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01	**30.05.17**		**Formal adaptation to Swissmedic's requirements management: Administrative ordinance converted into Guidance document; content unchanged**	**fua**

1 Terms, definitions abbreviations

1.1 Terms and definitions

1.1.1 Medicinal products with known APIs

Medicinal products with known APIs are those containing an active pharmaceutical ingredient that is or was contained in a medicinal product already authorised by the Agency (Article 12, para. 1, VAZV). The basis for justifying the simplified authorisation of known APIs is the ability to refer to full documentation on a reference product[1] that is already available. Differing salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an API are considered to contain the same API as long as the applicant is able to prove that the evidence with regard to quality, safety and efficacy is transferable to the product concerned by the new application.
Medicinal products that have already been authorised for some time (> 10 years) in a foreign country (so-called APIs with well-established use) but for which no authorisation has been granted in Switzerland to date for their active pharmaceutical ingredients are therefore not considered to be known APIs.
The authorisation granted by the Agency is considered to be equivalent to a first authorisation by the Intercantonal Office for the Control of Medicines (IOCM). Active pharmaceutical ingredients that to date have only been authorised for use in veterinary medicinal products are not considered to be known APIs when first used in a medicinal product for human use.

1.1.1.1 Known APIs without innovation

A product for which the indication, dosage form, dosage strength, route of administration and dosage recommendation and also the quality, efficacy and safety are all based on a reference product already authorised by the Agency.

1.1.1.2 Known APIs with innovation

A known API with, for example, a new indication, dosage form, route of administration and / or dosage recommendation, for which the corresponding requirements as stated in the Guidance document *Authorisation of human medicine with new active substance and major variation* must be fulfilled.

1.1.2 Reference product

Swissmedic considers a medicinal product that serves as a reference product for the simplified authorisation of a known API to be one that it has authorised on the basis of full[2] documentation in line with the procedure in accordance with Article 11, TPA and that contains the same API as the product pending authorisation. A reference product is a medicinal product that is used in the application documentation for the known API as a reference for the comparability of its preclinical efficacy and safety, i.e. the results of the tests on the product serve as the basis for applying for authorisation as a known API.
An applicant may also provide test results for other products as reference material if the application is for an indication, a dosage form, a dosage strength, a dosage recommendation and / or a route of administration for the known API that was not authorised for the reference product. In such cases, the innovative aspects regarding the additional reference product must have been authorised on the basis of full documentation.

[1] See, on this subject (in German), the decision by the former Federal Appeals Commission for Therapeutic Products of 20 September 2006, for the case HM 05.147, deliberation 3.2.1

[2] i.e. all test results to which the applicants wish to refer with regard to the known API must be included in the documentation for the reference product.

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1.1.2.1 Comparator product

The comparator product is the medicinal product with which the product pending authorisation is compared in an equivalence or comparative efficacy trial (see also Sections 6.6and 7.3.6).

1.1.3 Test product / product concerned by the authorisation application

The test product is understood to be:

- The product used in the comparative investigations which is compared with the reference product or comparator product
- Or the API that is used in preclinical investigations.

The product concerned by the authorisation application and the test product must have the same composition and specifications, and must be manufactured according to the same processes. Any differences between the test product and the product pending authorisation must be described and evaluated (see Section 7.3.4)

1.1.4 Therapeutic equivalence

Two medicinal products are considered to be therapeutically equivalent if they have, within certain limits, identical efficacy and side effect profiles. Proof is obtained by means of clinical trials, using appropriate trial designs and the corresponding statistical procedure (equivalence trial with prior definition of equivalence criteria, comparison on the basis of confidence intervals, definition of appropriate end points, high protocol compliance and a sufficient sample size to ensure adequate statistical power). Alternatively, proof of therapeutic equivalence may be provided by demonstrating the pharmacokinetic or, in certain cases, the pharmacodynamic equivalence.

1.1.5 Pharmaceutical equivalence

Products are pharmaceutically equivalent if they contain the same quantity of the API in the same dosage form, and are administered under the same conditions via the same route of administration. Pharmaceutical equivalence does not necessarily imply bioequivalence, since there can be differences in the composition of the excipients and / or the manufacturing process, or resulting from other influencing variables.

1.1.6 Bioequivalence

Two medicinal products with the same API(s) are considered to be bioequivalent after administration of the same molar doses if the absorption rate (C_{max} and t_{max}) and the extent of the systemic availability (AUC) are comparable. The individual requirements with regard to trial design, measurement parameters, statistical methods, threshold values, etc. are described in the guidelines that Swissmedic considers to represent the current status of science and technology (Annexes: Clinical, and in particular *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1, Section 4.1.8 Evaluation*).

1.1.7 Biopharmaceutics Classification System (BCS)

The biopharmaceutics classification system (BCS) classifies pharmaceutical substances on the basis of their solubility in aqueous solutions and their intestinal permeability. Together with the in vitro release of the active pharmaceutical ingredient from the pharmaceutical products, the BCS takes three main factors into account, which define the rate and extent of the absorption of oral forms. For details, see *WHO Prequalification Technical Report Series 937 – Annexes 7 and 8.*

1.1.8 Biowaiver

A biowaiver is the agreement – usually from a regulatory authority – that there is no need for a bioequivalence trial to be conducted in humans, subject to certain conditions. In such cases, the proof of equivalence is provided by other investigations or from in vivo bioequivalence tests (see Section 6.6).

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1.2 Abbreviations

AMZV	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Requirements for the Authorisation of Medicinal Products (Medicinal Products Authorisation Ordinance)
ASMF	Active Substance Master File
AW	(Anweisung) Instruction
API	Active Pharmaceutical Ingredient
AUC	area under the curve
BCS	Biopharmaceutics Classification System
CHMP	Committee for Medicinal Products for Human Use
C_{max}	maximum concentration (measurement for the absorption speed of a pharmaceutical agent)
CTD	Common Technical Document for the Registration of Pharmaceuticals for Human Use
DCI	La Denominación Común Internacional
DMF	Drug Master File
eCTD	Electronic CTD document (Modules 1-5)
EMA	European Medicines Agency
GD	Guidance Document
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IOCM	Intercantonal Office for the Control of Medicines, Switzerland
INN	International Nonproprietary Name
LS	List of Pharmaceutical Specialities (Federal Office of Public Health)
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PVP	Pharmacovigilance Plan
t_{max}	Time of maximum concentration of a pharmaceutical agent (measurement for the absorption speed of a pharmaceutical agent
TDDS	Transdermal drug delivery systems
TPA	Swiss Federal Law on Medicinal Products and Medical Devices of 15 December 2000 (Therapeutic Products Act)
VAM	Ordinance of 17 October on Medicinal Products (Medicinal Products Ordinance)
VAZV	Ordinance of the Swiss Agency for Therapeutic Products of 22 June 2006 on the simplified authorisation of medicinal products and the authorisation of medicinal products by the notification procedure
WHO	World Health Organisation

2 Introduction and Objective

These instructions describe the requirements regarding the documentation to be submitted for the authorisation of human medicines with known active pharmaceutical ingredients (known APIs). The document is a guidance document intended for administrative bodies, and thus does not directly address the rights and duties of individuals. For Swissmedic, the instructions serve primarily to provide assistance in applying the legal provisions relating to the authorisation of human medicines with known APIs in a uniform and equitable manner. The publication of these instructions is intended to provide transparency regarding the requirements to be fulfilled in accordance with Swissmedic's practices.
When Swissmedic evaluates the application documentation within the framework of these instructions, it also takes into consideration – to support the evaluation and also as a reflection of the current status of science and technology – the currently valid edition of the Pharmacopoeia, the relevant Guidelines of the European Committee for Medicinal Products for Human Use (CHMP), the

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International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), technical reports by the WHO or other guidelines listed in the annex to this document.

The instructions are intended to contribute towards clearly formulating the conditions and requirements for the submission of the application and for the authorisation of human medicines with known APIs in Switzerland.

3 Scope

The instructions are valid for the simplified authorisation of human medicines with known APIs in accordance with Art. 14, para. 1, section a, Therapeutic Products act (TPA).

The instructions apply to the following types of application:

- Authorisation applications for medicinal products for which the indication, dosage form[3],, route of administration and dosage recommendation are based on a reference product with the same API that is currently or has previously been authorised by the Agency.
  Authorisation applications for medicinal products with an indication, a dosage form, a route of administration and / or a dosage recommendation that have not been or are not authorised to date for the reference products with the same API; (taking the Guidance document *Authorisation of human medicine with new active substance and major variation* into consideration
- Authorisation applications for variations relating to indication, dosage form, dosage strength, route of administration and dosage recommendation for already authorised medicinal products with known APIs; taking the Guidance Document *Authorisation of human medicine with new active substance and major variation* into consideration)
- Authorisation applications for combination medicinal products consisting of several known APIs.

These instructions do not apply to:

- Major variations of original products (see the Guidance Document *Authorisation of human medicine with new active substance and major variation*)
- The following medicinal products (see Article 12, para. 4, Ordinance on the simplified authorisation of medicinal products and the authorisation of medicinal products by the notification procedure, VAZV):

a) Immunological medicinal products
b) Blood products
c) Medicinal products containing genetically modified organisms
d) Medicinal products manufactured using recombinant technologies and processes based on hybridomas and monoclonal antibodies
e) Advanced therapies based on gene transfer methods (gene therapy)

These instructions for the authorisation of human medicines with known APIs do not apply to the product categories regulated by the following guidance document (note: some of which are not available in English):

- *Guidance document for the authorisation of biosimilar*
- *Guidance document for the authorisation of antidote*
- *Guidance document for the authorisation of allergen product*
- *Instructions for the submission of authorisation applications for herbal medicinal products for human use (Phyto Guide)*
- *Guidance document for the authorisation of medicinal gas*
- *Guidance document for the authorisation of radiopharmaceuticals.*

[3] Dosage forms are defined in the currently valid versions of the Standard Terms of Reference of the EDQM (European Directorate for the Quality of Medicines), Section 1, "Pharmaceutical dosage forms" (I.S.B.N. 92-871-5734-0)

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4 Legal basis

The simplified procedure for the authorisation of human medicines with known APIs is in particular aligned with the following aspects of the legal framework (provisions from the law and from ordinance):
Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA[4]):

- Art. 12 Second notification
- Art. 14 Simplified authorisation procedure, medicinal products with known active pharmaceutical ingredients (para. 1, section a)

Ordinance of 17 October 2001 on Medicinal Products (Medicinal Products Ordinance, VAM[5]):

- Art. 17 Protection period for original preparations (Art. 12, TPA)

Ordinance of the Swiss Agency for Therapeutic Products of 22 June 2006 on the simplified authorisation of medicinal products and the authorisation of medicinal products by the notification procedure (VAZV[6]):

- Art. 12 Basic principle
- Art. 13 Documentation on the pharmacological and toxicological tests
- Art. 14 Proof of safety and therapeutic efficacy

5 Other valid documents

Document ID
ZL000_00_006e_WL Guidance document Time limits for authorisation applications
ZL101_00_001e_WL Guidance document Authorisation of human medicine with new active substance and major variation
ZL000_00_004e_WL Guidance document Authorisation human medicine under Art 13 ATP
ZL000_00_001e_WL Guidance document Formal requirements
ZL000_00_002e_VZ Overview of documents to submitted
Anleitung zum Einreichen von Zulassungsgesuchen für pflanzliche Arzneimittel der Humanmedizin (Phyto-Anleitung) (only in German and French)

6 General requirements and basic principles for the evaluation

6.1 Authorisation applications for known APIs with the same indication, dosage form, dosage strength, dosage recommendation and route of administration as the reference product

An authorisation for a known API that is completely based on one or more reference products with the same API currently or previously authorised by the Agency with regard to indication, dosage form, dosage strength, dosage recommendation and route of administration may be applied for as follows:

- Full quality documentation must be submitted
- Proof must be provided that the evidence regarding the preclinical, clinical safety and efficacy of the reference product(s) is applicable to the medicinal produce concerned by the authorisation application (see Section 6.6)
- If the reference product(s) is / are no longer authorised, the requirements stated in Section 6.4 also apply
- For details, see Section 8.6: Overview tables 1a and 1b.

4 SR **812.21**
5 SR **812.212.21**
6 SR **812.212.23**

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6.2 Authorisation applications for known APIs with new or additional indication, dosage form, dosage strength, dosage recommendation and / or route of administration compared with the reference product

A known API submitted for first authorisation, the application for which is based on a reference product that is, or has been, authorised by the Agency and with the same API may have a new or additional indication, a new or additional dosage form, a new or additional dosage strength, a new or additional dosage recommendation and / or a new or additional route of administration compared with the reference product.

- For the new aspects that have not been authorised in Switzerland to date, it is necessary fundamentally to provide forms of proof as stipulated in *the GD / Authorisation of human medicine with new active substance and major variation*
- The documentation for the authorised reference product t can be used as a basis to support the known aspects of the API (see Section 6.1)
- If the reference product is no longer authorised, the requirements stated in Section 6.4 also apply
- For details, see Section 8.6: Overview tables 2b, 3b, 4b, 5b, 6b and 2c, 3c, 4c, 5c, 6c

6.3 Applications for variations: new indication, dosage form, dosage strength, dosage recommendation and / or route of administration for an authorised known API

Applications for variations regarding a new indication, a new dosage form, a new dosage strength, a new dosage recommendation and / or a new route of administration for authorised known APIs, may be made as follows:

- For the new aspects that have not been authorised in Switzerland to date, it is of fundamental necessity to provide forms of proof as stipulated in *the GD / Authorisation of human medicine with new active substance and major variation*
- For the known aspects, the documentation for the authorised reference product can be used as a basis to support the known aspects of the API (see Section 6.1)
- For details, see Section 8.6: Overview tables 2a, 3a, 4a, 5a, 6a

6.4 Known API using a reference product that is no longer authorised as a basis

In order for a medicinal product to be qualified as a known API, it is no longer necessary for the reference product designated in the authorisation application to be authorised at the time of submission. If a reference medicinal product as defined in Art. 12, para. 2, VAZV is no longer authorised in Switzerland at the time of submission, the following possibilities are available to applicants:

a) The applicant refers to a medicinal product that was previously authorised by the Agency and based on full documentation
   For this purpose, the applicant provides proof of safety, tolerability and efficacy of the API by means of conclusive scientific evidence (see also Section 6.9). In particular, any new evidence that has arisen with regard to efficacy, safety and tolerability of the known API (from both a clinical and preclinical point of view) and / or any new treatment options that could result in a change to the risk – benefit ratio must be analysed accordingly.
   Particular attention should also be paid to those data that were not considered during the registration of the selected reference product, as a result of additional licencing requirements that were not in force at the time of approval of the reference product. In the case of any missing data or trial results, the applicant should demonstrate why the product is nevertheless considered to be sufficiently effective and / or safe
b) The applicant may refer to the documentation for a different product that is already authorised in Switzerland at the time of submitting the application, but for which full documentation is not available. In such cases, the Agency decides on a case-by-case basis whether the documentation for the medicinal product cited instead of the reference product is sufficient to guarantee the quality, efficacy and safety of the known API (Art. 12, para. 3, section a, VAZV)

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c) The applicant may cite documentation for an authorisation application in a country with comparable medicinal product control as defined in Art. 13, TPA. The Agency decides on a case-by-case basis whether the documentation on the medicinal product used as a reference is sufficient to guarantee quality, efficacy and safety. In this case, the applicant must submit documentation in accordance with Art. 5a, para. 1, VAM (Art. 12, para. 3, section b, VAZV)
d) The applicant may refer to published scientific literature in the application (see Section 6.9). In doing so, proof must be provided that the APIs in the applicant's product have been used for at least 10 years for the indication and use applied for, and that their safety and efficacy are well documented and generally recognised in scientific literature (Art. 12, para. 3, section c, VAZV). Aspects of particular importance are the extent of clinical use of the APIs, and whether the scientific evaluations are coherent.

The following requirements also apply:

- In all of the above cases, full quality documentation must be submitted to the Agency
- For details, see Section 8.6: Overview tables 1b, 2c, 3c, 4c, 5c, 6c.

6.5 Combination medicinal products with known APIs

For the authorisation of combination medicinal products with known APIs, the requirements in accordance with Art. 6, AMZV must be fulfilled, in addition to the provisions in Sections 6.1 to 6.4 above that apply to the individual products with known APIs. Detailed information on the status of knowledge regarding the documents required when applying for the authorisation of 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 needed also in other guidelines cited in this document, in addition for preclinical aspects in particular, the ICH Guideline M3.

The following aspects must also be taken into consideration:

a) For combination packs (i.e. two or more already authorised single products to be brought together, in unchanged form, in a combined pack)

- If no changes have been made to the single products (i.e. it can be proved that the single products brought together in the combination pack are identical to already authorised products with regard to formulation and manufacturing), a reference to the single products and details of the justified shelf life and storage instructions for the combination product are sufficient for the quality documentation. If, for example, the primary packaging is changed, the correspondingly modified Modules 3.2.P.1, 3.2.P.2.4, 3.2.P.3.3, 3.2.P.7 and 3.2.P.8 must be submitted
- For further details, see Section 8.6: Overview tables 7a, 7b, 7c.

b) For combination products (i.e. a single pharmaceutical end product consisting of two or more single products in a fixed dose combination)

- Full quality documentation (Modules 2.3 and 3) must be submitted
- For details, see Section 8.6: Overview tables 8a, 8b or 8c respectively

c) For combination products containing both known and new APIs, proof in accordance with *the GD / Authorisation of human medicine with new active substance and major variation* must be provided (see Section 8.6: Overview tables 7d, 8d)

6.6 Proof of transferability of the test results of the reference product

If an application is submitted for the simplified authorisation of a known API, proof must be provided that the evidence with regard to quality, efficacy and safety that led to the authorisation of the reference product in Switzerland is transferable, with a sufficient degree of certainty, to the product pending authorisation.

The type, scope and scientific reliability of the proof required depend on the dosage form, the route of administration, the type of API (its physicochemical and pharmacological properties) and also on the indication(s) applied for. The forms of proof selected by the applicant must be summarised in a critical analysis and must be justified scientifically.

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The following forms of proof can be submitted, and these may be combined as part of an application:
- Proof of pharmaceutical quality: for details, see Section 7.3
- Proof of pharmacokinetic comparability: for details, see Section 7.5.2
- Proof of pharmacodynamic comparability: for details, see Section 7.5.3
- Proof of the therapeutic comparability in clinical efficacy / safety trials: for details, see Section 7.5.4
- In vivo bioequivalence studies may be exempted if an assumption of equivalence in in vivo performance can be justified by satisfactory in vitro data. For more details of the requirements, see the *CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98)*

The transferability of the test results can be assumed without further proof in certain situations, i.e. if both the product concerned by the authorisation application and the reference product are aqueous solutions of the same API at the same concentration, without further excipients. Further examples whereby such proof is not necessary can be found in the *CHMP Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98)*.

6.7 Requirements relating to the dosage strengths to be examined

The dosage strength(s) and single doses to be examined and any cumulative requirements to be fulfilled in order for biowaivers to be granted are described in detail in the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1, Section 4.1.6 Strength to be investigated*.

6.8 Biowaivers based on BCS

A biowaiver based on BCS for rapid-release oral dosage forms may be granted under the conditions described in detail in the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1, Appendix III*. In summary, this guideline states that the application must concern a highly soluble API (BCS Classes 1 and 3), of which at least 85% of the API(s) must be released in vitro within 15 minutes, and that the excipients must have no influence on the bioavailability. For BCS Class 3 APIs, there must also be neither an absorption window nor interactions with transporter systems, and no therapeutic risk must be linked to the possible granting of a biowaiver. Swissmedic adheres to the detailed requirements of the currently valid EMA Guideline when evaluating this type of application.

6.9 Requirements relating to various dosage forms

Swissmedic adheres to the requirements of the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1, Appendix II.*
The requirements for a biowaiver for various pharmaceutical forms with a dissolved API are described therein, with cross-references to further guidelines.

6.10 Requirements relating to any scientific data cited

In addition to the documentation on the reference product available to the Agency, an applicant may also cite any scientific data that is accessible to the public.
The following in particular are recognised as types of scientific evidence:
- Specialised scientific literature
- Extracts from databases of pharmacology, toxicology and clinical side effects of the known API
- Compilations of individual case reports that permit a scientific assessment
- Up-to-date evaluations and treatment guidelines by professional associations
- Evidence relating to the use of the authorised reference product.

The conclusiveness of the scientific data use above all depends on the quality and scope of the material and the consistency of the conclusions that can be drawn.
The following quality criteria are considered as providing a guide for the evaluation:

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- The selection criteria for the compilation of literature (search strategy, list of databases searched, service providers) are presented in a clear and transparent way. Other, non-focused search strategies are also documented
- Both favourable and unfavourable evidence is used in the analysis, and contradicting evidence is discussed
- The publications cited – usually original works – correspond to the current status of science and technology and have been, for the most part, published in peer-reviewed journals
- It is clear that the studies cited have been carried out in compliance with GCP / GLP requirements. The publications provide enough detail for the results to be extrapolated with sufficient certainty to the product concerned by the authorisation application
- The results of any epidemiological trials (including comparative trials) are submitted as a supplement to data from published, controlled clinical trials. There must be conclusive evidence that the main properties (e.g. indication, dosage strength, dosage form, dosage recommendation, route of administration) are transferable to the medicinal product pending authorisation
- Scientific publications or data from literature are submitted in full, i.e. not the abstract alone, and with references.

If more than 12 months have passed between the research and the date on which the authorisation application is submitted, a supplement updating the main document is expected, or a justification for not including more recent data and evidence should be provided.

6.11 First applicant protection

For medicinal products with known APIs (with or without innovation), no first application protection can be granted since by definition, this is only applicable for the authorisation of new APIs.
An application for the authorisation of a known API can therefore only be based on the documentation of a reference product with first applicant protection if either the time limit for the said protection has expired or a corresponding permission by the authorisation holder of the reference product is available (Art. 12, para. 1, TPA and Art. 17, para. 1, VAM). If these formal requirements are not fulfilled, Swissmedic will not process the application.
An exception to this principle is that an application will be held as "pending" if it is submitted immediately prior to the expiry (within one month) of the first applicant protection.

6.12 Product name

The name of a known API must be in accordance with Article 7, para. 3, VAM and can be either a creative name of the name of the API (name according to DCI/INN) linked to a company name. For a known API developed without innovation, use should be made of a product name that consists of the name of the API according to DCI/INN connected to the company name.

6.13 Product information

For known APIs, the information texts for healthcare professionals in sections 4-15 and the patient information in sections 3-9 must be identical to those of the reference product(s) (see Annex 4, No. 1, para. 5 and Annex 5, No. 1, para. 6 of the AMZV).
Justified differences in the above-mentioned sections are possible. Examples are:

- If the first application protection for variations to the reference product (e.g. additional indications) has not yet expired. (In the case of an application for additions to such a partial indication after the time limit for first applicant protection, the application to be submitted is for a variation requiring approval)
- If there are differences with regard to the reference product that influence the text of the product information
- If there are new indications, new dosage forms, new dosage strengths, new dosage recommendations or new routes of administration requiring authorisation

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- If the applicant demonstrates, when submitting the corresponding evidence[7], that patent protection of the partial indication is still in effect. Such a partial indication must only be published in the product information for the known API once the patent protection has expired; Swissmedic may nevertheless already authorise such a patent-protected partial indication while the patent protection is still in effect (see Art. 9, para. 1, section c of the Patent Act)[8].

Other justified deviations are possible, on request.
In cases where it is not necessarily possible to identify a single reference product, e.g. for combination products with numerous differences compared to the first products authorised with these APIs, or if the product information for the known API is based on more recent knowledge than that used for the reference product, divergences from the above-mentioned rule regarding the design of the product information may be accepted.
If a single collective information text for healthcare professionals exists that combines multiple dosage forms, it is acceptable to use only the necessary and appropriate sections of the combined document for all dosage forms of the known API, if this is consistent with the indication and dosage instructions concerned.
Subsequent updates to the product information of the reference product must be adopted and submitted to the Agency as variations to the product information requiring approval or notification. If the product information texts for the product pending authorisation are identical to those of the reference product, subsequent changes can be submitted as variations requiring notification (see Annex 8, No. 2, para. 1, no. 4, AMZV[9]). The status of the product information for this known API is then the same as for the reference product.

In all cases where the reference product is no longer authorised, i.e. for which reference cannot be made to current product information, the applicant must provide updated information for healthcare professionals and patients, with reference to the new aspects.

6.14 Packaging materials

Medicinal products with known APIs without innovation and that contain no more than three APIs must, in accordance with Annex 1, No. 1, para. 4, AMZV[10], show the name of the APIs on the outer packaging (in the form of their usual international abbreviated designation (INN)) as follows:

- If, following the authorisation by Swissmedic, the applicant intends to apply for the product to be included in the FOPH LS as a medicinal product that is interchangeable with an original product (i.e. a generic), the names of the APIs must be placed directly before the trade name or company name.
- In other cases, the name of the APIs must be placed directly underneath the trade name.

The applicant states, in the cover letter, whether it is intended to have the product included in the LS as a generic.

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*.
If a comparator product obtained abroad is used in the bioequivalence trial(s), the data on the foreign comparator product must be submitted in Module 1 and mentioned in the cover letter. A tabulated summary of the comparison criteria between the foreign comparator product and the Swiss reference product must be provided.

7 e.g. extract from the registry of patents, showing the expiry date of the corresponding partial indication
8 SR **232.14**
9 SR **812.212.22**

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For applications requesting that the test results of foreign authorities are taken into consideration, the requirements of the Guidance Document *Authorisation human medicine under Art 13 ATP* must also be fulfilled.

7.2 Overviews and summaries (Module 2)

7.2.1 Quality Overall Summary (Section 2.3)

A full Module 3 is required for known APIs (with and without innovation). A summary of these data must be provided in the Quality Overall Summary (Section 2.3), as two separate copies.

7.2.2 Nonclinical Overview (Section 2.4)

A summary of nonclinical experimental and / or bibliographical data on pharmacodynamics, pharmacokinetics and toxicology, as well as a risk assessment, must be submitted in the Nonclinical Overview (Module 2.4).
New experimental trials must be listed under Section 2.4.1, Overview of the Nonclinical Testing Strategy, with the trial titles. The status of the quality system for safety-relevant trials (in accordance with GLP) must be provided. Trials included in Section 2.6, *Nonclinical Written and Tabulated Summaries* must be summarised, and the trial results must be documented in Module 4.
If no experimental trials have been carried out, justification for their omission must be provided in Section 2.4.1. When referring to a reference product, bibliographical data are sufficient. In both cases, the applicant must clarify initially in the cover letter whether or not the application includes experimental nonclinical data.
The document should not be more than five years old and should correspond to the requirements relating to scientific evidence (see Section 6.10). Updates to reflect the current status of knowledge should also be mentioned with regard to the information for healthcare professionals (e.g. in the area of safety pharmacology potential QTc interval extensions).
When using new excipients or different excipients from those used in the reference product, a critical assessment of the possible safety relevance must be provided.
New impurities in comparison with the reference product, or those that do not fall within the specifications with regard to their toxicity and genotoxicity must be analysed, and if appropriate examined in accordance with the *Note for Guidance on Impurities in New Drug Substances, ICH Topic Q3A (R2), October 2006*, und *Impurities in New Products, ICH Topic Q3B (R2), June 2006*.
Regarding impurities, the *Guideline on the Limits of Genotoxic Impurities EMEA/CHMP/QWP/251344/2006* should in particular be taken into account.
If new aspects are applied for in comparison with the reference product, documentation on the new aspects must be submitted in accordance with the principles for assessment stated in the *GD / Authorisation of human medicine with new active substance and major variation*, and must be critically analysed in order to prove the efficacy and safety of use of the medicinal product concerned by the authorisation application (benefit – risk ratio).
For topical forms, experimental trials on local tolerance to the product and on systemic exposure to the API must be provided. For transdermal drug delivery systems (TDDS) experimental trials for local tolerance (irritation and sensitisation) should be conducted on animals (see also Section 7.5.8). These studies may only be omitted if it can be demonstrated that the product pending authorisation is identical to the reference product.
For combination products, please see ICH M3. In particular, clarifications regarding potential pharmacodynamic and pharmacokinetic interaction risks must be provided.

7.2.3 Clinical Overview (Section 2.5)

A summary of all data from Module 5 must be submitted in the Clinical Overview (Section 2.5).

Known API without innovation:
If the authorisation application is entirely based on the documentation for a currently authorised reference product, only the summary of those investigations proving that the evidence obtained from the reference product is applicable to the product pending authorisation need be submitted in the

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Clinical Overview. The methodology of the investigations used and their results must be critically assessed and compared with results from the literature.
Justification of why the proof of therapeutic equivalence can be omitted must also be provided in the Clinical Overview. The design of the trials used for the authorisation application must be described in line with the current guidelines (in accordance with the Annex: Clinical aspects) on the basis of the pharmacological and Galenic properties of the medicinal product. More details on this subject can be found, in particular, in *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1, Section 4.1*.
A critical analysis should be provided to indicate whether the pharmacokinetic data and its variability, are in accordance with the published data in the reference product information or any data from peer reviewed publications (reprints to be submitted in Section 5.4).
For therapeutic equivalence trials, a critical discussion should particularly address the sensitivity of the study and if applicable, existing differences in efficacy should be identified. Where necessary, the values for the absolute differences with regard to the primary end points should be discussed with regard to their clinical relevance (Delta).
With regard to a possible biowaiver for various dosage strengths, the pharmacokinetic properties, and particularly the linearity of the absorption in the entire therapeutic range must be discussed and justified by means of detailed references. In the case of non-linearity, justification must be provided as to whether the increase in the AUC is too high or too low in proportion to the dose (*Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1, Section 4.1.6 Strength to be investigated*). In the event that high dosage strengths cannot be investigated in healthy volunteers for reasons of safety or tolerability, single dose or multiple dose trials on patients are recommended as an alternative option (above-mentioned document, *Section 4.1.1 Alternative Designs*).

Known API with innovation:
If new aspects are applied for the proposed medicinal product compared to those authorised for the reference product, the documentation submitted to prove the efficacy and safety of use regarding the new aspects must be fully evaluated and critically assessed (in accordance with the Guidance Document *Authorisation of human medicine with new active substance and major variation)*.

Reference product that is no longer authorised:
If the authorisation application concerns a reference product that is no longer authorised in Switzerland at the time of submission, the evidence obtained during the time since the expiry of the authorisation of the reference product, and in particular any published data on efficacy and safety (e.g. reports of adverse reactions) should also be included in the Clinical Overview and must be critically assessed. This assessment must also include the significance of the proposed product in comparison with newer treatment options for the claimed indications have become available in the intervening period. An assessment of the current risk – benefit ratio must be provided on the basis of literature that has been identified, and also with respect to guidelines from scientific associations or the results of consensus conferences.

7.2.4 Nonclinical Summary (Section 2.6)

A Nonclinical Summary (Section 2.6) must be submitted if data from experimental studies are submitted by the applicant.

7.2.5 Clinical Summary (Section 2.7)

A Clinical Summary must be submitted if the product concerned by the authorisation applicant refers to a product that is no longer authorised or if major new aspects are applied for.

7.3 Analytical, chemical and pharmaceutical documentation (Module 3)

7.3.1 General aspects

The analytical, chemical and pharmaceutical quality of a known API must be documented in accordance with Art. 3, AMZV. Relevant guidelines by the ICH and the EMA should be taken into consideration (see Section 8). The requirements of the Ph. Eur and the Ph. Helv. must be fulfilled. If

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other methods are used, their equivalence to the methods of the Ph. Eur. and the Ph. Helv. must be proved.
The presentation of analytical, chemical and pharmaceutical data is described in the ICH Guideline *Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality-M4Q. Quality Overall Summary of Module 2, Module 3: Quality*.
Concerning the scope of the documentation, see Sections 6.1 to 6.4 and Section 8.6:Overview tables.

7.3.2 Comment regarding the active pharmaceutical ingredient

If several manufacturers of the APIs are concerned, the applicant must submit consolidated specifications that are valid for all manufacturers. In the case of a test parameter having several acceptance criteria or methods, the manufacturer-specific tests must be referred to (e.g. residual solvent "at manufacturer X"). *(Guideline on Active Substance Master File Procedure, EMEA/CVMP/134/02 and CPMP/QWP/227/02).*
For further details in connection with the use of a Drug Master Files (DMF)/Active Substance Master File (ASMF) or the use of a Certificate of Suitability (CoS) see the Annex to this document or the *Swissmedic Journal 01/2006, pp. 46-49: Regulatory News: Drug Master* and the *Guideline on Active Substance Master File Procedure, EMEA/CVMP/134/02 and CPMP/QWP/227/02 .*

7.3.3 Impurities

Impurities in the API, the finished products and if applicable degradation products that occur during storage must be discussed. Any differences in the impurity profiles between the reference product and the proposed product must be evaluated (see Section 7.3.5). The currently valid pharmacopoeia monographs and current guidelines (e.g. *ICH Q3, EMEA/CHMP/QWP/251344/2006*) must be taken into consideration.

7.3.4 Test product

The batch size of the test product used for the bioavailability study or clinical trial must not for solid forms, be less than 10% of the production batch size or 100,000 units (the alternative representing the higher number of the two must be selected). If f a production batch is smaller than 100,000 units, a full production batch must be used.
In the case of bioequivalence trials, the content difference between the test and the reference product (identified by means of the test method for batch release) should not be greater than 5%.

The following details and documents are necessary with regard to the test product:

- Composition; manufacturer and manufacturing site; batch size; manufacturing date, expiry date or retest date; batch number; study number (stating the purpose of the study / study title)
- Batch number and manufacturer of the API used to manufacture the test product, including analysis results or the analysis certificate
- Proof of consistency between batches (between bio-, scale-up, validation, stability and production batches). For bioequivalence studies with the same dosage form, a comparison between the test and reference product is also required. For solid dosage forms, a comparison of the in vitro active ingredient release profile is required. The comparative examination should include the following types of batches: test product versus reference product, test batch versus validation, stability and / or production batch. A comparison between test and reference product for different dosage forms should also be carried out if possible (e.g. regarding content and purity). These investigations must be conducted and documented in line with the relevant guidelines (see Annex). The results must be presented in a clear, summarised form
- The analysis certificate for the test product used should be included
- A signed confirmation that the test product used is identical to the product pending authorisation should be supplied. Should this requirement not be fulfilled, the differences must be described and evaluated (see Section 1.1.3, Test product).

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7.3.5 Results of toxicology and clinical investigations

The result of any toxicology investigations (e.g. diverging forms of APIs, impurities) and clinical trials (e.g. results of the bioequivalence trial or in vitro or in vivo correlation trials) must be summarised in Module 3 (e.g. in the section 3.2.S.4.5 Justification of Specification / 3.2.P.2 Pharmaceutical development / 3.2.P.5.6 Justification of specification) and reference must be made to the original articles in Modules 4 or 5.
An overview of this summary must be presented in the Nonclinical Overview, with a cross-reference to the corresponding section in Module 3.

7.3.6 Comparability of a foreign comparator product with the Swiss reference product (pharmaceutical bridging)

If a product from a foreign country is used, the data on the foreign comparator product must be submitted in Module 1 and mentioned in the cover letter. All of the comparison criteria between the foreign comparator product and the Swiss reference product listed below must be included, presented as a tabulated comparison, and evaluated.
A comparator product from a foreign country may be used as such as long as it fulfils all of the criteria listed below for proving comparability with the Swiss reference product:

1st The product is authorised in a country with comparable medicinal product control as described in Art. 13, TPA. A current list of these countries is published on the Swissmedic website
2nd The following must be stated: name and address of the authorisation holder of the foreign product used, the product name, the country of authorisation, country of origin, source of the product (address of wholesaler or pharmacy), authorisation number, batch number, expiry date and analysis certificate
3rd If the foreign comparator product is used in a bioequivalence study, proof must also be provided of a comparable qualitative and quantitative active substance composition and qualitative excipient composition. If the data available indicate the possibility of differences, or if such differences are proven to exist, it is necessary to demonstrate that they have no effect on efficacy, safety and tolerance. Reference may be made to scientific literature in this connection
4th For solid dosage forms used in a bioequivalence study, differences with regard to the pharmaceutical forms used (tablets, film-coated tablets, capsules etc.) must be evaluated. The dimension and weight and, for products with modified release, the release principle must be defined
5th In order to define the similarity, in vitro active substance release profiles under various pH conditions must be carried out in accordance with the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1, Section 4.2. In vitro dissolution tests* and Appendix I.

7.3.7 Scorability test and test for uniformity of single doses

If dosage recommendations involving half tablets are intended for a known API, the dose accuracy must be demonstrated by testing the scorability of tablets and, for single-dose pharmaceutical forms, the uniformity of doses must be tested. The tests must be conducted in accordance with the requirements of the European Pharmacopoeia (Ph. Eur. Nr. 2.9.40).

7.4 Nonclinical and toxicology documentation (Module 4)

The documentation of the pharmacology and toxicology tests for a known API must be compiled as described in Art. 4, AMZV and must correspond to the current status of knowledge. The presentation of nonclinical data is described in the ICH Guideline*: 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 conducting studies, the relevant guidelines of the ICH and of the EMA must be taken into consideration (see Annex). Any safety-relevant investigations must be conducted in line with the *Ordinance on Good Laboratory Practice* (GLPV) of 18 May 2005.
The results from experimental, nonclinical studies and bibliographical documents must be submitted in Module 4.

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7.5 Clinical documentation (Module 5)

7.5.1 General aspects

The presentation of clinical data is described in the ICH Guideline: *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)*. Trial reports concerning the applicant's own trials conducted for the application (e.g. bioequivalence trials, comparative bioavailability trials, Phase 3 trials to justify new indications) should be written in accordance with the *ICH E3 Guideline (Structure and Content of Clinical Study Reports)* as is the case for new APIs.
The applicant's own trials must be conducted in accordance with the GCP guidelines. The relevant ICH guidelines and those of the EMA should also be taken into consideration.
The EMA Guidelines listed in the Annex are commented on below with regard to the requirements for the clinical documentation for a known API.
The possibility of proving that the test results for the reference product are transferable to a known API for which a new application is submitted, or to a variation thereof - as described in Section 7.6 – are described in more detail below. Emphasis is placed on those points that must be given particular attention with regard to the clinical documentation.

7.5.2 Pharmacokinetic comparability (pharmacokinetic bridging)

For a known API with the same indication, dosage strength, dosage recommendation and route of administration as the reference product, pharmacokinetic bridging can be applied. The pharmacokinetic proof that the efficacy and safety results of the reference product are transferable is primarily based on bioequivalence data or comparative bioavailability studies.
The required extent of the equivalence depends on both the dosage form, the route of administration, the type of API (its physical-chemical and pharmacological properties) and on the indication(s) claimed in the authorisation application.
For the proof of bioequivalence and conducting of bioavailability studies or the granting of a biowaiver, the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1*, applies. In this guideline, the requirements for the design, execution and evaluation of bioequivalence trials for (oral) rapid-release dosage forms with systemic effect are also described in detail. In Appendix II, the requirements for the various dosage forms are described, according to whether bioequivalence data are necessary or if a biowaiver can be granted.
Reports of pharmacometric analyses must written up in accordance with the instructions in the *Guideline on Reporting the Results of Population Pharmacokinetic Analyses (CHMP/EWP/185990/06)*.
If bioequivalence trials or comparative bioavailability studies are not possible, e.g. because the reference product is no longer on the market, the results of pharmacokinetic trials with the product pending authorisation can be compared with results of pharmacokinetic trials with the reference product published in the literature.

7.5.3 Pharmacodynamic comparability (pharmacodynamic bridging)

The requirements for pharmacodynamic bridging are the availability of a quantifiable end point for clinical efficacy or a validated, reproducible biomarker with a proven relation to the clinical effect.
When assessing pharmacodynamic equivalence trials, Swissmedic in particular takes the following aspects into consideration, in addition to the fulfilment of the scientific and ethical principles valid for all clinical trials:

- The trial was conducted with a sufficiently large sample size, the number of the test subjects to be recruited was defined as a result of preliminary trials or meticulous research into literature according to scientific and statistical criteria, and the planning is well documented
- Before being included in the clinical trial, the trial subjects underwent a preliminary examination to exclude non-responders to the API. The procedure in this connection and the criteria used are defined prospectively in the trial plan
- If the trial concerned patients, the natural progression of the disease must have been taken into account when planning the trial design, and the reproducibility of the baseline was demonstrated

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- The statistical analysis of the results was defined prospectively and is in line with recognised scientific criteria, such as those also used for pharmacokinetic trials. The choice of the acceptance thresholds for the decision regarding equivalence has been justified scientifically by the applicant in the trial protocol, taking into consideration the disease to be treated
- The method used to measure the pharmacodynamic values has been validated with regard to precision, accuracy, reproducibility, specificity and robustness
- Objective values were used, and subjective end points such as scales or scores (e.g. verbal rating scales or visual analogue scales) have been avoided to the greatest possible extent
- A dose-effect curve was identified in advance. In the trial itself, several doses distributed over the dose-effect curve were investigated. If only a single dose was investigated, the comparison of the test and reference product took place in a range in which changes to the dose or to the concentration had clear effect on the pharmacodynamic response. Neither the test nor the reference product led to a maximum response during the investigation, otherwise differences between the two products would not be detectable
- The measurement of the end point or biomarker took place on a recurring basis, over an appropriate period of time
- If the pharmacodynamic response to the API could be measured continuously, the evaluation – as is the case for pharmacokinetic trials – also includes the parameters area under the effect – time curve, the maximum response and the time to maximum response
- The trials were conducted with a double blind design. For pharmacodynamic investigations in general, this is more critical than in pharmacokinetic studies, since pharmacodynamic parameters are more easily influenced
- In situations where a clear placebo effect is to be expected, a placebo group was included in the trial design
- If possible, a crossover design was selected, and a parallel group comparison was preferred
- No post-hoc adjustment of the equivalence criteria took place.

While it is rarely possible to fulfil all of the above-mentioned criteria in a single trial, taking these points into consideration increases the likelihood that Swissmedic will consider the results of a trial to be acceptable for confirming a sufficient degree of equivalence between the test and reference product.

7.5.4 Proof of therapeutic comparability in clinical efficacy / safety trials

Although proof of therapeutic equivalence (see Section 1.1.4) is the true objective of evidence of transferability of test results as described in Section 6.6, this proof is usually obtained by means of surrogate values, such as plasma profile (for pharmacokinetic bridging, see Section 7.5.2), because the necessary studies (bioequivalence or bioavailability trials) are simpler and can be conducted by following a generally recognised plan.
For cases in which the plasma profiles are not measurable or are not relevant to the therapeutic effect of the API (e.g. products for topical use) and for which no useful or appropriate pharmacodynamic parameters (see Section 7.5.3) are available, therapeutic comparative trials must be conducted on patients for provision of the necessary evidence. The results of therapeutic comparative trials must be compared using appropriate statistical tests, whereby pre-defined, medical and scientific non-inferiority margins are respected.
The following principles for the methodology of clinical comparative trials can be specified:

- The primary target parameter for proving non-inferiority by means of statistical analysis is a clinically relevant end point for the indication investigated, whose change in the course of the treatment with both compared products (and possibly placebo) can be identified as objectively as possible. Often this will be the parameter that was used in clinical trials which have led to the authorisation of the reference product. In all cases, comprehensive scientific proof must be provided to justify the choice of the parameter.
- The choice of the non-inferiority margin must be justified on a case-by-case basis, and take into consideration the type and severity of the indication to be treated with the product (including the natural progression of the diseases), the therapeutic alternatives available and their efficacy, and the common standards that are either defined in guidelines or the literature

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- It is essential to prove that the efficacy (and possibly safety) parameters that are investigated make it possible to identify any differences between the safety and efficacy of the products investigated (assay sensitivity). In particular, if the difference between the efficacy of the reference product compared to the placebo is too small according to relevant literature, a three-arm study including a placebo group is required in order to provide a sufficient level of assay sensitivity. If the trial demonstrates a statistically significant difference – in line with data from literature – between the effect of the reference product and the placebo, there is a strong argument for the assay sensitivity being sufficiently sensitive. The maximum Delta limits for non-inferiority that were predefined for the trial must take this expected difference into consideration.

In addition to the points stated above, the *ICH Guideline E 9: Statistical Principles for Clinical Trials und E-10 Choice of Control Group and Related Issues*, and in particular *Section 1.5 1.5 Assay Sensitivity and the CPMP Guideline: Choice of a Non-Inferiority Margin* should be taken into consideration.

7.5.5 Post-marketing surveillance studies

Post-marketing surveillance studies may be submitted: not as proof that of transferability of the test results of the reference products, but as a possibility of proving the safety and efficacy of the known API concerned by the authorisation application. It is essential that such studies fulfil the following quality requirements:

- Systematic, objective and targeted data collection with valid criteria that are appropriate for measuring safety and efficacy
- Sufficiently large sample size of the target population
- Standardised, scientific assessment of the data.

"Registry-relevant post-marketing surveillance studies" on a large number of patients usually fulfil these requirements.

7.5.6 Bibliographical documentation

The efficacy and safety of the known API pending authorisation can also be proved by bibliographical documentation or scientific data as long as the applicant can demonstrate that the results are transferable to the medicinal product. The quality criteria to be fulfilled with regard to these scientific data are described in Section 6.9.

7.5.7 Proof of tolerance

Proof of sufficient tolerance can usually be provided within the framework of the trials conducted. Exceptions may exist (e.g. regarding TDDS, see below).

7.5.8 Formulations with Transdermal Drug Delivery Systems

For TDDS, single dose and multiple dose trials are usually necessary, particularly in order to quantify any accumulation. A "replicate design' is usually required.
A biowaiver for dosage strengths other than the highest strength, is only possible on condition that the formulations are precisely proportional and the composition is identical. The dosage strength must be proportional to the effective area of the skin.
Since the effective release rates of TDDS are defined by the gradients between the API released in the test plaster (which is usually not identical in its construction to the reference plaster) and the individual’s skin as the point of absorption, in order for a biowaiver to be permitted the absolute release rates must be known and be comparable. This is particularly relevant when the absolute release rate explicitly defines the dosage strength.
The local tolerance and adhesion capacity can be investigated within the context of the bioequivalence study. In particular, specific clinical trials with the test plaster are required to investigate the phototoxic potential and the immunological sensitisation. Specific investigations into long-term use (such as the Repeated Insult Patch Test (RIPT)), involving a large number of patients ($n \approx 100$) are required in order to clarify the contact allergy potential.

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8 Annexes

8.1 Principle

When evaluating an application for the authorisation of a known API, Swissmedic refers to international guidelines as a reflection of the current status of science and technology. This includes, in particular, the currently valid versions of the *Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)* and the European Medicines Agency (EMA) – Committee for Medicinal Products for Human Use (CHMP).

8.2 General international guidelines

- ICH Guidelines
  - 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
- Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1
- WHO Technical Report Series 937 – WHO Expert Committee on Specifications for Pharmaceutical Preparations
- WHO Technical Report Series 937 (Annex 7, S.347) Multisource (generic) pharmaceutical products: guidelines on registration requirements to *establish interchangeability*
- WHO Technical Report Series 937 (Annex 8, S.391) Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms
- Investigation of Chiral Active Substances 3CC29a
- Guideline on the Limits of Genotoxic Impurities (CPMP/SWP/5199/02; EMEA/CHMP/QWP/251344/2006

8.3 Quality guidelines

The guidelines mentioned below are shown in connection with the requirements for Modules 2.3 and 3. Other relevant guidelines for specific requirements can be found in the EMA Overview List, including the Quality Guidelines for human medicines (see Human Medicines: Scientific Guidelines: Quality Guidelines)

Active pharmaceutical ingredient

- Guideline on Control of Impurities of Pharmacopeial Substances: Compliance with the European Pharmacopeial General Monograph Substances for Pharmaceutical Use and General Chapter Control of Impurities in Substances for Pharmaceutical Use (CPMP/QWP/1529/04)
- Active Substance Master File Procedure (EMEA/CVMP/134/02 Rev 1; CPMP/QWP/227/02 Rev 1)
- Active Substance Master File Procedure (EMEA/CVMP/134/02 Rev 2 Consultation; CPMP/QWP/227/02 Rev 2 Consultation)
- *Summary of Requirements for Active Substances i*n the Quality Part of the Dossier (CHMP/QWP/297/97 Rev. 1/EMEA/CVMP/1069/02)
- Regulatory News: Drug Master Files (Swissmedic Journal 01/2006, pp.46-49 (German and French only))
- Regulatory News: New form for the submission of Drug Master Files (Swissmedic Journal 01/2010, pp.39-40, (German and French only))

Finished product:

- Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)

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- Pharmaceutical Development (ICH Q8 (R2)) (EMEA/CHMP/167068/2004 – ICH) (replaces Annex)
- Quality of Modified Release Products A) Oral Solid Dosage Forms B) Transdermal Dosage Forms Section I (Quality) (CPMP/QWP/604/96)
- Note for Guidance on Manufacture of the Finished Dosage Form (CPMP/QWP/486/95)
- Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02, rev 1 corr)
- Note for Guidance on In-use Stability Testing of Human Medicinal Products (CPMP/QWP/2934/99)
- Regulatory News: Change of practice regarding instructions for storage (Swissmedic Journal 02/2009, pp. 112 / 113 (German and French only))

8.4 Nonclinical guidelines

The guidelines mentioned below are shown in connection with the individual sections of the current instructions regarding the requirements for Modules 2.4 and 4. Other relevant guidelines for specific requirements or sub-modules can be found in the EMA Overview List on Non-Clinical Guidelines.

- ICH Safety and Multidisciplinary (M3, M4) Guidelines for Non-Clinical Testing (Overview)
- Ordinance on Good Laboratory Practice (GLPV) of 18 May 2005 (SR813.112.1)
- Guideline on the Environmental Risk Assessment of Human medicines (CHMP/SWP/4447/00 corr 1*)

8.5 Clinical guidelines

The guidelines mentioned below are shown in connection with the individual sections of the current instructions regarding the requirements for Modules 2.5 and 5. Other relevant guidelines for specific requirements or sub-modules can be found in the EMA Overview List, Clinical Efficacy and Safety Guideline.

- Guideline on reporting the results of population pharmacokinetic analyses CHMP/EWP/185990/06
- Guideline Choice of a Non-Inferiority Margin CPMP/EWP/2158/99
- Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and clinical evaluation) CPMP/EWP/280/96
- Note for Guidance on the Clinical requirements for locally applied, locally acting products containing known constituents CPMP/EWP/239/95
- Guideline on fixed combination medicinal product CPMP/EWP/240/95 Rev.1
- Points to Consider on Clinical Investigation of Medicinal Products in the Chronic Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD) (CPMP/EWP/562/98), including specific requirement for the paediatric population
- Note for Guidance on Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95 rev 1
- Guidelines for registration of fixed-dose combination medicinal products WHO Technical report series, No. 929, 2005: Annex 5
- ICH E3 Structure and Content of Clinical Study Reports
- ICH E6 (R1) Guideline for Good Clinical Practice
- ICH E8 General Considerations for Clinical Trials
- ICH Guidelines E 9 Statistical Principles for Clinical Trials
- ICH Guidelines E 10 Choice of Control Group and Related Issues

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8.6 Overview tables regarding the documentation required

Table 1: Authorisation applications for known APIs that are fully based on one or more reference products with the same API already authorised by the Agency with regard to indication, dosage form, dosage recommendation and route of administration

Application	***Quality requirements***	***Clinical requirements***	***Preclinical requirements***	***Requirements for product information***
1a) Reference to test results for an authorised reference product (can contain one or more known APIs)	Full quality documentation consisting of Module 2.3 + Module 3; CEPs and DMFs are accepted	Documentation proving that the test results for the reference product are transferable to the proposed product (Section 6.6)	Bibliographical summary in Module 2.4; justification for not submitting experimental trials; if applicable, special evaluation on impurities and new or critical excipients	Must correspond to the product information for the reference product; divergences possible in justified cases and if proved, except for safety-relevant sections (pregnancy / breast feeding, preclinical data, interactions)
1b) Reference to product authorised by Swissmedic or the IOCM if reference product is currently no longer authorised	As for 1a)	As for 1a) plus literature update dating from the point that the product was no longer on the market	As for 1a) plus literature update dating from when the product was no longer on the market	Prepare new product information with references, on the basis of the old product information for the reference product, including current literature or foreign reference products

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Table 2: Authorisation applications for known APIS with new or additional indication that is not, or has not been, authorised for the reference product

Application	***Quality requirements***	***Clinical requirements***	***Preclinical requirements***	***Requirements for product information***
2a) new, additional indication for known API that is already authorised	If the product remains the same, Swissmedic is in possession of the quality documentation. If the quality documentation has changed because of the new indication (e.g. scorability of tablets), an expanded Module 3.2.P must be submitted with a list of changes.	For the new indication: documentation in accordance with the *GD / Authorisation of human medicine with new active substance and major variation*, i.e. clinical trial data must be submitted on the new indication	Prepare critical safety-relevant points relating to the new indication in Module 2.4. As a rule, new experimental trials must be submitted for newly identified risks or extension of the duration of use	New indication plus, if applicable, expand on its effect on safety-relevant aspects in the existing product information; otherwise, the texts of the product information must correspond to those of the authorised product
2 b) new known API with additional indication compared with the currently authorised reference product[10]	As for 1a)	Combination of 2a) and 1a)	Combination of 2a) and 1a)	Combination of 2a) and 1a)
2 c) new known API with additional indication compared with the product that is no longer authorised[11]	As for 1a)	Combination of 2a) and 1b)	Combination of 2a) and 1b)	Combination of 2a) and 1b)

[10] Reference product is authorised but does not have this additional indication
[11] Reference product was authorised but did not have this additional indication

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Table 3: Authorisation applications for known APIS with new or additional dosage strength that is not, or has not been, authorised for the reference product

Application	***Quality requirements***	***Clinical requirements***	***Preclinical requirements***	***Requirements for product information***
3a) new, additional dosage strength for known API that is already authorised	A full Module 3.2.P. must be submitted	Justification for new dosage strength and proof that it is appropriate and that the clinical results for the previous dosage strengths can be transferred to the new dosage strength	Include critical safety-relevant points in Module 2.4 (for lower safety margins between exposure from animal experiments and from treatment on humans)	Expand product information to include new dosage strength (usually in combination with new dosage instructions). Changes to the section "Preclinical data" only necessary for new safety margins
3b) new known API with additional dosage strength compared with the currently authorised reference product	As for 1a)	Combination of 3a) and 1a)	Combination of 3a) and 1a)	Combination of 3a) and 1a)
3c) new known API with additional dosage strength compared with the reference product that is no longer authorised	As for 1a)	Combination of 3a) and 1b)	Combination of 3a) and 1b)	Combination of 3a) and 1b)

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Table 4: Authorisation applications for known APIs with new or additional dosage form[12] that is not, or has not been, authorised **for the reference product**

Application	***Quality requirements***	***Clinical requirements***	***Preclinical requirements***	***Requirements for product information***
4a) new dosage form for known API that is already authorised	As for 1a)	Proof that the clinical results for the authorised dosage form are transferable to the new form in accordance with Section 6.6 or own clinical trial(s) to prove efficacy and safety in accordance with the GD / *Authorisation of human medicine with new active substance and major variation*	As for 1a): Submit experimental study data for the formulation. For topical forms, and additionally: local tolerance and systemic exposure should be taken into account in particular	As for 1a) plus, if applicable, necessary additions to the section "Preclinical data, pregnancy / breast feeding and ADRs for the new dosage form
4b) new known API with additional dosage form compared with the currently authorised reference product	As for 1a)	Combination of 4a) and 1a)	Combination of 4a) and 1a)	Expand product information for the reference product with details on the new dosage form 4a) and 1a)
4c) new known API with additional dosage form compared with the reference product that is no longer authorised	As for 1a)	Combination of 4a) and 1b)	Combination of 4a) and 1b)	Combination of 4a) and 1b)

[12] Usually combined with new dosage strength, new dosage recommendation and additional indication

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Table 5: Authorisation applications known APIS with new or additional dosage recommendation that is not, or has not been, authorised **for the reference product**

Application	***Quality requirements***	***Clinical requirements***	***Preclinical requirements***	***Requirements for product information***
5a) new dosage recommendation for known API that is already authorised	If the product remains the same, Swissmedic is in possession of the quality documentation. If the quality documentation has changed because of the new dosage recommendation (e.g. scorability of tablets), an expanded Module 3.2.P must be submitted with a list of changes	For the new dosage recommendation, documentation in accordance with the *GD / Authorisation of human medicine with new active substance and major variation*, i.e. clinical trial data must be submitted for the dosage recommendation	Include critical safety-relevant points in Module 2.4 and prepare risk – benefit ratio assessment with regard to the new dosage recommendation, with particular emphasis on the safety margins	As for 1a) plus additions for the new dosage recommendation
5 b) new known API with additional dosage recommendation compared with the currently authorised reference product	As for 1a)	Combination of 5a) and 1a)	Combination of 5a) and 1a)	Combination of 5a) and 1a)
5c) new known API with additional dosage recommendation compared with the reference product that is no longer authorised	As for 1a)	Combination of 5a) and 1b)	Combination of 5a) and 1b)	Combination of 5a) and 1b)

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Table 6: Authorisation applications for known APIS with new or additional route of administration that is not, or has not been, authorised for the reference product

Application	***Quality requirements***	***Clinical requirements***	***Preclinical requirements***	***Requirements for product information***
6a) new route of administration for known APIs that are already authorised	If the product remains the same, Swissmedic is in possession of the quality documentation. If the quality documentation has changed because of the new route of administration (e.g. different injection needles), an expanded Module 3.2.P must be submitted with a list of changes	For the new route of administration, documentation in accordance with the *GD / Authorisation of human medicine with new active substance and major variation* must be submitted	As for 1a): Submit experimental study data for the new route of administration. In addition, for topical forms: particular emphasis should be given to local tolerance and systemic exposure	As for 1a) plus additions for the new route of administration
6b) new known API with new route of administration compared with the currently authorised reference product	As for 1a)	Combination of 6a) and 1a)	Combination of 6a) and 1a)	Combination of 6a) and 1a)
6c) new known API with new route of administration compared with the reference product that is no longer authorised	As for 1a)	Combination of 6a) and 1b)	Combination of 6a) and 1b)	Combination of 6a) and 1b)

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Table 7: Combination pack with known APIs

Application	***Quality requirements***	***Clinical requirements***	***Preclinical requirements***	***Requirements for product information***
7a) new combination pack consisting of two or more single products that have already been authorised, with unchanged dosage form, and for which combined use is not yet authorised	If there is to be no change to the single products, a reference to the single products and provision of the justified shelf life plus storage instructions for the combination pack. In the case of changes (e.g. to the primary packaging), the modules affected by these changes (e.g. 3.2.P.1, 3.2.P.2.4, 3.2.P.3.3, 3.2.P.7 and 3.2.P.8) must be submitted together with a list of changes	Justification for the combination pack, taking into account possible pharmacokinetic, pharmacodynamic and clinical interactions and proof of superiority of the combined use, for which clinical trials in accordance with the *GD / Authorisation of human medicine with new active substance and major variation* and Art. 6, AMZV must be submitted	Bibliographical references to potential benefits and risks (in particular, clarification regarding potential risks of interactions); references to preclinical and clinical data (ICH M3)	New product information containing references must be prepared using the product information from the single products
7b) as for 7a), but combined use is authorised	As for 7a)	Justification for the combination pack	Justification for the combination pack	New product information containing references must be prepared using the product information from the single products
7c) new combination pack of two or more single products that are no longer authorised, with unchanged dosage form: combined use is, or has been, authorised	As for 1a)	Combination of 7b) and 1b)	Combination of 7b) and 1b)	New product information containing references must be prepared using the product information from the single products
7d) combination pack consisting single products with known and new APIs	As for new APIs	As for new APIs	As for new APIs	As for new APIs

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Table 8: Combination product with known APIs

Application	***Quality requirements***	***Clinical requirements***	***Preclinical requirements***	***Requirements for product information***
8a) new combination product consisting or two or more currently authorised known APIs that are newly combined in a single dosage form and whose combined used is not yet authorised	As for 1a)	Proof of superiority of the combined compared with the single products, for which - among other aspects -clinical trials in accordance with the *GD / Authorisation of human medicine with new active substance and major variation* and Art. 6, AMZV must be submitted (Section 6.5)	Bibliographical references to potential benefits and risks (in particular, clarification regarding potential risks of interactions); references to preclinical and clinical data (ICH M3)	Adjustment of the product information with regard to the reference products (prepare new information for healthcare professionals and patient information, with references)
8b) new combination product consisting of two or more currently authorised APIs whose combined use is already authorised	As for 1a)	Justification for the combination product and documentation proving that the test results for the reference product are transferable to the product pending authorisation	Bibliographical references to potential benefits and risks; References to preclinical and clinical data (ICH M3) and taking potential new risks into consideration (e.g. longer QTc interval)	New product information with reference to the product information for the single products, with additional material on the combination
8c) new combination product consisting of two or more APIs that are no longer authorised and whose combined use is, or has been, authorised	As for 1a)	Combination of 8b) and 1b)	Combination of 8b) and 1b)	Combination of 8b) and 1b)
8d) Combination of known and new APIs	As for new APIs	As for new APIs	As for new APIs	As for new APIs

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