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1 Terms, definitions, abbreviations

1.1 Definitions and terms

1.1.1 Medicinal products with new active pharmaceutical ingredients

A new active pharmaceutical ingredient (New API) is considered to be a chemical, biological, biotechnological or radiopharmaceutical¹ active substance that to date has not been included in any medicinal product that is or has been authorised by the Agency². This includes both diagnostic and therapeutic products.

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 material³ 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 substance⁴ 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

1.1.2 Major variations

A major variation is considered to be one that requires a new authorisation procedure to be submitted for the medicinal product. In accordance with Art. 12 of the VAM⁵ and Art. 22a in connection with Annex 9 of the Medicinal Products Authorisation Ordinance (AMZV)⁶ the following are considered to be major variations:

- variations regarding active pharmaceutical ingredient
- variations regarding the galenic form
- variations regarding a genetically modified organism in a medicinal product
- variations regarding dosage (dosage strength with dosage recommendation) or additional dosages
- variations regarding route of administration or additional route of administration
- variations regarding an indication or additional indication
- variation regarding a dosage recommendation or additional dosage recommendation

A major variation regarding the active pharmaceutical ingredient is considered to be replacing one active chemical substance with a different salt, a different complex, a different derivate of a functional group, a different isomer or a different isomeric mixture, or the replacement of a mixture by an isolated isomer (e.g. replacing a racemate by a single enantiomer).

¹ See [ZL000_00_003e_WL Guidance document Authorisation radiopharmaceutical](#) (Only in German and French)

² Authorisation by the Agency is comparable to a registration by the Intercantonal Office for the Control of Medicines. Active substances previously authorised in veterinary medicines are considered to be new active pharmaceutical ingredients when first used in human medicines.

³ This is understood to be a 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) or human or animal origin. The organisms originating from the biological starting materials naturally enter the environment (in the sense of Art. 3, section 1, letter f of the Ordinance on the Handling of Organisms in the Environment ([Release Ordinance, RO SR 814.911](#)))

⁴ A biotechnological substance is considered to be a substance manufactured by means of cell culture and/or genetic technology processes

⁵ Ordinance on Medicinal Products of 17 October 2001 ([VAM SR 812.212.21](#)) (Only in German and French)

⁶ Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 concerning the Requirements for Marketing Authorisations for Medicinal Products ([Medicinal Products Authorisation Ordinance, AMZV](#)), [SR 812.212.22](#)) (Only in German and French)

If the different isomers or isomeric mixtures have a clinical and/or toxicological influence on efficacy and safety, they are considered to be New APIs (see Chapter 1.1.1). Variations to a genetically modified organism in a medicinal product are considered to be those to active pharmaceutical ingredients manufactured using recombinant technologies or processes, including changes to manufacturing processes.

1.1.3 Fixed combinations of medicinal products

Products consisting of several new active pharmaceutical ingredients or those that consist of known and new active pharmaceutical ingredients, and that are used as fixed combinations, are considered to be combinations of medicinal products. The relevant requirements are addressed in Chapter 6.4 and in the annex in Chapter 9.1.9. For fixed combinations that consist exclusively of known active substances, see the Guidance Document *authorisation of human medicine with known active pharmaceutical ingredient*.

1.2 Abbreviations

AMZV	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 concerning the Requirements for Marketing Authorisations for Medicinal Products (Medicinal Products Authorisation Ordinance, AMZV SR 812.212.22)
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical Classification System
Auth.	Authorisation
CEP	Certificate of Suitability of monographs of the European Pharmacopoeia
CHMP	EMA Committee for Medicinal Products for Human Use
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
FAP	First applicant protection
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GC	Guidance Document
GLP	Good Laboratory Practice
GLPV	Ordinance of 18 May 2005 on Good Laboratory Practice (SR 813.112.1)
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
KAPI	Medicinal product with known active pharmaceutical ingredient
MedDRA	Medical Dictionary for Regulatory Activities
New API	New Active Pharmaceutical Ingredient
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamic
PDP	Pediatric Development Plan
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PVP	Pharmacovigilance Plan
RMP	Risk Management Plan
TPA	Federal law of 15 December on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA SR 812.21)
TSE	Transmissible Spongiform Encephalopathy
VAM	Ordinance on Medicinal Products of 17 October 2001 VAM SR 812.212.21)

VAZV	Ordinance of the Swiss Agency for Therapeutic Products of 22 June 2006 concerning the Requirements for Marketing Authorisations for Medicinal Products (Medicinal Products Authorisation Ordinance, VAZV SR 812.212.23)
WHO	World Health Organisation

2 Introduction and objective

These instructions describe the requirements regarding documentation for the submission and authorisation of medicinal products for human medicines that contain new active pharmaceutical ingredients and major variations thereto. It is a guidance document intended for administrative bodies and thus does not directly address the rights and obligations of the individual. For Swissmedic, the instructions serve above all to provide assistance in applying the legal provisions relating to the authorisation of medicinal products uniformly and with equality. For third parties, the publication of the instructions provides transparency regarding the requirements to be met in accordance with Swissmedic's practices. They are also intended to set out the requirements to obtain the authorisation of human medicines with new active pharmaceutical ingredients and of major variations to such authorisations in Switzerland.

3 Scope

The Guidance document apply to the authorisation of human medicines with new active pharmaceutical ingredients in accordance with Arts. 9, 10 and 11, TPA⁷, major variations in accordance with Art. 12, VAM⁸ in connection with Annex 9, AMZV⁸ and fixed combinations of medicinal products in accordance with Art. 6 AMZV⁹.

For excipients not previously authorised in Switzerland, these instructions are also valid if applicable.

For radiopharmaceuticals, these instructions are valid together with those relating to the authorisation of radiopharmaceuticals.

The instructions are also valid for important medicines for rare diseases in accordance with Art. 14, para. 1, letter f, TPA⁷.

The instructions are not valid for medicines eligible for simplified authorisation in accordance with Art. 14, TPA¹⁰, for blood and labile blood products and for product categories regulated by means of the relevant specific instructions and information sheet below (some of which are available in German and French only):

- *Guidance document for the authorisation of human medicine with known active pharmaceutical ingredient*
- *Guidance document for the authorisation of antidote*
- *Guidance document for authorisation of allergen product*
- *Instructions for the submission of authorisation applications for herbal medicines for human use (Instructions for herbal medicines)*
- *Guidance document for the authorisation of medicinal gas*
- *Guidance document for the authorisation of biosimilar*
- *Information sheet Requirements relating to authorisation documentation for transplant products (TpP)*

⁷ Federal Law of 15 December 2000 on Medicinal Products and Medical Devices, (TPA SR 812.21)

⁸ Ordinance on Medicinal Products of 17 October 2001 (VAM) SR 812.212.21) (Only in German and French)

⁹ Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 concerning the Requirements for Marketing Authorisations for Medicinal Products (Medicinal Products Authorisation Ordinance, AMZV), SR 812.212.22) (Only in German and French)

4 Legal basis

The procedure for the authorisation of medicinal products with new active pharmaceutical ingredients and major variations thereto is in particular aligned with the following aspects of the legal framework: TPA¹⁰

- Art. 9 Authorisation for placing products on the market
- Art. 10 Conditions for the granting of a marketing authorisation
- Art. 11 Application for a marketing authorisation
- Art. 12 Second notification (protection of documents of the first applicant)
- Art. 13 Medicinal products and procedures authorised in foreign countries

VAM¹¹

- Art 5 Fast track authorisation procedure
- Art. 5a Medicinal products and procedures authorised in foreign countries (Art. 13, TPA)
- Art. 5c Application with regard to medicinal products with new active pharmaceutical ingredients and additional indications for them
- Art. 5d Parallel procedures in Switzerland and abroad
- Art. 12 New authorisation in the case of major variations (see description in Art. 22a in connection with Annex 9)
- Art. 17 Protection period for originator products (Art. 12, TPA)

AMZV¹²

- Art. 3 Documentation of the analytical, chemical and pharmaceutical investigations
- Art. 4 Documentation of the pharmacological and toxicological investigations
- Art. 5 Documentation of the clinical investigations
- Art. 6 Specific requirements relating to fixed combinations of medicinal products
- Art. 12 Information and texts on containers and packaging material
- Art. 22a in connection with Annex 9, AMZV, description of the major variations in accordance with Art. 12, VAM that require a new authorisation.

¹⁰ Federal Law of 15 December 2000 on Medicinal Products and Medical Devices, ([TPA SR 812.21](#))

¹¹ Ordinance on Medicinal Products of 17 October 2001 ([VAM SR 812.212.21](#)) (Only in German and French)

¹² Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 concerning the Requirements for Marketing Authorisations for Medicinal Products ([Medicinal Products Authorisation Ordinance, AMZV](#)), [SR 812.212.22](#)) (Only in German and French)

5 Other valid documents

These instructions apply to the following processes:

First authorisation of medicinal products (New API) and miscellaneous, including major variations for synthetics and biologicals (ZL 101).

Document ID (some documents in German and French only)

[ZL000_00_006e_WL Guidance document Time limits for authorisation applications](#)

[ZL000_00_004e_WL Guidance document Authorisation human medicine under Art 13 ATP](#)

[ZL000_00_016d_MB Erläuterungen zur Patienteninformation](#) (only in German, French and Italian)

[ZL000_00_017d_MB Erläuterungen zur Fachinformation](#) (only in German and French)

[ZL105_00_001e_WL Guidance document Meetings for applicants held with the Authorisation sector](#)

[Swissmedic eCTD Documentation](#)

[ZL000_00_001e_WL Guidance document Formal requirements](#)

[ZL000_00_002e_VZ Overview documents to submitted](#)

[ZL000_00_010e_CL Formal control of application authorisation human medicines](#)

[OS000_00_001e_FO technical validation](#)

6 General requirements and principles relating to the assessment of the submission

6.1 General principles

The authorisation application must include comprehensive, complete documentation of the quality, preclinical and clinical aspects in accordance with Arts. 3, 4 and 5, AMZV¹³. The aforementioned documentation must provide proof that the medicinal product is effective and safe in the indication applied for, in accordance with the valid law and the recognised scientific norms, and in addition, has a favourable risk-benefit ratio. These conditions apply to both the normal and the fast track authorisation procedure.

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 may obtain scientific advice from the Agency in order to clarify any questions¹⁴. Such advice does not pre-empt an evaluation of the dossier by the Agency.

6.1.1 Requirements relating to scientific evidence provided

If an applicant also refers to scientific evidence that is accessible to the public, such evidence must refer to the medicinal product and indication applied for, and must include a sufficient level of detail to permit the evaluation of efficacy and safety.

¹³ Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 concerning the Requirements for Marketing Authorisations for Medicinal Products ([Medicinal Products Authorisation Ordinance, AMZV](#)), SR 812.212.22) (Only in German and French)

¹⁴ For the process flow and procedure, see the guidance document [ZL105_00_001e_WL Guidance document Meetings for applicants held with the Authorisation sector](#)

6.1.2 Requirements relating to the investigation of the medicinal product in specific age groups

Paediatric development work/paediatric test concept

Swissmedic recognises the ICH Guideline *Clinical Investigation of Medicinal Products in the Paediatric Population E11*, which describes when, and in which situations, paediatric data must be submitted. As with the EU Directive, which requires such data to be submitted, applicants in Switzerland are also required to submit the corresponding data. If a decision on the part of the EMA Paediatric Committee or the FDA Pediatric Group has been issued regarding the provision of development work on the medicinal product in paediatric populations, this decision should be submitted to Swissmedic with the authorisation application.

The submission of the Paediatric Investigation Plan (EU) or the Pediatric Development Plan (USA) is also recommended.

Data relating to the elderly

Reference should be made to the current version of the ICH Guideline *Studies in Support of Special Populations Geriatrics E7*, also recognised by Swissmedic, which should be taken into account regarding data required for geriatric patients or the extrapolation of the data from clinical trials to the geriatric population.

6.1.3 New findings in the course of the application process

New aspects related to efficacy and safety with regard to the application submitted should be provided spontaneously, as and when they are identified, and the application should be amended accordingly. This should not, however, be a "rolling submission", i.e. a subsequent improvement to a dossier already submitted. In the quality part, only long-term stability data or validation data from production should be submitted at a later date.

Data on clinical studies, that was not finalised prior to the submission of the application although the outcome of the trial was already foreseeable, is not accepted as a subsequent submission in the sense of "new findings during the course of the application process". Such subsequent submissions, which require a new evaluation, result in increased processing time¹⁵ and may incur extra charges for the additional resources required (see also Guidance Document *on time limits for authorisation applications* and Art. 5, VAM¹⁶).

6.1.4 Requirements relating to the product information

The requirements relating to the product information are described in the Guidance Document *Formal requirements* and the information sheets (only in German and French) *Explanations concerning Information for healthcare professionals/Patient information*.

6.1.5 Requirements following the granting of an authorisation

When the authorisation for a medicinal product with a new active pharmaceutical ingredient is granted, it is mandatory for the authorisation holder to submit Periodic Safety Update Reports (PSURs). The reports on the safety of the product in question must be submitted periodically and spontaneously for 5 years following the granting of the authorisation (Art. 34, VAM¹⁶). The requirement to submit PSURs may be re-imposed if major variations are authorised.

6.2 Applications for the authorisation of medicinal products with a new active pharmaceutical ingredient

An authorisation for a medicinal product with a new active pharmaceutical ingredient (as described in Chapter 1.1.1) is applied for as follows:

¹⁵ See Guidance document [ZL000_00_006e_WL Guidance document Time limits for authorisation applications](#)

¹⁶ Ordinance on Medicinal Products of 17 October 2001 ([VAM SR 812.212.21](#)) (Only in German and French)

Full documentation in accordance with Arts. 3, 4 and 5, AMZV¹⁷ must be submitted. Any deviations with regard to complete documentation are only possible for applications in accordance with Art. 18, VAZV¹⁸ in connection with Art. 9, para. 4, TPA¹⁹.

Details regarding the documentation are described in Chapter 7 below and also in the Annex in Chapter 9.1.1.

6.3 Major variations that require a new authorisation procedure in accordance with Art. 12, VAM

The authorisation of a new variation (as described in Chapter 1.1.2) is applied for as follows:

The new aspects of the major variation that have not previously been authorised in Switzerland must be documented in accordance with Arts. 3, 4 and 5, AMZV¹⁷.

The known aspects can be supported by the documentation for the product that has already been authorised.

Details regarding the documentation are described in Chapter 7 below and in the Annex in Chapters 9.1.1 to 9.1.9.

6.3.1 Proof of the transferability of the original investigational results in the case of major variations

If an application for a variation to a medicinal product with a new active pharmaceutical ingredient is submitted, proof must be provided that the findings concerning preclinical and clinical efficacy, and safety and tolerance that led to the authorisation of the medicinal product with a new active pharmaceutical ingredient are applicable to the new application.

The type and extent of the necessary proof depends on the physico-chemical and pharmacological properties of the active pharmaceutical ingredients, the indication(s), the galenic form, the route of administration, the dosage strengths and the dosage recommendations. The rationale provided by the applicant must be scientifically justified and critically summarised in a statement forming part of the Nonclinical and Clinical overviews. The cover letter should briefly refer to the fact that earlier data has been used for certain aspects, noting the parts of the application in which the transferability is justified.

6.4 Authorisation application for fixed combinations of medicinal products

The requirements and the documentation to be submitted for combination products are described in Art. 6, AMZV²⁰. 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 pharmaceutical ingredients, 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 pharmaceutical ingredient that has already been authorised and one new active pharmaceutical ingredient, is acceptable from a clinical perspective without the necessity for the product with the new active pharmaceutical ingredient to have been authorised previously as a single medicinal product with a new active pharmaceutical ingredient. Regarding the new active pharmaceutical ingredient, such a new combination product will be dealt with as a medicine with a new active pharmaceutical ingredient in accordance with Chapter 6.2 of these

¹⁷ Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 concerning the Requirements for Marketing Authorisations for Medicinal Products ([Medicinal Products Authorisation Ordinance, AMZV](#), SR 812.212.22) (Only in German and French)

¹⁸ Ordinance of the Swiss Agency for Therapeutic Products of 22 June 2006 on the simplified marketing authorisations for and mandatory notifications of medicinal products ([VAZV SR 812.121.23](#)) (Only in German and French)

¹⁹ Federal Law of 15 December 2000 on Medicinal Products and Medical Devices, ([TPA SR 812.21](#))

²⁰ Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 concerning the Requirements for Marketing Authorisations for Medicinal Products ([Medicinal Products Authorisation Ordinance, AMZV](#), SR 812.212.22) (Only in German and French)

instructions. For the known active pharmaceutical ingredient(s) in the combination product, documentation submitted earlier can be used as supporting material as described in Chapter 6.3. Details regarding the documentation are described in the Annex in Chapter 9.1.9.

6.5 First applicant protection

6.5.1 Basic principles

The documentation submitted by the first applicant within the framework of the authorisation application for a product with a new active pharmaceutical ingredient, and in particular the pharmacological, toxicological and clinical test data, are protected from use by third parties (First Applicant Protection, FAP).

For the procedure in Switzerland, it is irrelevant whether the medicinal product whose authorisation is applied for is already authorised in another country or not, or whether an FAP of any kind has already been granted for it outside of Switzerland.

6.5.2 10-year first applicant protection

In accordance with Art. 12, para. 2, TPA²¹ in connection with Art. 17, para. 1, VAM²², second applicants may not use the documentation submitted by the first applicant as supporting material²³ for 10 years unless the authorisation holder for the medicinal product with the new active pharmaceutical ingredient in question is in agreement.

The 10-year FAP is valid for a medicinal product with a new active pharmaceutical ingredient, i.e. for a medicinal product authorised for the first time with a new active pharmaceutical ingredient (New API). For the same active substance, there can only be one medicinal product with a new active pharmaceutical ingredient. The FAP is also granted for the first authorisation of a human medicine for which the active pharmaceutical ingredient is contained in a previously authorised veterinary medicine and vice-versa.

The 10-year FAP and the authorisation will be granted simultaneously (Art. 17, para. 4, VAM²⁴). The authorisation holder will have been informed, as part of the preliminary decision, whether or not a FAP can be granted.

The 10-year FAP is established in law, i.e. it exists even if it is not explicitly stated in the decision issued at the time of authorisation and remains in force – due to its legally binding nature – even if the authorisation is withdrawn or cancelled.

The 10-year FAP is only considered for fixed combinations of medicinal products if at least one new active pharmaceutical ingredient is contained therein. If all the active pharmaceutical ingredients contained therein are or have already been authorised in a medicinal product, i.e. if it is a combination of known active pharmaceutical ingredients, there can be no claim to FAP.

6.5.3 3-year first applicant protection

In accordance with Art. 17, para. 2, VAM²⁴, an FAP is granted for 3 years for the following new developments regarding an original product:

- new indication
- new route of administration
- new dosage form
- new dosage (particularly applies to dosage recommendation)

²¹ Federal Law of 15 December 2000 on Medicinal Products and Medical Devices, ([TPA SR 812.21](#))

²² Ordinance on Medicinal Products of 17 October 2001 ([VAM SR 812.212.21](#)) (Only in German and French)

²³ For more detailed explanations regarding requirements for an FAP, please see the Swissmedic Journal (SMJ) [1/2010 7/2003](#) (Only in German and French).

The term "Original product" mentioned in Art. 12, TAP, is in part used in a slightly different sense in the various groups of medicinal products at present, and in particular regarding FAP. The use of the term "Original product" is not fully consistent with the EU Directive relating to Medicinal Products for Human Use (2001/83/EU). With a view to clarity, the term "medicinal product with a new active pharmaceutical ingredient" or "medicinal product with new active pharmaceutical ingredients" is used in this Administrative Ordinance instead of the term "Original product".

²⁴ Ordinance on Medicinal Products of 17 October 2001 ([VAM SR 812.212.21](#)) (Only in German and French)

The 3-year FAP for new developments is established in law, i.e. it exists for the new development even if it is not explicitly stated in the decision issued at the time of authorisation and remains in force – due to its legal nature – even if the authorisation is withdrawn or cancelled.

For a 3-year FAP to be granted, it is irrelevant whether the 10-year FAP for the medicinal product with a new active pharmaceutical ingredient still exists or has expired at the moment of the official decision relating to the new development. The 10-year FAP for the medicinal product and the supplementary 3-year FAP for its new development run independently (i.e. they can exist together, consecutively/sequentially or in parallel, within the 10-year duration).

Only the authorisation holder of the medicinal product with a new active pharmaceutical ingredient or its legal successor (if the authorisation is transferred) may claim the 3-year FAP for the documentation specifically relating to the new development.

6.5.4 Extension of the FAP from 3 to 5 years for significant improvements

If the new development of the medicinal product with a new active pharmaceutical ingredient in accordance with Chapter 6.5.3 constitutes a significant therapeutic improvement, the FAP may be extended from 3 to 5 years (see Art. 17, para. 3, VAM)²⁴. The 5-year FAP will only be granted if the corresponding application has been submitted. This application can also be submitted after the authorisation of the new development the extension of the FAP is always granted retrospectively, commencing on the same date as the approval for the authorisation of the new development. A significant therapeutic improvement is considered to be one that, on the basis of clinical data, demonstrates that in comparison to available therapeutic options, the risk-benefit ratio in the therapeutic scope is significantly improved.

This applies when:

- clearly improved efficacy in an actively controlled study using a clinically significant end point in comparison to the current therapeutic/diagnostic standard can be documented
- a clinically significant improvement in safety compared with the existing therapies/diagnostics in a majority of the population treated can be documented by means of comparative studies
- the new development is in the area of paediatrics, and all of the following criteria are met:
 - the new development was not previously authorised for the medicinal product and
 - it enables or significantly improves the likelihood of the correct use of the medicinal product for the target age group.

The following aspects are taken into account:

- the therapeutic improvement is assessed by comparing the new development with the available products in the same area of use
- efficacy and safety (risk-benefit analysis)
- with combinations of medicinal products, an improvement in efficacy and safety compared to the individual components can be demonstrated.

7 Requirements regarding documentation to be submitted

7.1 Administrative documents (Module 1)

The formal requirements regarding application documents in general, and the formal requirements for Module 1 and the cover letter, are laid down in the Guidance Document *Formal requirements* and in the associated list, *Overview of documents to be submitted*.

7.2 Overviews and summaries (Module 2)

7.2.1 Quality Overall Summary (Section 2.3)

A summary and critical evaluation of all important data from Module 3 must be submitted as a Quality Summary. Please use summary tables and graphical representations to illustrate the key data.

If the authorisation application for a major variation refers entirely to the documentation for a currently authorised medicinal product with a new active pharmaceutical ingredient, only a summary of the new information is required in the Quality Overview.

7.2.2 Nonclinical Overview (Section 2.4)

A summary of the experimental and bibliographical data on pharmacodynamics and toxicology in accordance with ICH M4S, plus a risk assessment as a separate document, must be submitted in the Nonclinical Overview. A critical assessment of the data on the medicinal product with a new active pharmaceutical ingredient 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.

New experimental studies carried out for the application concerning the medicinal product with a new active pharmaceutical ingredient, should be included as a specific list of the titles of the studies in the *Overview of the Nonclinical Testing Strategy* (Section 2.4.1). The status of the GLP quality system for safety-relevant trials should also be included.

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 pharmaceutical ingredient and the product for which authorisation is applied. The corresponding references to this risk assessment should be made in the quality section of the documentation.

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

For topical forms, experimental trials on local tolerance to the product (e.g. eye and skin irritation studies, and clarification regarding the sensitisation and phototoxic potential) and on potential risks in the case of systemic exposure to the active pharmaceutical ingredient should be provided.

Combination products should be submitted as described according to the points and cases listed in ICH M3(R2). The information on nonclinical safety trials in support of the paediatric development programme is also described in ICH M3(R2). The critical points should be shown on a case by case basis in the Paediatric Investigation Plan.

7.2.3 Clinical Overview (Section 2.5)

The Clinical Overview should include a summary of the key data on efficacy and safety that permit an evaluation of the product. Efficacy and safety, as well as the risk-benefit ratio and the medical benefit of the indication applied for and in the patient group concerned should also be critically and comprehensively evaluated in comparison with medical and non-medical alternatives. Summary tables and graphical representations to illustrate the key data should be used.

If the authorisation application for a major variation is entirely based on the documentation of a currently authorised medicinal product with a new active pharmaceutical ingredient, it is only necessary to provide, in the Clinical Overview, a summary of those investigations that prove that the findings from the medicinal product with a new active pharmaceutical ingredient can be applied to or extrapolated to the major variation. The method for the investigations and their results must be critically assessed and compared with findings from literature.

7.2.4 Nonclinical Summary (Section 2.6)

A nonclinical summary *Written and Tabulated Summaries* (Section 2.6) in accordance with ICH M4S must be provided.

For major variations to a medicinal product with a new active pharmaceutical ingredient it may be possible – if appropriately justified – to omit the submission of sub-modules (Sections) of the Nonclinical Summary.

7.2.5 Clinical Summary (Section 2.7)

A clinical summary (Section 2.7) must be provided.

For major variations to a medicinal product with a new active pharmaceutical ingredient it may be possible – if appropriately justified – to omit the submission of sub-modules (Sections) of the Clinical Summary.

7.3 Quality (Module 3)

7.3.1 General aspects

The composition and presentation of the documentation relating to the pharmaceutical quality of a medicinal product with a new active pharmaceutical ingredient (Module 3) should be in accordance with Art. 3, AMZV²⁵. 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 should be taken into consideration.

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

Additional details regarding documentation to be submitted according to the type of application are described in the Annex, Chapter 9.1 of this document.

7.3.2 Documentation on the quality of the active pharmaceutical ingredient (Section 3.2.S)

The documentation on the quality of the active pharmaceutical ingredient or, for fixed combinations, of the active pharmaceutical ingredients, is described in Module 3, Section 3.2.S.

In the case of more than one manufacturer of an active pharmaceutical ingredient, the applicant must provide grouped, consolidated active pharmaceutical ingredient specifications. In addition, manufacturer-specific inspection points, specifications or methods should be indicated separately (e.g. residual solvents for manufacturer X) (see *Guideline on Active Substance Master File Procedure, EMEA/CVMP/134/02*).

Drug Master File

When a Drug Master File (DMF/Active Substance Master File ASMF) is included, the restricted part of the Drug Master File from the manufacturer of the active pharmaceutical ingredient in question, should be referred to the sections, where the content is not available to the applicant.

For further examples relating to the use of a DMF/ASMF or the use of a CEP, reference should be made to the details in the Swissmedic Journal 01/2006, pp. 46-49: *Regulatory News: Drug Master Files* and the *Guideline on Active Substance Master File Procedure, EMEA/CVMP/134/02 and CPMP/QWP/227/02*.

Heparin

If a CEP for the starting material Heparin does not correspond to the test methods in the current monograph of the European Pharmacopoeia nos. 0332 or 0333, Section 3.2.S.2.3 must be expanded accordingly. For the manufacturing of Heparin, documentation on viral safety must be submitted in all cases (Section 3.2.S.A.2). Details on animal starting materials should also be mentioned in Section 3.2.S.2.3.

Stable blood products

For stable blood products, the Plasma Master Files for both active substances and excipients (e.g. human albumin) should be included.

7.3.3 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, active pharmaceutical ingredient content

²⁵ Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 concerning the Requirements for Marketing Authorisations for Medicinal Products ([Medicinal Products Authorisation Ordinance, AMZV](#)), [SR 812.212.22](#) (Only in German and French)

- 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 Section 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 5.

7.3.4 Adventitious Agents Safety Evaluation (Section 3.2.A.2)

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

7.4 Nonclinical documentation (Module 4)

The documentation on the pharmacological and toxicological studies of a medicinal product with a new active pharmaceutical ingredient (Module 4) should be compiled in accordance with Art. 4, AMZV²⁶ and must reflect the latest status of science and technology.

The presentation of nonclinical data is described in the ICH Guideline: *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*.

When carrying out the studies, the relevant ICH guidelines and other guidelines listed in the Annex to the present document must be taken into consideration. Safety-relevant studies should be carried out in accordance with the GLPV²⁷.

The following documents, structured in accordance with the ICH, should be provided: 4.1 *Table of Contents* (stating where documents can be found), 4.2. *Study reports* containing the individual study reports and, if available, 4.3 *Details from literature*.

Further details on the documentation according to application type are described in the Annex in Chapter 9.1 of this document.

7.5 Clinical documentation (Module 5)

The documentation regarding the clinical investigations relating to a medicinal product with a new active pharmaceutical ingredient (Module 5) should be compiled in accordance with Art. 5, AMZV.

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 regarding the applicant's clinical studies carried out for the application should be drawn up in accordance with the ICH *E3 Guideline Structure and Content of Clinical Study Reports*. The studies must be carried out in accordance with GCP guidelines. In addition, other ICH guidelines and those in the Annex should also be taken into consideration.

Published works (reprints) should normally be included separately, with the corresponding reference in the summary and in the original documentation. Further details regarding the documentation depending on application type are described in the Annex in Chapter 9.1 of this document.

²⁶ Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 concerning the Requirements for Marketing Authorisations for Medicinal Products ([Medicinal Products Authorisation Ordinance, AMZV](#)), SR 812.212.22 (Only in German and French)

²⁷ [Ordinance of 18 May 2005 on Good Laboratory Practice \(GLPV SR 813.112.1\)](#)

8 Annexes

8.1 Basic principle

When assessing application documentation within the framework of these instructions, Swissmedic refers specifically to the latest valid version of the Pharmacopoeia, relevant Guidelines by the ICH, the European Committee for Medicinal Products for Human Use (CHMP), the FDA or other guidelines mentioned herein as the basis for evaluation and takes into account the current standards of science and technology.

The summary below provides an overview of relevant guidelines and publications (including those to be found on the Swissmedic website). The list is not exhaustive.

8.2 General international guidelines

ICH Guidelines

In particular, the following:

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

And therein, 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: [eSubmission Swissmedic: Documentation](#)

8.3 Quality guidelines

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

- [The guidelines on quality](#) should be taken from the ICH overview list
- [Guidelines on specific requirements](#) and sub-modules should be taken from the EMA overview list on quality guidelines

Active pharmaceutical ingredient:

- Regulatory News: Drug Master Files (Swissmedic Journal [01/2006](#), pp.46-49) (Only in German and French)
- Regulatory News: New form for submitting Drug Master Files (Swissmedic Journal [01/2010](#), p.39) (Only in German and French)

Finished product:

- Regulatory News: Change of practice regarding storage instructions (Swissmedic Journal [02/2009](#), p. 112) (Only in German and French)
- Instructions related to minimising the risk of transmission of TSE of animal origins by human and veterinary medicines ([TSE instructions](#)) (Only in German and French)
- Information sheet [Confirmation regarding substances from GMO](#) and use of the form [Confirmation regarding substances from GMO](#)

8.4 Nonclinical guidelines

The legal sources and guidelines listed below are provided in connection with the individual sections of these instructions regarding requirements for Section 2.4 and Module 4. Other relevant guidelines on specific requirements and sub-modules can be found under the following links:

- [ICH Safety Guidelines](#)
- [ICH Safety and Multidisciplinary Guidelines](#)
- [EMA Nonclinical Guidelines](#)
- [FDA Pharm/Tox Guidances](#)
- [Ordinance of 18 May 2005 on Good Laboratory Practice \(GLPV²⁸ SR 813.112.1\)](#)

8.5 Clinical guidelines

Relevant clinical guidelines on specific requirements and sub-modules can be found in the following overview lists by the ICH, the EMA or the FDA. They include links to individual guidelines for numerous areas.

- [ICH guidelines on clinical aspects](#)
in particular Guideline E6: Good Clinical Practice (GCP)
- [Multi-disciplinary ICH Guidelines](#) (e.g. on coding in accordance with MedDRA)
- [EMA guidelines on clinical aspects](#)
- [FDA guidelines on clinical aspects](#)

9 Summarised presentation of the requirements

9.1 Requirements for Modules 2 to 5

9.1.1 Requirements relating to an application for the authorisation of a medicinal product with a new active pharmaceutical ingredient (New API)

Quality requirements

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

Preclinical requirements

- Complete preclinical documentation: Sections 2.4, 2.6 and Module 4.

Clinical requirements

- Complete clinical documentation: Sections 2.5, 2.7 and Module 5.

9.1.2 Requirements relating to an application for a variation or a new indication

Quality requirements

- For new indications that involve modified quality documentation, an expanded Section 3.2.P together with an index of modifications and a comparative table must be submitted.

Preclinical requirements

- Critical safety-relevant points should be included in Section 2.4. A risk benefit analysis with regard to the new indication must be drawn up. For newly identified risks, or for an extension of the treatment duration, new experimental studies should normally be submitted. These should be summarised accordingly in Section 2.6 and the studies included in Module 4. If new populations are involved, specific nonclinical studies and the corresponding dose-finding studies should be taken into consideration.

²⁸ [Ordinance of 18 May 2005 on Good Laboratory Practice \(GLPV SR 813.112.1\)](#)

Clinical requirements

Studies on efficacy and safety for the new indication must be submitted. If the new indication is linked to a new dosage strength and/or a new dosage recommendation, reference must also be made to Chapters 9.1.3 and 9.1.5. The following studies are required:

Pharmacokinetic (PK) studies (Sections 5.3.1 and 5.3.3) (if applicable)

For example, investigation of PK in specific populations that were not investigated for the primary indication (Section 5.3.3.3) investigation of PK in patients with the new indication(s) applied for (Section 5.3.3.2) (e.g. if the organ system for which the product's new indication is intended is different from the primary organ system treated with the product) additional interaction studies population kinetics (Section 5.3.3.5)

Pharmacodynamic (PD) studies (Section 5.3.4):

- Investigation of the mechanism of action in the new indication(s) applied for
- PK/PD analysis to define the effective concentration where appropriate

Studies on efficacy and safety (Section 5.3.5):

- Dose-finding studies or appropriate justification that the dosage to date is also appropriate for the new indication(s)
- Studies on efficacy and safety of the new indication(s) applied for, including specific, indication-related studies such as long-term studies
- Pooled analyses of the Phase III (and Phase II) data where appropriate.

9.1.3 Requirements relating to an application for a variation or new dosage(s) (dosage strengths, NDO)

Quality requirements

- A complete Section 3.2.P. must be submitted.

Preclinical requirements

- Critical, safety-related points should be included in Section 2.4 and a risk-benefit analysis with regard to the new dosage strength must be drawn up with particular attention to the safety margins.

Clinical requirements

- Justification for the new dosage strength and proof that this is appropriate, and that the clinical results for the previous dosage strengths are applicable to the new one(s).
- If the new dosage strength is linked with a new dosage recommendation, please also refer to Chapter 9.1.5.

9.1.4 Requirements relating to an application for a variation of the galenic form (NGF)

Quality requirements

- Complete documentation: Section 2.3 and Module 3 (as in 9.1.1 Requirements relating to an authorisation for a medicinal product with a New API).
- CEPs or DMFs are acceptable: reference should be made to them in Section 3.2.S.

Preclinical requirements

- Experimental formulation studies must be submitted.
- For topical products, investigations relating to the local tolerability (e.g. eye and skin irritation studies, and clarification of the sensitising and phototoxic potential) and experimental investigations into systemic exposure to the product applied for must have been carried out. In the case of indications where the systemic exposure is significantly higher for the new galenic form, the corresponding experimental studies on animals must be submitted.

Clinical requirements

- Proof of the transferability of the clinical results of the authorised galenic form to the new form, in accordance with Chapter 6.3.1, and/or independent clinical study or studies to prove efficacy and safety must be submitted. Such proof requires:

Pharmacokinetic studies

- Bioequivalence studies comparing the new and already authorised galenic forms. (Section 5.3.1.2)
- If the new galenic form is not bioequivalent to the form that has already been authorised, complete pharmacokinetic data (Section 5.3.3.1) must be submitted (including the effect of food intake studies if applicable).

9.1.5 Requirements relating to an application for a new dosage recommendation (NDE) or a variation thereto

Quality requirements

- For changes to the quality documentation as a result of a new dosage recommendation, an expanded Section 3.2.P must be submitted together with a list of modifications and a comparison in tabulated form.

Preclinical requirements

Critical safety-relevant points should be included in Section 2.4 and a risk-benefit analysis relating to the new dosage recommendation must be drawn up that particularly takes the safety margins into consideration.

Clinical requirements

- The requirements depend on the type of variation. Normally, the corresponding efficacy and safety studies (Section 5.3.5) must be submitted including specific studies depending on the indication, such as long-term studies. For higher dosages, the focus must be on safety, whereas for lower dosages it must be on efficacy. Additional data on safety pharmacology may also be required, in particular for doses higher than those previously recommended.
- If the only change concerns the dosing interval, a PK bridging or PD bridging study may be sufficient.

9.1.6 Requirements relating to an application for a new route of administration or a variation thereto

Quality requirements

- If parts of the quality documentation are modified as a result of a new route of administration, an expanded Section 3.2.P must be submitted together with a list of modifications.

Preclinical requirements

- Experimental studies for the new route of administration must be submitted (new studies with the new route of administration or bridging studies). For topical forms, experimental studies with the product for which authorisation is being applied for (final formulation) on local tolerability (e.g. eye and skin irritation studies, and clarification of the sensitising and phototoxic potential) must be submitted.

Clinical requirements

- Proof of the transferability of the clinical results of the authorised routes of administration to the new route in accordance with Chapter 6.3.1 and/or independent clinical study or studies to prove efficacy and safety must be submitted.
- In general, pharmacokinetic studies (Sections 5.3.1 and 5.3.3), and in particular bioavailability studies (Sections 5.3.1.1 and 5.3.1.2) must be provided.

- If the application concerns the same medicinal product which has already been authorised (e.g. previously s.c. and not i.m. or vice-versa, without change to the injectable solution), a pharmacokinetic bridging study may be sufficient.
- If, however, the new route of administration is accompanied by a new galenic form (or with other variations such as new dosage, retarding, etc.), studies on efficacy and safety (Section 5.3.5) must be provided.

9.1.7 Requirements relating to an application for a variation to the active pharmaceutical ingredient

Quality requirements

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

Preclinical requirements

- Complete preclinical documentation: Sections 2.4, 2.6 and Module 4 (in accordance with ICH M4 and ICH M4S(R2)).

Clinical requirements

- The documentation to be submitted depends on the type of variation to be applied for.

9.1.8 Requirement relating to an application for variations to the manufacturing process of a biotechnological substance

Quality requirements

- Complete documentation: Section 2.3 and Module 3.
- CEPs or DMFs are acceptable: reference should be made to them in Section 3.2.S.
- If applicable, the Guideline *EMEA/CHMP/BMWP/101695/2006 (comparability)* should be used.

Preclinical requirements

- Complete preclinical documentation: Sections 2.4, 2.6 and Module 4 (including ERA (in accordance with ICH M4 and ICH M4S(R2) in Module 1)).

Clinical requirements

- Complete clinical documentation: Sections 2.5, 2.7 and Module 5.

9.1.9 Instructions relating to an application for a new fixed combination of medicinal products

Quality requirements

- Complete documentation: Section 2.3 and Module 3
- CEPs or DMFs are acceptable: reference should be made to them in Section 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 pharmaceutical ingredients in the fixed combination has not yet been authorised by Swissmedic, the application for approval must be submitted in accordance with Chapter 9.1.1 (Requirement relating to an authorisation for a medicinal product with a new active pharmaceutical ingredient), i.e. with complete preclinical documentation (see Chapter 6.4).

Clinical requirements

- It is usually assumed that when applying for a fixed combination of medicinal products, the pharmacokinetics, efficacy and safety of the individual components have already been demonstrated.
- In general, the following documentation must be submitted:

Pharmacokinetics (Sections 5.3.1 and 5.3.3)

- Bioequivalence studies comparing fixed combinations and single components.
If bioequivalence cannot be demonstrated, complete pharmacokinetic data (Section 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 (Section 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 (Section 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 to investigate the efficacy and safety, i.e. proof that the combination is superior to monotherapy (including specific studies depending on the indication such as long-term studies, and paying particular attention to safety aspects that could be problematic because of the combination, e.g. because of additive effects).
- If the combination of the active pharmaceutical ingredients has already been acknowledged in specialised medical literature, the corresponding references (including possible therapy guidelines) must also be submitted.
- The summary in the Clinical Overview must in particular present the rationale for the fixed combination of medicinal products. The summary must demonstrate the efficacy of the individual components and also the advantage of the combination. Similarly, with regard to safety (Summary of Clinical Safety), both the safety of the individual components and possible specific risks of the combination must be discussed (if applicable, with the inclusion of post-marketing surveillance data from the international environment).
- If at least one of the active substances has not yet been authorised by Swissmedic, the application for approval must be submitted in accordance with Chapter 9.1.1 (Requirements relating to an authorisation application for a medicinal product with a new active pharmaceutical ingredient), i.e. with complete clinical documentation (see Chapter 6.4).