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Change history

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2.0	**24.10.2019**	**Section 5.1.3: Declaration requirements expanded and refined.**	**rin**
1.0	**01.01.2019**	**Implementation of TPO4**	**rin**

1 Definitions, terms, abbreviations

1.1 Definitions and terms

1.1.1 Herbal medicinal products

Herbal medicinal products are medicinal products with specified indications, exclusively containing as active substances one or more herbal substances or one or more herbal preparations and which are not classified as complementary medicines (Art. 4 para. 1 let. a^{quinquies} TPA).

The following are not considered to be herbal medicinal products:

- Medicinal products with pure substances isolated from plants as the active substance (for example atropine or digoxin);
- Medicinal products with synthetic or partially synthetic active substances, even if these are synthesised from raw plant-based materials (for example codeine, troxerutin or menthol).
- Medicinal products additionally containing vitamins or minerals as active substances.

1.1.2 Herbal medicinal product with a new active substance

A herbal substance or herbal preparation is considered to be a new active substance if it is not, or has not been, included in any medicinal product authorised by Swissmedic[1] in connection with an ordinary procedure according to Art. 11 TPA.

1.1.3 Comparator product

A comparator product is a medicinal product to which reference is made in connection with the simplified authorisation procedure for a herbal medicinal product.

1.1.4 Therapeutic equivalence

Therapeutic equivalence refers to an identical efficacy and safety profile, within certain limits, possessed by two medicinal products. This equivalence is proved in clinical trials with suitable study designs and corresponding methodological procedures.

1.1.5 Pharmaceutical equivalence

Herbal medicinal products are pharmaceutically equivalent if they contain a comparable quantity of a comparable herbal active substance, are administered via the same route of administration and there is evidence to indicate that the release and distribution of the active substance in the body are comparable.

[1] Registration by the Intercantonal Office for the Control of Medicines (IOCM) should be considered equivalent to authorisation by Swissmedic.

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1.2 Abbreviations

Ann.	Annex
Art.	Article
CHMP	EMA Committee for Medicinal Products for Human Use
CVMP	EMA Committee for Medicinal Products for Veterinary Use
CEP	Certification of Suitability of Monographs of the European Pharmacopoeia
CTD	Common Technical Document for the Registration of Pharmaceuticals for Human Use
DER	Drug-extract ratio
DMF	Drug Master File
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HMPC	EMA Committee on Herbal Medicinal Products
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
KPTPO	Ordinance of the Swiss Agency for Therapeutic Products of 7 September 2018 on the simplified authorisation of complementary and herbal medicinal products (SR 812.212.24)
let.	Letter
no.	Number
NO(A)EL	No Observed (Adverse) Effect Level
para.	Paragraph
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPLO	Ordinance of the Swiss Agency for Therapeutic Products of 22 June 2006 on the Simplified Licensing of Therapeutic Products and the Authorisation of Therapeutic Products by the Notification Procedure (SR 812.212.23)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22)
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

2 Introduction and objective

This guidance document describes the requirements pertaining to the documentation for the submission and authorisation of herbal medicinal products. Since this guidance document is aimed at administrative bodies, it does not directly specify the rights and obligations of private individuals. Swissmedic uses this guidance 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.

3 Scope

This guidance document applies to the new authorisation of herbal medicinal products according to Art. 4 para. 1 let. a^{quinquies} TPA. Therefore, it does not apply to medicinal product categories regulated in any of the following guidance documents:

- Guidance document *Authorisation of human medicinal product with new active substance HMV4*
- Guidance document *Authorisation of human medicinal product with known active substance HMV4*
- Guidance document *Authorisation of veterinary medicinal product with known API HMV4*
- Guidance document *Authorisation of Homeopathics, anthroposophics and other complementary medicinal products HMV4*

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- Guidance document *Authorisation of Asian medicinal products HMV4*
- Guidance document *Authorisation of individual teas, cough and throat lozenges and pastilles in the notification procedure HMV4*

For authorisation extensions and variation applications, the provisions of the guidance document *Variations and extensions HMV4* apply.

For renewals and the waiver of product authorisation, the provisions of the guidance document *Renewal and discontinuation of authorisation on change of status (main authorisation/export licence) HMV4* apply.

4 Legal framework

The procedure for the authorisation of herbal medicinal products is based, in particular, on the following legislative texts:

Therapeutic Products Act (TPA)

Art. 10	Conditions for granting a marketing authorisation
Art. 11	Application for a marketing authorisation
Art. 14 para. 1 let. c^{bis}	Simplified authorisation procedure
Art. 14a para. 1 let. e	Authorisation application in the simplified authorisation procedure

Therapeutic Products Licensing Requirements Ordinance (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-dose combination medicinal products
Art. 7	Documentation on the analytical, chemical and pharmaceutical tests (veterinary medicinal products)
Art. 8	Documentation on innocuousness (veterinary medicinal products)
Art. 9	Additional documentation on innocuousness and residues for tests on livestock
Art. 10	Admissibility of pharmacologically active substances and proposed withdrawal periods
Art. 11	Documentation on preclinical and clinical trials (veterinary medicinal products)

Complementary and herbal medicinal products (KPTPO)

Art. 5	Principle of simplified authorisation
Art. 6	Documentation on the pharmacological and toxicology tests
Art. 7	Proof of therapeutic efficacy and safety
Art. 9	Analytical, chemical and pharmaceutical documentati
Art. 10	Toxicological and pharmacological documentation
Art. 11	Clinical documentation

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5 General requirements and review principles

5.1 General principles

When evaluating application documents in connection with this guidance document, and in order to reflect the current situation in science and technology, Swissmedic always relies on the latest versions

- of the pharmacopoeia,
- relevant guidelines issued by the International Council of Harmonisation (ICH) or VICH, or the European Committee for Medicinal Products for Human Use (CHMP), the European Committee on Herbal Medicinal Products (HMPC) and the European Committee for Medicinal Products for Veterinary Use (CVMP)
- as well as the herbal monographs published by the European Union (EU) and the EU plant list (*European Union list entry*).

Before submitting the application, the applicant can obtain advice from the Agency in order to clarify any questions (Scientific Advice Meeting). However, such advice does not anticipate the outcome of the review of the dossier by the Agency.

5.1.1 Requirements relating to the scientific data consulted

If an applicant refers to publicly accessible scientific data, the data must relate to the proposed herbal active substance and the proposed indication and must be sufficiently detailed to enable the efficacy and safety to be adequately assessed.
The evidential value of the scientific data used depends primarily on the quality and scope of the material and on the consistency of the derived conclusions.
The following quality attributes are considered to be guiding factors for the review:

- The selection criteria for the literature compilation (search strategy, list of searched databases, service providers) are presented in a transparent and comprehensible manner.
- Both advantageous and less advantageous results are incorporated in the analysis, and contradictory findings are discussed.
- The cited publications – usually full texts of original publications – correspond to the latest scientific and technical findings and have been predominantly published in peer-reviewed journals.
- The cited studies must have been conducted in accordance with GCP/GLP requirements. The publications are sufficiently detailed to enable the results to be extrapolated to the product to be authorised with a sufficient degree of certainty.
- The results of any epidemiological studies (particularly those with a comparative design) must have been submitted to supplement data from published, controlled clinical trials. The transferability of the key data (e.g. product used, proposed indication, dosage strength, pharmaceutical form, dosage recommendation, administration route) to the product to be authorised was explained.
- If reference is made to the latest EU herbal monographs or Assessment Reports, the Agency does not require the submission of the underlying original literature, but reserves the right to request these at a later date if needed.
- Scientific publications and literature data are complete, i.e. not just submitted and referenced as abstracts.

If more than 12 months have elapsed between the search and the submission date of the authorisation application, a supplement updating the main document is expected, or an explanation as to why newer data and findings were not included.

5.1.2 New findings discovered during the application procedure

New aspects on the efficacy and safety in relation to the application should be submitted continuously and without being asked, and the documentation 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.

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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 (in this connection see the guidance document *Time limits for authorisation applications HMV4*).

5.1.3 Declaration requirements

The requirements pertaining to the declaration of the active substances and pharmaceutical excipients are described in Annex 3 TPLRO.

The declaration of herbal substances and herbal preparations is based on the EMA *Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products* (EMA/HMPC/CHMP/CVMP/287539/2005).

For herbal substances and herbal preparations, the following aspects should be taken into account:

- The plant part used and the botanical name of the primary plant should be stated.
- Herbal substances and herbal preparations monographed in the pharmacopoeia (Ph. Eur. or Ph. Helv.) must be named as stated in the monograph.
- For herbal extracts, the declaration requirements of the Ph. Eur. monograph "Plantarum medicinalum extracta" apply; the quantity of native extract and the native drug extract ratio should be stated.
- Quantities should be declared in mg per dosage unit or in mg per ml / mg per g.
- For alcohol-containing medicinal products for oral administration, the alcohol content in the finished product should be stated in percent by volume.
- The statements in the medicinal product information must correspond to the declaration in the *Full declaration HMV4* form and the *Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products*.
  The Latin active substance name should correspond to the name of the herbal substance or herbal preparation in the pharmacopoeia.
  In the official Swiss language versions, the herbal active substances must appear as follows:

Formulation	Plant part	*Latin name of the primary plant* and the plant part (in brackets, primary plant in italics)	Extracts: Native drug-extract ratio, extraction solvent
Powder from/powdered	valerian root	(*Valeriana officinalis* L., radix)	
Dry extract of	valerian root	(*Valeriana officinalis* L., radix)	Drug-extract ratio: 3 - 6 :1 Extraction solvent ethanol 70 % V/V
Tincture of	valerian root	(*Valeriana officinalis* L., radix)	Drug-extract ratio: 1: 4.0 - 4.5 Extraction solvent ethanol 70 % V/V

- If the space on the packaging elements is insufficient when specifying the medicinal product composition, the short Latin form may be used. This should correspond to the name of the herbal preparation or herbal substance in the pharmacopoeia:

Pharmacopoeia monograph	Possible short name	Extracts: Native drug-extract ratio in brackets
Valerianae radix (Ph. Eur.)	Valerianae radicis pulvis	
Valerianae extractum hydroalcoholicum siccum (Ph. Eur.)	Valerianae extractum hydroalcoholicum siccum	(3 - 6 :1)
Valerianae tinctura (Ph. Eur.)	Valerianae tinctura	(1: 4.0 - 4.5)

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- Specifying the active substance underneath the name of the medicinal product is optional yet recommended for herbal medicinal products. If the active substance is specified, this must be done in the official Swiss languages and must correspond to the name of the herbal preparation or herbal substance in the pharmacopoeia. For extracts, specifying the extract type (dry, liquid) and the extraction solvent is not necessary (short designation):

Pharmacopoeia monograph	Short designation, in two official Swiss languages
Valerianae radix (Ph. Eur.)	Valerian root powder
Valerianae extractum hydroalcoholicum siccum (Ph. Eur.)	Valerian extract
Valerianae tinctura (Ph. Eur.)	Valerian tincture

Examples:
Capsule with 300 mg powder from valerian root

- Full declaration HMV4 form:
  Valerianae radicis pulvis 300 mg
  (*Valeriana officinalis* L. *s.l.*, radix)
- Medicinal product information:
  One capsule contains 300 mg pulverised valerian root (*Valeriana officinalis* L. *s.l.*, radix).
- The following short name is permitted on the packaging elements for specifying the medicinal product composition:
  300 mg Valerianae radicis pulvis
- Short designation of the active substance underneath the name of the medicinal product:
  Valerian root powder

Tablet with 160 mg dry extract, native from valerian root

- *Full declaration HMV4* form:
  Valerianae extractum hydroalcoholicum siccum 160 mg
  (*Valeriana officinalis* L. *s.l.*, radix)
  DER: 3 - 6 :1
  Extraction solvent ethanol 70 % V/V
- Medicinal product information:
  One tablet contains 160 mg dry extract of valerian root (*Valeriana officinalis* L. *s.l.*, radix), drug-extract ratio 3 - 6 :1, extraction solvent ethanol 70% V/V
- The following short name is permitted on the packaging elements for specifying the medicinal product composition:
  160 mg Valerianae extractum hydroalcoholicum siccum (3 - 6 :1)
- Short designation of the active substance underneath the name of the medicinal product:
  Valerian extract

Valerian tincture

- *Full declaration* form:
  Valerianae tinctura 1 ml
  (*Valeriana officinalis* L. *s.l.*, radix)
  DER: 1: 4.0 – 4.5
  Extraction solvent ethanol 70 % V/V
- Medicinal product information:
  1 ml (corresponding to … g) solution contains 1 ml tincture of valerian root (*Valeriana officinalis* L. *s.l.*, radix), DER 1: 4.0 - 4.5, extraction solvent ethanol 70 % V/V.
- The following short name is permitted on the packaging elements for specifying the medicinal product composition:
  1 ml Valerianae tinctura (1: 4.0 - 4.5)
- Short designation of the active substance underneath the name of the medicinal product:
  Valerian tincture

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5.1.4 Requirements for medicinal product information

The requirements pertaining to the medicinal product information are described in the guidance document *Formal requirements HMV4* and in the guidance document *Product information for human medicinal products HMV4* and in *the guidance document Product information for veterinary medicinal products HMV4*.

5.1.5 Requirements for packaging materials

The requirements pertaining to the packaging materials are described in the guidance document *Packaging materials for human medicinal products HMV4* and in the guidance document *Packaging materials for veterinary medicinal products HMV4*.

5.1.6 Requirements after authorisation

Once authorisation has been officially granted for a herbal 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. 59 Therapeutic Products Ordinance).
PSURs do not need to be submitted for herbal medicinal products with a new active substance authorised in the simplified procedure on the basis of traditional or well-established use or for known active substances. According to Art. 16 para. 1 TPA, Swissmedic can require PSURs to be submitted on a case-by-case basis.

5.1.7 Documentation requirements

a) **Analytical, chemical and pharmaceutical documentation**
Complete documentation on quality according to Art. 3 TPLRO or Art. 7 TPLRO (for veterinary medicinal products) should be submitted.

b) Documentation on the pharmacological and toxicological tests
The pharmacology and toxicology of a herbal medicinal product should be fully substantiated according to Art. 4 TPLRO and Arts. 8 and 9 TPLRO (for veterinary medicinal products). Reference can be made to bibliographical data for herbal active substances and excipients whose toxicological properties are sufficiently known.
Evidence must also be provided to show that medicinal products for livestock only contain active substances listed as permitted pharmacologically active substances in foodstuffs legislation. If necessary, withdrawal periods should be proposed and substantiated accordingly (Art. 10 TPLRO).

c) Documentation on clinical trials
If the published scientific literature contains sufficient evidence from clinical trials, and if the results can be applied to the proposed product, bibliographical documentation can be submitted. Otherwise, the requirements of Art. 5 TPLRO or Art. 11 TPLRO (for veterinary medicinal products) must be fulfilled.

5.2 Authorisation applications for fixed-dose combination medicinal products

The requirements and required documents for fixed-dose combination medicinal products are described in Art. 6 TPLRO and Art. 14a TPLO. The usefulness of the proposed combination should be explained, and the efficacy and safety compared to the individual components substantiated.
The requirements for fixed-dose combination medicinal products are described in the "Fixed-dose combination medicinal products" section and in the Annex under "Requirements for an application for a new fixed-dose combination medicinal product".

Tea blends should not contain more than 5 active substances. Herbal substances that are relevant to the visual appearance and improved taste can also be added. The proportion of these cosmetic- and taste-enhancing plant drugs should not account, overall, for more than 30% of the tea blend.

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5.3 Time limits

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

5.4 Fees

The fees specified in the Ordinance on Fees Levied by the Swiss Agency for Therapeutic Products (FeeO-Swissmedic; SR 812.214.5) apply.

6 Ordinary authorisation procedure

6.1 General principles

The authorisation application for a herbal medicinal product with a new active substance in the procedure according to Art. 11 TPA must include comprehensive and complete documentation on quality, preclinical and clinical aspects according to Art. 2, 3, 4 and 5 TPLRO and Art. 2, 7, 8, 9, 10 and 11 TPLRO (veterinary medicinal products). 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.

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

Paediatric Investigation Plan
Swissmedic recognises the ICH guideline on the *Clinical Investigation of Medicinal Products in the Pediatric Population E11*, which describes when, and in what situations, paediatric data should be submitted.
A paediatric investigation plan according to Art. 54a TPA must be submitted with an application for the authorisation of a herbal medicinal product with a new active substance for which document protection is requested. For further details see the guidance document *Paediatric investigation plan HMV4.*

Data for 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 has recognised.

6.1.2 Document protection

The documents submitted by the first applicant in connection with an ordinary authorisation procedure, particularly the pharmacological, toxicological and clinical trial data, are protected from use by third parties. See guidance document *Document protection HMV4*.

6.2 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 HMV4* and in the associated *Overview of documents to be submitted HMV4*. Module 1.4 with information about the experts is an obligatory component.

6.2.1 Environmental Risk Assessment (ERA, Module 1.6)

The application for authorisation of a herbal medicinal product with a new active substance must be accompanied by an *Environmental Risk Assessment (ERA)*, or else an appropriate reason should be stated for not submitting one in the specific case.

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6.3 Overviews and summaries (Module 2)

6.3.1 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. For veterinary medicinal products, the *Detailed And Critical Summary (DACS)* relating to quality should be submitted under Part 1c.

6.3.2 Nonclinical Overview (Module 2.4)

A *Nonclinical Overview (Module 2.4)* should be submitted. This document includes a summary of the experimental and bibliographical data on pharmacodynamics, pharmacokinetics (relating to constituents that individually or jointly determine efficacy, if possible) and toxicology according to ICH M4S, and a risk assessment in respect of the possible consequences of the herbal medicinal product on the safety of patients.

The following items should be included:

- Tabular overview of the safety margins between the data from animal safety studies (basis for NO(A)EL) and the therapeutic exposure in clinical practice;
- Information on the GLP status of the preclinical studies;
- Evaluation of the safety relevance of new excipients, with presentation of experimental studies, if required.

For topical forms, experimental studies on the local tolerance of the 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.

For veterinary medicinal products, the *Detailed And Critical Summaries (DACS)* relating to safety and residues should be submitted under Part 1c.

6.3.3 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 product. The overview should include a comprehensive and critical appraisal of the scientific and medical environment, the efficacy and safety, the benefit/risk profile and the medical value in the proposed indications and in the relevant patient population. The use of synoptic tables and graphics to illustrate essential data is encouraged.

The methodology of the investigations employed and their results should be critically assessed and compared with results from the latest literature findings.

Full clinical documentation reflecting the latest findings (no older than 5 years) must be submitted with all modules (Modules 1, 2.5, 2.7, 5), and an appropriately qualified Clinical Expert named.

The clinical documentation should include the following:

- Evidence of the efficacy of the product in the proposed indication by at least one controlled clinical trial of good quality. This may be documented by a Study Report or may have been published in a scientific peer-reviewed journal.
- A clear description of the product / active substance used in the study / studies, including the DER, excipients, dosage strength, dosage recommendation should be provided. The study population must match that in which the product is to be used.
- The study / studies must have recruited a sufficiently large number of patients to produce statistically meaningful results. The primary study endpoint must correspond to the proposed indication. The clinical relevance of the endpoints and the effect size must be documented and adequately discussed with the aid of the literature or guidelines issued by professional associations.
- If several studies are involved (possibly summarised in a meta-analysis), the scientific statements must be consistent; no contradictory results may be documented.

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- The clinical documentation includes evidence of a systematic literature search with suitable search terms and relating particularly to safety and risks, including long-term use. Older data must be examined for scientific credibility.
- A sufficient level of evidence can be generated through meta-analyses, systematic reviews, randomised controlled trials (RCT), case-control studies and cohort studies, provided these do not show methodological shortcomings.
- Observational studies and scientifically assessed case reports can be employed for evaluating safety. Since these are non-confirmatory studies, they are not suitable for proving efficacy.

For veterinary medicinal products, the *Detailed And Critical Summary (DACS)* relating to efficacy should be submitted under Part 1c.

6.3.4 Nonclinical Summary (Module 2.6)

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

6.3.5 Clinical Summary (Module 2.7)

A Clinical Summary (Module 2.7) should be submitted.

6.4 Quality (Module 3)

6.4.1 General

The analytical, chemical and pharmaceutical quality of a herbal medicinal product should be documented according to Art. 3 TPLRO or Art. 7 TPLRO (veterinary medicinal products). The quality-related guidelines issued by ICH (or VICH) and EMA should be taken into account (see Ann. under "Quality guidelines").

The documentation of analytical, chemical and pharmaceutical data is described in the ICH guideline *The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality-M4Q. Quality Overall Summary of Module 2, Module 3: Quality*, while the specific requirements relating to the documentation of the quality of a herbal medicinal product can be found in the EMA *Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products, EMA/HMPC/71049/2007*.

The requirements as per the pharmacopoeia must be met in respect of starting materials, active substances, intermediates, excipients and the finished product. If different methods are used, their equivalence with the methods in the pharmacopoeia should be demonstrated.

As regards the quality-related documentation, the same requirements apply to all herbal medicinal products; for example, complete quality documentation should be submitted even for a simplified authorisation with reference to a monograph or the authorisation of traditional herbal medicinal products.

The following remarks on the requirements pertaining to the quality-related documentation are not conclusive, but explain certain selected aspects.

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

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 / ASMF 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, refer to the information in the Swissmedic Journal 01/2006, p. 46-49 and to the EMA *Guideline on Active Substance Master File Procedure (CPMP/QWP/227/02).*

Starting material

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The requirements of the general Ph. Eur. monograph *Herbal Drugs / Plantae medicinales* must be taken into account. If a specific monograph in the pharmacopoeia exists for a starting material, the corresponding requirements of this monograph must be fulfilled. The primary plant / primary plants must be named. The geographical origin, isolation and processing of the starting material must be documented.

Manufacture of the active substance
The manufacture of the active substance must be described in both narrative and schematic form. The implemented in-process controls must be documented (specifications, analytical methods and test frequencies, if possible in tabular form). The standard batch size or batch mix size must be defined.

The manufacturing process must be validated and the corresponding validation report submitted. If validation is to be omitted, such omission should be justified by means of a risk assessment of the individual manufacturing steps.

Characterisation of contaminants
The methods for the tests for contaminants must be validated using the substance-specific matrix.

Control of the active substance
The requirements of the relevant general pharmacopoeial monographs must be observed. The active substance specification, a description of the analytical methods used and the documentation on the validation of the analytical methods must exist.

Certificates of analysis for at least two active substance batches manufactured close together in time, including coloured reproductions of the thin-layer chromatic fingerprints and/or the GC/HPLC fingerprints, must be included in the quality documentation.

Reference standards for the active substance
Reference substances used in connection with active substance testing must be documented.

For reference substances used in assays, complete documentation on the primary standards used must be submitted.

Container for the active substance
The documentation on the primary container should at least include the specifications and design drawings as well as documentation on the materials used and their suitability. The required declarations of conformity must also be enclosed. Particularly for liquid and semi-solid active substances, potential interactions with the container materials must be discussed.

Stability documentation for the active substance
Data on the stability of the active substance must be submitted. The requested retest period must be justified. The relevant guidelines issued by the ICH (or VICH) and the EMA must be taken into account.

6.4.3 Documentation on the quality of the finished product (Module 3.2.P)

Manufacture of the finished product
The manufacture of the finished product must be described in both narrative and schematic form. The implemented in-process controls must be documented (specifications, analytical methods and test frequencies, if possible in tabular form). A standard batch size and/or the batch size range must be defined.

The manufacturing process must be validated and the corresponding validation report submitted. The validation must be carried out according to the *Guideline on process validation for finished products, EMA/CHMP/CVMP/QWP/BWP/70278/2012*.

If validation is omitted, the reason for omitting it must be justified, taking into account the pharmaceutical form: The individual manufacturing steps must be subjected to a risk assessment showing that a manufacturing validation is not necessary.

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Excipients
Excipients must be documented with specifications and analytical methods. If excipients are the subject of a monograph in the pharmacopoeia, the documented requirements must be satisfied, in which case a reference to the monograph is sufficient. For excipients without a pharmacopoeia monograph, a sample certificate of analysis must be submitted.

Control of the finished product
The specifications and analytical methods and the documentation on method validation must exist. The requirements of the respective Ph. Eur. monograph for the pharmaceutical form must be taken into account during the preparation of the specifications.

The requirements for the microbiological quality of oral pharmaceutical forms must satisfy the requirements of Ph. Eur. monograph 5.1.8. Otherwise, the requirements of Ph. Eur. Chapter 5.1.4 are decisive.

Certificates of analysis for at least three production batches manufactured close together in time (at least two batches at the time of submission) including coloured reproductions of the thin-layer chromatographic fingerprints and/or the GC/HPLC fingerprints form part of the quality documentation.

Reference standards for the finished product
For reference substances used in connection with testing of the finished product, the same requirements applicable to the reference substances for active substance testing apply (see "Reference standards for the active substance").

Containers for the finished product
For containers used for the finished product, the same requirements applicable to the active substance container apply (see ***Container for the active substance***).

Stability documentation for the finished product
The stability of the finished product must be investigated in accordance with ICH (or VICH) and EMA guidelines, and the rationale for the proposed shelf life must be provided.

The test results must be documented clearly in tabular form. For the stability batches, the manufacturing date, batch size and associated primary container must be stated. The colour illustrations of the thin-layer chromatographic fingerprints and/or the GC/HPLC fingerprints obtained at the individual test times must be enclosed with the quality documentation.

The submitted data must be discussed: out-of-specification results, trends and significant changes during the course of storage.

If applicable, the stability after opening must be checked. A use-by period backed by appropriate reasons must be requested.

6.4.4 Adventitious Agents Safety Evaluation (Module 3.2.A.2)

If applicable, all documents on viral safety and the TSE risk assessment should be presented, together with the relevant certificates, in Module 3.2.A.2.

6.5 Non-clinical documentation (Module 4)

The documentation on pharmacological and toxicological tests for a medicinal product with a new herbal active substance should be compiled according to Art. 4 TPLRO or Art. 8 to 10 TPLRO (veterinary medicinal products) and must accord with the latest scientific and technical findings. The presentation must conform to ICH M4S. During the implementation of studies the relevant ICH (or VICH) guidelines and other guidelines listed in the Annex must be observed. Safety-relevant studies must be performed in conformity with GLP.
Further information on the documentation according to type of application are described in the Annex under "Summary of requirements for Modules 2 to 5".

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6.6 Clinical documentation (Module 5)

The documentation on the clinical trials for a medicinal product with a new herbal active substance should be compiled according to Art. 5 TPLRO or Art. 11 TPLRO (veterinary medicinal products). The presentation of 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 (or VICH) and the guidelines listed in the Annex 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. Further information on the documentation according to type of application are described in the Annex under "Summary of requirements for Modules 2 to 5".

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7 Simplified authorisation procedure

7.1 General principles

For herbal medicinal products that are authorised in the simplified procedure according to Art. 14 c^{bis} TPA, the results of the pharmacological and toxicological tests and clinical trials, including all results from trials with special population groups, can be replaced by bibliographical evidence of efficacy and safety, provided that all aspects of safety and efficacy of the active substance can be substantiated by meaningful scientific data (see "Requirements relating to the scientific data consulted").

Paediatric investigation plan
A Paediatric Investigation Plan according to Art. 54a TPA is not required.

Pharmacovigilance Plan
A Pharmacovigilance Plan according to Art .11 para. 2 let. a no. 5 TPA is not required.

Environmental Risk Assessment (ERA)
An Environmental Risk Assessment (ERA) is not required.

7.1.1 Authorisation applications for a herbal medicinal product with known active ingredient

An authorisation for a herbal medicinal product that is comparable with an existing authorised medicinal product can be applied for as follows:
- Complete documentation relating to quality should be submitted.
- Complete documentation relating to toxicology and pharmacology should be submitted in accordance with the requirements of Art. 10 and Ann. 1 no. 3 KPTPO.
- Complete clinical documentation should be submitted, including evidence to show that the herbal medicinal product is therapeutically or pharmaceutically equivalent to an authorised medicinal product (see "Evidence of comparability").
- For the known aspects reference can be made to the authorised comparator product.
- For new aspects that have not yet been authorised in Switzerland, bibliographical evidence (see "Requirements relating to the scientific data consulted") or evidence according to the "Ordinary authorisation procedure" section should be provided.

7.1.2 Authorisation applications for herbal medicinal products with well established use

An authorisation for a herbal medicinal product with well established use can be applied for as follows:
- Complete documentation relating to quality should be submitted.
- Complete documentation relating to toxicology and pharmacology should be submitted in accordance with the requirements of Art. 10 and Ann. 1 no. 3 KPTPO.
- Complete clinical documentation should be submitted, including evidence to show that the herbal medicinal product has been used medically for at least 10 years in an EU/EFTA country.
- The applicant should demonstrate that the efficacy and safety of the active substance is well documented in the scientific literature (see "Requirements relating to the scientific data consulted") and generally recognised, or evidence according to the "Ordinary authorisation procedure" section should be provided.

7.1.3 Authorisation applications for a herbal medicinal product with traditional use

An authorisation for a herbal medicinal product with traditional use can be applied for as follows:
- Complete documentation relating to quality should be submitted.
- Complete documentation relating to toxicology and pharmacology should be submitted in accordance with the requirements of Art. 10 and Ann. 1 no. 3 KPTPO.
- Complete clinical documentation should be submitted, including evidence to show that the herbal medicinal product, or a comparable medicinal product (comparator product), has been used medically for at least 30 years, and for at least 15 years in an EU / EFTA country. If reference is made to a comparator product, evidence should be provided to show that this is therapeutically or

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pharmaceutically equivalent to the herbal medicinal product to be authorised (see "Evidence of comparability").
- The applicant should show that the safety of the herbal medicinal product is sufficiently proven and that the efficacy is explained in a plausible manner, or should provide evidence according to the "Ordinary authorisation procedure" section.

7.1.4 Evidence of comparability

If the authorisation of a herbal medicinal product with known active substance or a herbal medicinal product with traditional use is applied for on the basis of a comparator product, the comparability of the product to be authorised with the authorised medicinal product or comparator product must be demonstrated. The comparability can be demonstrated by evidence of therapeutic equivalence with (comparative) clinical trials or by evidence of pharmaceutical equivalence.

The pharmaceutical equivalence between two herbal medicinal products is considered to be proven theoretically if the following conditions are satisfied:
a) same herbal substance of comparable quality;
b) comparable variation of the native drug extract ratio;
c) comparable extraction solvent;
d) comparable manufacturing process;
e) for standardised extracts: identical content of constituents with known therapeutic efficacy;
f) for quantified extracts: identical content range for the key active substances;
g) comparable dosage;
h) same indication, same method of administration and
i) comparable pharmaceutical formulations.

Any differences that exist between the medicinal product to be authorised and the existing authorised medicinal product or comparator should be presented and discussed. The specific aforementioned conditions that have to be satisfied to serve as proof of pharmaceutical equivalence and the variations that can be accepted depend on the respective medicinal product.

7.1.5 Fixed-dose combination medicinal products

As regards the authorisation of a fixed-dose combination medicinal product, apart from the provisions applicable to the individual medicinal products, the requirements of Art. 6 TPLRO also need to be fulfilled. More detailed information on the scientific state of the art concerning documentation for obtaining authorisation for combination products can be found in the WHO Guidelines for registration of fixed-dose combination medicinal products, (WHO Technical report series, No. 929, 2005: Annex 5) and, if necessary, in the other guidelines cited in this document and, for preclinical aspects, particularly in ICH guideline M3.
For fixed-dose combination medicinal products that involve a reference to traditional use, the traditional use of the combination, and not just the use of the individual active substances, must be demonstrated. If – for safety reasons, for example – individual active substances have to be removed from a traditionally used active substance combination, the applicant must demonstrate that the plausibility of the efficacy in the indication still applies, or else the indication should be made more restrictive.

7.1.6 Document protection

Document protection is not granted for authorisations according to the simplified authorisation procedure. Additional information on document protection can be found in the guidance document *Document protection HMV4*.

7.2 Administrative documents (Module 1)

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

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7.3 Overviews and summaries (Module 2)

7.3.1 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. For veterinary medicinal products, the Detailed And Critical Summary (DACS) relating to quality should be submitted under Part 1c.

7.3.2 Nonclinical Overview (Module 2.4)

In Module 2.4, a summary of the non-clinical experimental and bibliographical data on pharmacodynamics, pharmacokinetics and toxicology, as well as a risk assessment, should be submitted as a Nonclinical Overview. The nature and scope of the required documentation depend, in particular, on the composition of the medicinal product, the therapeutic use and range, the method of administration and the duration of treatment.

Those active substances and excipients that are considered to be sufficiently known in terms of toxicology are defined in Ann. 1 no. 3.2 KPTPO. For these substances and for herbal medicinal products with well established use or traditional use, reference can be made to bibliographical data, taking account of the section on "Requirements relating to the scientific data consulted", provided that the transferability of the bibliographical data to the herbal preparation or herbal substance in the medicinal product to be authorised can be shown (e.g. by discussion or by the demonstration of pharmaceutical equivalence with reference medicinal products cited in the monograph).

Since they have been used medically for many years, the safety profile of these herbal medicinal products is usually sufficiently characterised. However, since aspects relating to mutagenicity, carcinogenicity and reproductive toxicity cannot be adequately recorded clinically, these should be discussed from the preclinical standpoint. Pharmacokinetic substance interactions should be discussed.

For veterinary medicinal products, the Detailed And Critical Summaries (DACS) relating to safety and residues should be submitted under Part 1c.

7.3.3 Clinical Overview (Module 2.5)

A summary of all the data from Module 5 should be submitted in the Clinical Overview. For veterinary medicinal products, the Detailed And Critical Summaries (DACS) relating to efficacy should be submitted under Part 1c.

Herbal medicinal product with known active substance
If the authorisation application refers to a currently authorised medicinal product, a summary of those investigations required for demonstrating that the product to be authorised is equivalent to the comparator product should be included in the Clinical Overview (see also "Evidence of comparability").
If new aspects compared to the authorisation granted for the comparator product are requested, documentation on these new aspects should be submitted and critically appraised in order to demonstrate efficacy and safety of use.

Herbal medicinal product with well established use:
If authorisation is requested for the product on the basis of well established use, a summary of those documents showing that the herbal medicinal product has been used medically for at least 10 years in at least one EU / EFTA country should be included in the Clinical Overview. The published data on efficacy and safety (e.g. reports on adverse reactions) should be summarised and critically appraised (see the corresponding statements ("Clinical Overview (Module 2.5)") in the "Ordinary authorisation procedure" section). A statement should be provided on the current benefit-risk profile on the basis of the existing literature and any existing European Union herbal monograph and the associated Final Assessment Report.

Herbal medicinal product with traditional use:

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If authorisation is requested for the product on the basis of traditional use, a summary of those documents showing that the herbal medicinal product or a comparable medicinal product (comparator product) has been used medically for at least 30 years, and for at least 15 years in an EU / EFTA country should be provided.
The plausibility of efficacy is accepted on the basis of sufficiently long market experience with the traditional comparator product, provided that no relevant safety signals or risks have been documented over the whole 30-year period.
The market experience with the traditional comparator product in other countries must be documented, e.g. by authorisation decisions; Summary of Product Characteristics (SPC), entries in medicinal product lists, manuals, monographs; sales statistics.
The indication must be derived from the traditional use, must be self-limiting in nature and be compatible with basic medical considerations. The only intended use for traditional herbal medicinal products is as simplified self-medication (dispensing category D). Accordingly, the indication must be clearly described, diagnosable by the patients themselves (or, in the case of a veterinary medicinal product, by the animal owner); it must not be associated with risks such as a delay in respect of diagnosis or causal treatment.
The safety and local tolerance of products for topical use or inhalation can depend on the preparation or on the excipients. If the product to be authorised differs in this respect from the traditional comparator product, the local tolerance must be demonstrated by means of a suitably designed study.

7.3.4 Nonclinical Summary (Module 2.6)

Nonclinical Summaries should be submitted if experimental studies have been presented by the applicant.

7.3.5 Clinical Summary (Module 2.7)

Herbal medicinal product with known active substance:
A complete Clinical Summary should be submitted if a known active substance is not involved or if important new aspects are requested. In all other cases, the submission of a Clinical Safety Summary (Module 2.7.4) is sufficient.

Herbal medicinal product with well established use:
The data on efficacy from the clinical trials should be presented in detail and, if necessary, in pooled form. The data on safety from the clinical trials should be presented in detail and in pooled form. Data from postmarketing experience should be presented (including narratives) and critically appraised. The benefit-risk profile should be evaluated on the basis of this data and the available literature. Reference can also be made to a Final Assessment Report for a European Union herbal monograph, if one exists, and to the latest knowledge in this area.

Herbal medicinal product with traditional use:
The clinical documentation must list and discuss the results of a systematic search of the literature and databases on safety and the postmarketing experience with the comparator product, and include the sales figures and/or number of exposed patients (Module 2.7.4).

7.4 Quality (Module 3)

As regards the documentation on quality, the same requirements also apply to all herbal medicinal products. Complete quality documentation should be submitted even for a simplified authorisation. See the corresponding statements ("Quality (Module 3)") in the section "Ordinary authorisation procedure".

7.5 Non-clinical documentation (Module 4)

The study reports from experimental non-clinical investigations and the bibliographical documents should be submitted in Module 4. The documentation on new pharmacological and toxicological tests should be presented in accordance with the corresponding statements ("Non-clinical documentation (Module 4)") in the "Ordinary authorisation procedure" section.

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7.6 Clinical documentation (Module 5)

Any study reports on clinical trials conducted by the applicant, as well as the bibliographical documents (references) and a current Module 5.3.6 (no older than 2 years) should be submitted in Module 5. The documentation on new clinical trials should be presented in accordance with the corresponding statements ("Clinical documentation (Module 5)") in the "Ordinary authorisation procedure" section.

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8 Annexes

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

8.1 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

EMA Guidelines on herbal medicinal products

VICH Guidelines

EMA Guidelines on veterinary medicinal products

8.2 Quality guidelines

The quality-related guidelines issued by ICH (or VICH) and EMA should be taken into account. Guidelines on specific requirements or submodules can be found in the EMA summary list of Quality Guidelines. A compilation of Quality Guidelines, including for herbal medicinal products, can also be found in the *Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products, EMA/HMPC/71049/2007*.

8.3 Non-clinical guidelines

The legal sources / guidelines mentioned below are highlighted in connection with individual sections 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

8.4 Clinical guidelines

Relevant guidelines on specific requirements / submodules and clinical guidelines 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
- EU-Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products, Final revision 1
- FDA Clinical Trials Guidance Documents
- FDA Guidances for Industry and Food and Drug Administration Staff

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9 Summary of requirements for Modules 2 to 5

9.1 Requirements for an authorisation application in the ordinary procedure according to Art. 11 TPA

Quality requirements
- Complete documentation: Module 2.3 and Module 3

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

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

9.2 Requirements for an authorisation application in the simplified procedure according to Art. 14 let. c^{bis} TPA

9.2.1 Herbal medicinal product with known active substance

Quality requirements
- Complete documentation: Module 2.3 and Module 3

Preclinical requirements
- Summary of the non-clinical experimental and bibliographical data on pharmacodynamics, pharmacokinetics and toxicology, as well as a risk assessment in Module 2.4.

Clinical requirements
- Documentation showing that the herbal medicinal product is therapeutically or pharmaceutically equivalent to an authorised medicinal product and is therefore effective or its efficacy is plausible.
- For new aspects that have not yet been authorised in Switzerland: Bibliographical evidence or evidence according to the requirements stated in the "Ordinary authorisation procedure" section.
- Documentation demonstrating the safety of the herbal medicinal product via the submission of a Clinical Safety Summary (Module 2.7.4)

9.2.2 Herbal medicinal product with well established use

Quality requirements
- Complete documentation: Module 2.3 and Module 3

Preclinical requirements
- Summary of the non-clinical experimental and bibliographical data on pharmacodynamics, pharmacokinetics and toxicology, as well as a risk assessment in Module 2.4.

Clinical requirements
- Documentation showing that the herbal medicinal product has been used medically for at least 10 years in an EU / EFTA country.
- Evidence showing that the efficacy and safety of the active substance is well documented in the scientific literature and generally recognised, or evidence according to the requirements stated in the "Ordinary authorisation procedure" section.
- Submission of a Clinical Safety Summary (Module 2.7.4)

9.2.3 Herbal medicinal product with traditional use

Quality requirements
- Complete documentation: Module 2.3 and Module 3

Preclinical requirements
- Summary of the non-clinical experimental and bibliographical data on pharmacodynamics, pharmacokinetics and toxicology, as well as a risk assessment in Module 2.4.

Clinical requirements

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- Evidence showing that the herbal medicinal product, or a comparable medicinal product (comparator product), has been used medically for at least 30 years, and for at least 15 years in an EU / EFTA country.
- If the application is based on a comparator product: Evidence showing that this is therapeutically or pharmaceutically equivalent to the herbal medicinal product to be authorised.
- Evidence showing that the safety of the herbal medicinal product is sufficiently proven and that the efficacy is explained in a plausible manner, or evidence according to the requirements stated in the "Ordinary authorisation procedure" section.
- Submission of a Clinical Safety Summary (Module 2.7.4)

9.3 Requirements for an application for a new fixed-dose combination medicinal product

Quality requirements

- Complete documentation: Module 2.3 and Module 3

Preclinical requirements

- If at least one of the active substances in the fixed-dose combination medicinal product has not yet been authorised by Swissmedic, then this should be submitted in accordance with the section on "Requirements for an authorisation application in the ordinary procedure according to Art. 11 TPA", i.e. with complete preclinical documentation.

Clinical requirements

- When an application for a fixed-dose combination medicinal product is submitted, it is usually assumed that the efficacy and safety of the individual components have already been demonstrated at an earlier stage, or that the fixed combination is documented as a result of traditional use.
- The following documentation generally needs to be submitted:

Studies on efficacy and safety

- Dose-finding studies (unless reference is made to traditional use)
- 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 appraised in the specialist medical literature or documented as a result of traditional use, corresponding references should also be submitted.
- Except for traditional herbal medicinal products, the rationale for the fixed-dose combination medicinal product 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 has not yet been authorised by Swissmedic, the key data should be submitted in complete clinical documentation (see section on "Requirements for an authorisation application in the ordinary procedure according to Art. 11 TPA").

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