinal products with new active substances is based on the following legislative texts in particular:

TPA

- Art. 9 Marketing authorisation
- Art. 10 Conditions for granting a marketing authorisation
- Art. 11 Application for a marketing authorisation
- Art. 14 Important medicinal products for rare diseases (para. 1 f)

TPO

- Art. 7 Fast-track authorisation

TPLRO

- Art. 2 General preconditions
- Art. 3 Documentation on the analytical, chemical and pharmaceutical tests
- Art. 4 Documentation on the pharmacological and toxicology tests
- Art. 5 Documentation on clinical trials
- Art. 6 Special requirements for fixed combinations of medicinal products

5 General requirements and review principles

5.1 General principles

The authorisation application for a human medicinal product with a new active substance must include comprehensive, complete documentation of the quality, preclinical and clinical aspects in accordance with Arts. 2, 3, 4 and 5 TPLRO. This documentation should prove that the medicinal product is effective and safe in the proposed indication according to the applicable law and the

recognised scientific standards and possesses a favourable benefit-risk profile. This applies to both the standard and the fast-track authorisation procedures.

When evaluating the application documentation within the framework of these instructions, Swissmedic considers the following to reflect the current status of science and technology: the currently valid version of the Pharmacopoeia, the relevant guidelines/directives of the ICH, the European Committee for Medicinal Products for Human Use (CHMP), those of the FDA, and other guidelines as mentioned.

Before submitting the application, the applicant can obtain scientific advice from Swissmedic in order to clarify any questions (cf. Guidance document *Meetings for applicants held with the Authorisation sector HMV4*). Such advice does not pre-empt an evaluation of the dossier by Swissmedic.

5.1.1 Requirements relating to the scientific data consulted

If an applicant refers to publicly accessible scientific evidence, such evidence must relate to the proposed active substance and the proposed indication and must be sufficiently detailed to enable the efficacy and safety to be adequately assessed.

5.1.2 Requirements concerning the investigation of the medicinal product in specific age groups

Paediatric Investigation Plan

For authorisation applications for a human medicinal product with stated indications pursuant to Art. 11 TPA or for an important medicinal product for rare diseases (orphan drug) that contains at least one new active substance, paediatric investigation plans pursuant to Art. 54a TPA must be submitted. The relevant requirements are set out in the guidance document *Paediatric Investigation Plan HMV4*.

Data on elderly patients

As regards the data required for geriatric patients or the transferability of the data obtained in clinical trials to the geriatric population, refer to the provisions of the latest version of the ICH guideline on *Studies in Support of Special Populations Geriatrics E7*, which Swissmedic also recognises.

5.1.3 New findings in the course of the application process

New aspects on the efficacy and safety in relation to the application should be submitted continuously and unsolicited, and the application should be supplemented accordingly. However, this requirement must not be used for the delayed rectification of a submitted dossier (in the form of a rolling submission). In the quality section, for example, only long-term stability data or validation data from production may be submitted subsequently.

Data relating to clinical trials that were not yet finalised before submission, even though the study conclusion was already foreseeable, will not be recognised as subsequent submissions within the meaning of "new findings discovered during the application procedure". Such subsequent submissions, which require a new evaluation, usually involve additional time and a possible fee incurred for the extra work involved (cf. Guidance document *Time limits for authorisation applications HMV4* and Art. 5 TPO).

5.1.4 Requirements relating to product information

The requirements applicable to product information are described in the Guidance documents *Formal requirements HMV4* and *Product information for human medicinal products HMV4*.

5.1.5 Requirements after authorisation

Once authorisation has been officially granted for a medicinal product with a new active substance, the authorisation holder is obliged to submit Periodic Safety Update Reports (PSURs). Unsolicited and for a period of four years after the authorisation decision, the authorisation holder must periodically submit reports on the safety of, and benefit-risk profile for, the medicinal product (Art. 60 TPO).

5.2 Authorisation applications for medicinal products containing a new active substance

The authorisation of a medicinal product with a new active substance (as described in chapter 1.1.1) is applied for as follows:

Full documentation in accordance with Arts. 2, 3, 4 and 5 TPLRO must be submitted. Any deviation from the "full documentation" requirement is permitted for applications pursuant to Art. 18 TPLO only. The relevant requirements are addressed in chapters 6ff and 8.1.1.

5.3 Authorisation applications for fixed medicinal product combinations

The requirements and required documents for fixed medicinal product combinations are described in Art. 6 TPLRO. The rationale for the fixed combination must be provided, i.e. the combination applied for must be clinically appropriate. In addition to the pharmacokinetics of the individual active substances, details on the pharmacokinetics in the fixed combination must also be provided. In addition, the efficacy and safety of the fixed combination must be justified in comparison to the individual components.

In general, combinations are only appropriate if their pharmacokinetics are comparable in the population applied for and in special populations. Experimental studies to support the clinical trials are recommended, as described for the individual cases in ICH M3 (R2).

A combination product with one active substance that has already been authorised and one new active substance is acceptable from a clinical perspective without the necessity for the product with the new active substance to have been authorised previously as a single medicinal product with a new active substance. Regarding the new active substance, a new combination product of this type will then be treated as a medicinal product with a new active substance in accordance with chapter 5.2 of these instructions. For the known active substance(s) in the combination product, documentation submitted for a previously authorised medicinal product can be used as supporting material. The documentation requirements are addressed in chapter 8.1.2.

5.4 Document protection

The documentation submitted by the first applicant within the framework of the authorisation application for a product with a new active substance, and in particular the pharmacological, toxicological and clinical test data, are protected from use by third parties (document protection). The granting of document protection and the related rights and obligations are set forth in the Guidance document *Document protection HMV4*.

5.5 Time limits

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

5.6 Fees

The fees are charged in accordance with the *Ordinance on Fees Levied by the Swiss Agency for Therapeutic Products (FeeO-Swissmedic)*.

6 Requirements for documents to be submitted

6.1 Administrative documents (Module 1)

The general formal requirements regarding application documents, i.e. the formal requirements for Module 1 and the cover letter, are laid down in the guidance document *Formal requirements HMV4* and in the associated Directory *Overview of documents to be submitted HMV4*.

6.1.1 Environmental Risk Assessment (ERA, Module 1.6)

When applying for authorisation of human medicinal products with a new active substance, an Environmental Risk Assessment (ERA) must be submitted or else an appropriate reason given for not submitting one.

6.2 Overviews and summaries (Module 2)

6.2.1 Quality Overall Summary (Module 2.3)

A summary and critical assessment of all key data from Module 3 must be submitted as a Quality Summary. The use of synoptic tables and graphics to illustrate essential data is encouraged.

6.2.2 Nonclinical Overview (Module 2.4)

A summary of the non-clinical experimental and bibliographic data on pharmacodynamics, pharmacokinetics and toxicology as per ICH M4S, as well as a risk assessment, must be submitted in the form of a *Nonclinical Overview*. A critical assessment of the data on the medicinal product with a new active substance with regard to effects on patient safety must be submitted. Here, a tabulated overview comparing the safety margins in safety-relevant experimental animal trials (NO(A)EL) and therapeutic exposure in clinical practice must be provided.

The status of the GLP quality system for preclinical studies must be indicated.

In addition, a critical assessment of the safety relevance of new excipients plus potential impurities should be provided and, where necessary, supported by experimental trials. For impurities (with the exception of biotechnology products) a risk assessment should be provided which justifies the basis for impurity limits for the active substance and the medicinal product for which authorisation is applied, and this must be referenced accordingly in the quality section of the documentation.

For biotechnology products, the comparability of the medicinal product used in the nonclinical and clinical studies with that forming the subject of the authorisation application must be assessed. Any deviations must be justified accordingly.

For topical forms, experimental studies on the local tolerance of the medicinal product (e.g. eye and skin irritation studies, investigation of the sensitising and phototoxic potential) and on potential risks of possible systemic exposure to the active substance should be submitted.

6.2.3 Clinical Overview (Module 2.5)

The *Clinical Overview* should comprise a summary of the key data on efficacy and safety that are sufficient for an evaluation of the medicinal product. Efficacy and safety, as well as the risk-benefit ratio and the medical benefit of the indications applied for and in the patient group concerned should also be critically and comprehensively evaluated in comparison with medical and non-medical alternatives. The use of synoptic tables and graphics to illustrate essential data is encouraged. The methodology applied to the investigations and their results must be critically assessed and compared with findings from literature.

6.2.4 Nonclinical Summary (Module 2.6)

A Nonclinical Summary *Written and Tabulated Summaries* (Module 2.6) according to ICH M4S should be submitted.

6.2.5 Clinical Summary (Module 2.7)

A Clinical Summary (Module 2.7) should be submitted.

6.3 Quality (Module 3)

6.3.1 General aspects

The composition and presentation of the documentation relating to the pharmaceutical quality of a medicinal product with a new active substance (Module 3) should be in accordance with Art. 3 TPLO. Relevant ICH guidelines, such as *The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality-M4Q* and other guidelines and specification documents listed in chapter 8 should be taken into consideration.

Various dosages of the same pharmaceutical form should be submitted in the same binder.

6.3.2 Documentation on the quality of the active substance (Module 3.2.S)

The documentation on the quality of the active substance – or substances in the case of fixed medicinal product combinations – is described in Module 3.2.S.

If there are several active substance manufacturers, a joint consolidated active substance specification should be submitted. In addition, manufacturer-specific inspection points, specifications or methods should be indicated separately (e.g. residual solvents for manufacturer X).

Drug Master File

If a Drug Master File (DMF) / Active Substance Master File (ASMF) is involved, reference must be made to the Restricted Part of the DMF of the respective active substance manufacturer in those chapters whose content is not accessible to the applicant.

For further requirements on the use of a DMF / ASMF, please refer to the Guidance document *Formal requirements HMV4* and the *Guideline on Active Substance Master File Procedure, CPMP/QWP/227/02*.

Plasma Master File

For the production of stable blood products and/or when stable blood products are used as an excipient, the documentation on the selection and control of the blood plasma may be submitted as a Plasma Master File.

6.3.3 Documentation of quality data in connection with test products for toxicological and clinical studies

The following must be submitted:

- Summarised results of the quality data from the test products used in the toxicological studies, such as details of composition, batch description, impurities content with details such as No Observed Effect Level (NOEL), No Observed Adverse Effect Level (NOAEL), Acceptable Daily Intake (ADI), Threshold of Toxicological Concern (TTC)
- Summarised results from the quality data for the test product used in clinical investigations, and in particular details of composition, batch size, batch name and active substance content
- Presentation of dissolution profiles in connection with the correlation to in vitro/in vivo studies or to pharmacokinetic data.

These details should be provided in Module 3 (e.g. in chapter 3.2.S.4.5 Justification of Specification, 3.2.P.2 Pharmaceutical Development or 3.2.P.5.6 Justification of Specification) with source references in Modules 2, 4 and/or 5.

6.3.4 Adventitious Agents Safety Evaluation (chapter 3.2.A.2)

If applicable, all documents relating to viral safety and TSE risk assessment must be provided in chapter 3.2.A.2.

6.4 Non-clinical documentation (Module 4)

The documentation on the pharmacological and toxicological studies of a medicinal product with a new active substance (Module 4) should be compiled in accordance with Art. 4 TPLRO and must reflect the latest scientific and technological findings. The presentation must conform to ICH M4S. When carrying out the studies, the relevant ICH guidelines and other guidelines listed in chapter 8 must be taken into consideration. Safety-relevant studies must be performed in conformity with GLP.

6.5 Clinical documentation (Module 5)

The documentation regarding the clinical investigations relating to a medicinal product with a new active substance (Module 5) should be compiled in accordance with Art. 5 TPLRO. The presentation of the clinical data is described in the ICH Guideline *The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy-M4E (Clinical Overview and Clinical Summary of Module 2, Module 5: Clinical Study Reports)*.

The study reports for (the applicant's own) clinical trials conducted for the application should be drafted according to ICH *E3 Guideline Structure and Content of Clinical Study Reports*.

The studies must be carried out in accordance with GCP guidelines. Other guidelines issued by the ICH and the guidelines listed in chapter 8 should also be taken into account.

Published works (offprints) should usually be enclosed separately, with corresponding references in the summary and in the original documentation.

7 Other relevant guidelines

7.1 Basic principle

When evaluating the application documentation within the framework of these instructions, Swissmedic considers the following to reflect the current status of science and technology: the currently valid version of the Pharmacopoeia, the relevant guidelines/directives of the ICH, the European Committee for Medicinal Products for Human Use (CHMP), those of the FDA, and other guidelines as mentioned.

The following compilation provides an overview of relevant guidelines and publications (including publications on the Swissmedic website). This compilation is not exhaustive.

7.2 General international guidelines

- [ICH Guidelines](#)

Particularly the following guideline:

- Organisation of the [Common Technical Document](#) for the Registration of Pharmaceuticals for Human Use

Within which, in particular:

- The Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use: M4
- The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality-M4Q. Quality Overall Summary of Module 2, Module 3: Quality
- The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety - M4S. Non-Clinical Overview and Non-Clinical Summaries of Module 2, Organisation of Module 4
- The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy-M4E. Clinical Overview and Clinical Summary of Module 2, Module 5: Clinical Study Reports
- ICH Harmonised Tripartite Guideline Pharmacovigilance Planning E2E
- For eCTD submissions, see: [Swissmedic Homepage eCTD](#)

7.3 Quality guidelines

The guidelines mentioned below should be taken into consideration with regard to the compilation, format and content of Modules 2.3 and 3.

- [The guidelines on quality](#) should be taken from the ICH overview list:
- [Guidelines on specific requirements](#) or submodules can be found in the EMA summary list of Quality Guidelines

Finished product:

- Regarding storage, see Swissmedic Journal [02/2009](#), p.112
- Instructions related to minimising the risk of transmission of TSE of animal origins by human and veterinary medicines (cf. Guidance document *Minimising the risk of TSE HMV4*).

7.4 Non-clinical guidelines

The legal sources / guidelines mentioned below are highlighted in connection with individual chapters in this document on requirements for Modules 2.4 and 4. Other relevant guidelines on specific requirements / submodules can be found under the following links:

- [ICH Safety Guidelines](#)
- [ICH Safety and Multidisciplinary Guidelines](#)
- [EMA Nonclinical Guidelines](#)

- [FDA Pharm / Tox Guidances](#)

7.5 Clinical guidelines

Relevant guidelines on specific requirements / submodules can be found in the following summary lists issued by the ICH, EMA or FDA. The individual guidelines can be consulted for information on numerous questions.

- [ICH Efficacy Guidelines](#)
- [ICH Multidisciplinary Guidelines](#)
- [EMA Clinical Efficacy and Safety Guidelines](#)
- [FDA Clinical Trials Guidance Documents](#)

8 Summarised presentation of the requirements

8.1 Requirements for Modules 2 to 5

8.1.1 Requirements relating to an application for the authorisation of a medicinal product with a new active substance (NAS)

Quality requirements

- Complete documentation: Module 2.3 and Module 3
- CEPs or DMFs are acceptable: reference should be made to them in Module 3.2.S.

Preclinical requirements

- Complete preclinical documentation: Modules 2.4, 2.6 and 4.

Clinical requirements

- Complete clinical documentation: Modules 2.5, 2.7 and 5.

8.1.2 Requirements relating to an application for a new fixed medicinal product combination

Quality requirements

- Complete documentation: Module 2.3 and Module 3
- CEPs or DMFs are acceptable: reference should be made to them in Module 3.2.S.

Preclinical requirements

- Depending on the situation, animal studies to support the clinical studies are recommended, as described in ICH M3(R2).
- If at least one of the active substances in the combination product has not yet been authorised by Swissmedic, the application for approval must be submitted in accordance with 8.1.1 (Requirement relating to an authorisation application for a medicinal product with a new active substance), i.e. with complete preclinical documentation (see Chapter 5.3).

Clinical requirements

- It is usually assumed that, when authorisation of a fixed medicinal product combination is applied for, the pharmacokinetics, efficacy and safety of the individual components have already been demonstrated.
- The following documentation generally needs to be submitted:

Pharmacokinetics (chapters 5.3.1 and 5.3.3)

- Bioequivalence studies comparing fixed combinations and single components
If bioequivalence cannot be demonstrated, complete pharmacokinetic data (chapter 5.3.3.1) must be submitted (if applicable, including studies on the effect of food intake).
- Interaction study between the two components

- If the product for which authorisation is sought does not correspond to the formulations used in the clinical studies, bioequivalence studies comparing the study formulations and the market formulations applied for must be submitted..

Pharmacodynamics (chapter 5.3.4)

- Depending on indication, additional data on safety pharmacology may be required (particularly if new risks arise from the combination).
- Depending on the type of combination partners and the indications applied for, pharmacodynamic interaction studies between the two substances may be required..

Studies on efficacy and safety (chapter 5.3.5)

- Dose-finding studies to answer the following questions:
 - If bioequivalence between the combination and the individual components is demonstrated: must the dose of one or several components be adjusted as a result of additive or multiplicative pharmacodynamic effects?
 - If there is no bioequivalence between the combination and the individual components: investigate the appropriate dose while taking possible pharmacokinetic and/or pharmacodynamic interactions between the components into consideration.
- Studies investigating efficacy and safety, i.e. proof of superiority of the combination compared to monotherapy (including specific studies required depending on the indication, e.g. long-term studies, taking particular account of safety aspects that might be problematic as a result of the combination, e.g. due to additive effects).
- If the combination of the active substances has already been acknowledged in specialised medical literature, the corresponding references (including possible therapy guidelines) must also be submitted.
- In particular, the rationale for the fixed medicinal product combination must be presented in the summary in the Clinical Overview. Both the efficacy of the individual components and the intended benefit arising from the combination should be demonstrated. Similarly, both the safety profiles of the individual components and possible specific risks of the combination must be discussed in the Summary of Clinical Safety (if applicable including international postmarketing surveillance data).
- If at least one of the active substances in the fixed combination has not yet been authorised by Swissmedic, the application for approval must be submitted in accordance with 8.1.1 (Requirement relating to an authorisation application for a medicinal product with a new active substance), i.e. with complete clinical documentation (see chapter 6.4).