Requirements relating to the authorisation documentation for transplant products (TP), gene therapy medicinal products (GT) and medicinal products consisting of or containing genetically modified organisms (GMO)

Contents

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1 Legal basis / scope

The present recommendations apply to transplant products (TP), gene therapy medicinal products (GT) and medicinal products consisting of or containing genetically modified organisms (GMO), for human use, abbreviated to TP/GT/GMO. An authorisation by Swissmedic is required for these products.

Article 49 of the Transplantation Act states that in addition to the requirements therein, the provisions of Article 3, Articles 5 to 33, Articles 58 to 67 and Articles 84 to 90 of the Therapeutic Products Act (TPA) must be applied analogously for transplant products. According to Article 49, paragraph 3, Articles 36-41 and 53-57 of TPA also apply analogously to the handling of transplant products prepared from human organs, tissues or cells. The requirements relating to marketing authorisation for transplant products have thus been aligned more closely to those for medicinal products.

Because of the specific nature of TP/GT/GMO, adjustments are necessary for certain requirements, since the type and scope of the analytical, nonclinical and clinical data that is required to prove quality, safety and efficacy are specific, taking into account their biological and functional characteristics.

The purpose of the present information sheet is therefore to clarify the authorisation documentation that must be submitted with an application for a marketing authorisation for transplant products. These recommendations will be regularly adapted in accordance with practical experience acquired.

The present information sheet applies only to organs, tissue and cells that are covered by the definition of transplant products and to gene therapies and medicinal products with GMO. Annex 1 of this information sheet provides a non-exhaustive list of transplants to which the definition does not apply.

2 Definitions and abbreviations

Active substance	Substance responsible for the therapeutic effect, such as manipulated cells (e.g. from a cell multiplication procedure, etc.) in a cell therapy or from a tissue culture, TpP, genetically modified cells from an *ex vivo* GT or active nucleic acid sequence from an *in vivo* GT product (e.g. plasmid, genetically modified virus or microorganism).
CTD	Common Technical Document[1] (CTD)
ERA(R)	Environmental Risk Assessment (Report)
Excipients for the use of transplant products	Substances that together with matrices, medical devices or additives remain in the finished product but their mechanism of action is not primarily responsible for the main intended mechanism of action of the overall product (e.g. growth factors, fibrin glues, etc.)
GMO	Genetically modified organisms, more specifically – genetically modified bacteria and viruses. According to the Release Ordinance (RO), a GMO is an organism whose genetic material has been modified by genetic engineering techniques in a way that does not occur naturally by crossbreeding or natural recombination. According to Article 6 of the Therapeutic Products Ordinance (TPO), as well as the requirements of the TPA, those specified in Article 28 of the RO must also be satisfied for the authorisation of a medicinal product containing

[1] See 'Volume 2B, Notice to Applicants, Presentation and format of the dossier, Common Technical Document (CTD)' of the European Commission

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	GMP. Taking account of the RO, the competent authority (i.e. Swissmedic) manages and coordinates the authorisation procedure.
GT	Gene therapy: A gene therapy product refers to a biological medicinal product with the following attributes: a) It contains an active substance containing, or consisting of, a recombinant nucleic acid, which is used in, or administered to, humans in order to regulate, repair, replace, add or remove a nucleic acid sequence. b) Its therapeutic, prophylactic or diagnostic effect is directly related to the recombinant nucleic acid sequence or to the product resulting from the expression of this sequence. The finished medicinal product consists of a plasmid or viral vector (*in vivo* gene therapy) or genetically modified cells (*ex vivo* gene therapy), formulated in its definitive primary packaging for the intended medical purposed. The finished medicinal product can be combined with a medical device or an active implantable medical device. According to Article 2 c, the Therapeutic Products Act (TPA) also applies to therapeutic treatments such as gene therapy, insofar as they relate directly to therapeutic products. The Federal Council may enact provisions specific to this subject.
Manufacturing additives	Additives refer to all materials (e.g. growth factors, cytokines, carrier solutions, etc.) – with the exception of medical devices – that come into contact with organs, tissues or cells during the harvesting, preserving, manufacturing, transforming or packaging prior to the therapeutic use of the transplantation product in human beings, but which are not present in the finished product.
Method of administration	This refers to the type of application, e.g. percutaneous implantations, intra-dermal applications or intravenous infusions.
Pharmaceutical form	This refers to galenic forms such as cell suspension, two-layer human skin equivalent, etc.
PSUR	Periodic Safety Update Report
SmPC	Summary of Product Characteristics
Starting material	For a cell therapy or for tissue cultures, the starting material is considered to be the biological material from which the active substance is manufactured: organs, tissue or cells taken from the patient in person (autogenous transplants), from a donor (allogeneic transplants) or from an animal (xenogenous transplants). For *in vivo* GT, starting material refers to components from which viral, non-viral vectors and genetically modified microorganisms are obtained, e.g. packaging and/or production cells, plasmids, recombinant microbial cells, etc. For *ex vivo* GT, starting material refers to cells (autologous, allogeneic or xenogeneic) and the vectors used for their genetic modifications.

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TP	Transplant product: According to Article 3 Transplantation Act, transplant products are defined as products obtained from human or animal organs, tissues or cells which can be standardised (or whose production process can be standardised). The definition of a transplant product formulated in the Transplantation Act has been extended in consultation with the FOPH to produce the following working definition: „A transplant product (TP) is a product that is intended for transfer to a human and , or whose production process, can be, standardised which consists of, or contains, autogenous, allogeneic or xenogeneic vital organs, tissues or cells and which is manufactured by means of a standardised procedure. When transplanted, these organs, tissues or cells are generally manipulated in such a way that their original biological characteristics, physiological functions or structural properties are affected (see definition in Annex 1 to the EU Regulation 1394/2007 of 13 November 2007 on Advanced Therapy Medicinal Products), or the cells or tissues are not intended to perform essentially the same function(s) in the recipient as in the donor. These can be products from somatic cell therapy or *ex vivo* gene therapy (as defined in Annex I, part IV of Directive 2003/63/EC) or tissue engineering (as defined in the EU Regulation 1394/2007 of 13 November 2007 on Advanced Therapy Medicinal Products). Among other aspects, the TP serves to regenerate, improve or influence the human physiological body functions by means of a pharmacological, immunological or metabolic effect on humans, or can be used to replace human tissue in order to heal or protect against illnesses, injuries or impairments.
TPA	Therapeutic Products Act, SR 812.21

3 General information

Information (guidance documents and information sheets) and forms relating to the authorisation of a transplant product, a gene therapy medicinal product (GT) or a medicinal product consisting of, or containing, genetically modified organisms (GMO) can be found on the Swissmedic website → Services and Lists → Documents and Forms → Transplant products. The time limits are those stipulated in the guidance document „ZL000_00_014d_WL Guidance document Time limits for authorisation applications HMV4". In the event of formal complaints, the applicant is granted a maximum period of 60 calendar days to rectify the situation. Extensions cannot be granted.

Signatory authorised to commit the firm: Applicants may delegate third parties to submit applications and notifications on their behalf. In such cases, the corresponding power of attorney must be submitted with the application.

Signatures: Cover letters, forms and other documents requiring an original signature must be submitted in paper form and bear the original signature of an authorised signatory. The signature does not have to be that of a person recorded in the Commercial Register as having signatory authority. It may also be that of a person duly authorised by the applicant to sign documents for the corresponding operation. Users of the Swissmedic eGov Portal are subject to the applicable contractual conditions.

Confirmation of receipt: Swissmedic does not send confirmations of receipt by post. Authorisation holders may consult the status of their application online on the Swissmedic eGov Portal. For details, see the Swissmedic website and the Guidance for the Swissmedic eGov Portal.

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For information concerning applications for the **Fast-track authorisation procedure** (FTP) and **Orphan Drug Status** (ODS), see guidance documents „ZL104_00_002e_WL Guidance document Fast-track authorisation procedure HMV4“ and „ZL100_00_002e_WL Guidance document Orphan Drugs HMV4“ on the Swissmedic website → Services and Lists → Documents and Forms → Transplant products → Authorisations TpP/GT/GMO → Applications and meetings TPO4.

For information concerning the submission of **Change Requests** see Guidance document „ZL300_00_001e_WL Guidance document Variations and extensions HMV4“ on the Swissmedic website → Services and Lists → Documents and Forms → Transplant products → Authorisations TpP/GT/GMO → Variations and extensions TPO4.

For information concerning **Renewals/discontinuations** see Guidance document „ZL201_00_001e_WL Guidance document Renewal and discontinuation of authorisation on change status (main authorisation/export licence) HMV4“ on the Swissmedic website → Services and Lists → Documents and Forms → Transplant products → Authorisations TpP/GT/GMO → Renewal and discontinuation of authorisation.

4 Requirements relating to the application documentation: general aspects

You can submit the application either as paper version together with an electronic copy, or in the eCTD format. For further information on requirements and document formatting please consult the Swissmedic website → Services and Lists → eGovernment Services/Swissmedic Portal. You can also find further information in Guidance documents „ZL101_00_005e_WL Guidance document Authorisation of human medicinal product with new active substance HMV4“, „ZL000_00_020e_WL Guidance document Formal requirements HMV4“ and „ZL000_00_006e_VZ Overview of documents to be submitted HMV4“.

Summary of submission formats

		eGOV Portal	eCTD	Paper	
				Paper original with eDok copy	Entirely paper-based submission
Module 1 Parts Ia/Ib in paper form	**Cover letter, forms, etc. of each**	--	1 copy	1 copy	1 copy
	Drafts IHP/PI/VMPI of each	--	--	1 copy	1 copy
	Packaging of each	--	--	1 copy	1 copy
	Staples	--	Permitted	Permitted	**Not permitted**
Paper documentation (Modules 2-5 / Parts 1c to IV)		--	--	1 copy	1 copy
Electronic documentation on CD/DVD (Modules 1-5 / Parts I to IV)		--	1 copy	1 copy	--
Electronic documentation by eGov Portal (Modules 1-5 / Parts I to IV)		1 copy			
Cover sheets (Modules 1-5 / Parts I to IV)		--	--	--	1 cover sheet per section
Dividers (Modules 2-5 / Parts 1c to IV)		--	--	--	1 set of dividers per section
Additional Word documents Packaging (also accepted as PDF) and or IHP/PI/VMPI		Contained in the electronic submission	On eCTD data carrier	On data carrier with electronic documentation	On data carrier

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Module 1 of an application for the authorisation of a TP/GT/GMO must be submitted in one of Switzerland's official languages, whereas it is also possible to submit Modules 2 to 5 in English. If individual sections or chapters are not submitted in CTD format, this must be justified.

The documentation should be sent to the following address:

Swissmedic
Swiss Agency for Therapeutic Products
Division Inspectorates and Licences (IBE)
Case Manager, Section Transplants
Hallerstrasse 7
3012 Bern

Authorisation documents (AD) will only be sent, subject to a fee, if specifically requested by the applicant. If an authorisation document is required, this must be expressly stated in the cover letter for all submission types.

5 Requirements for Module 1

The forms can all be downloaded from the Swissmedic website → Human medicines → Special categories → Transplant products.

Cover letter (for paper-based submission and eCTD 1 original)
The letter must contain at least the following information:

- The subject line should clearly indicate that the product in question is a transplant product, a gene therapy medicinal product (GT) or a medicinal product consisting of, or containing, genetically modified organisms (GMO).
- Name of the TP/GT/GMO with all required information in the case that other identifiers are used in the documentation (other names for the product, development code, etc.)
- Description of the active substance
- Dosage, pharmaceutical form of the finished product, method of administration and packaging
- Summary of the product characteristics
- List of all the general information and documentation submitted (if applicable, number of binders or folders per module)
- List of all administrative documents and other documentation submitted (for each Module/Part, with number of binders)
- For eCTD submissions: number of data carriers
- If documents required by Swissmedic are not submitted, the reasons for omitting them must be explained in the cover letter

Application form „ZL100_00_001e_FO Form New authorisation of human medicinal products HMV4“ (for paper-based submission and eCTD, 1 original)

- An original of the form must be submitted for each authorisation number and for each application type. Dosage strengths: state the various dosage strengths.

Application form „ZL000_00_032e_FO Form Full declaration HMV4“ (for paper-based submission and eCTD, 1 original)

- Qualitative and quantitative information on the composition of the finished product.
- The composition of the product must include weight/volume units (mg/ml), biological units (number of cells) per packaging unit (e.g. patch) or in mg/ml for a suspension.

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Application form „ZL000_00_031e_FO Form Substances of animal and human origin HMV4)“ (for paper-based submission and eCTD, 1 original)

- The information on the form must be identical with that in Module 3 (Quality) of the documentation.

Application form „ZL000_00_037e_FO Form Manufacturer information HMV4“ (for paper-based submission and eCTD, 1 original)

- Include the address and type of activity for the various domestic and foreign manufacturers (including contract manufacturers) or sites (active substances, processing, packaging, quality control and batch release).

Establishment licences / GMP certificate

- For foreign firms involved in the manufacturing and/or distribution of the product, a GMP certificate or an establishment licence must be submitted. A separate Guidance document is available listing exactly which documents must be provided, and can be downloaded from the Swissmedic website → Services and Lists → Documents and Forms → Transplant products → Authorisations TpP/GT/GMO → New application TPO4 → Authorisation of TpP/GT/GMO with new active substance HMV4 „ZL000_00_036e_WL Guidance document GMP compliance by foreign manufacturers HMV4“. If medical devices are components of the TP/GT/GMO, a corresponding CE certificate must be stated and submitted.

Application form „ZL000_00_030e_FO Form Status of authorisation applications abroad HMV4“ (for paper-based submission and eCTD, 1 original)

- Indicate whether the authorisation application has already been submitted, approved, suspended or withdrawn. If the status changes while an application is in progress, the form containing the response to the List of Questions or the response to the preliminary decision must be resubmitted. If no submission/authorisation for the relevant medicinal product exists in other countries, there is no need to submit the form. The reasons for omitting the form should be set out in the cover letter.

Application form „ZL000_00_028e_FO Confirmation regarding substances from GMO HMV4“ (for paper-based submission and eCTD 1 original)

- If the product contains genetically modified organisms (GMO), this must be declared. In addition, the product information and the packaging must note that the product is a GMO or contains GMO.
- A corresponding guidance document „I-315.AA.01-A11e Guidance document Gene therapy/GMO Environmental Data“ can be downloaded from the Swissmedic website → Services and Lists → Documents and Forms → Transplant products → Clinical trials TpP/GT/GMO.

Information relating to the experts

- A signed CV for all experts contributing to the CTD must be submitted either in Module 1.4 or in Module 2, with the overviews. The original of the document is not required.

Risk assessment of the environmental data

- An Environmental Risk Assessment Report need only be submitted if the transplant product will be released into the environment after being administered to patients. If this is not the case, provide a short justification. An ERA must be submitted for all gene therapy medicinal products (GT) and medicinal products consisting of or containing genetically modified organisms (GMO). The above-mentioned guidance document „I-315.AA.01-A11 Guidance document Gene therapy/GMO Environmental Data“ under Clinical trials applies analogously.

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Pharmacovigilance system / risk management

- Information regarding the pharmacovigilance and risk management system must be submitted under Module 1.8 (see also requirement regarding Module 5). Documentation on Pharmacovigilance Planning according to Annex 3 TPO must be submitted. The content and form of the Risk Management Plan (RMP) to be submitted to Swissmedic must be based on the ICH E2E Guideline „Pharmacovigilance Planning“ and the EMA Guideline “Good pharmacovigilance practices (GVP): Module V – Risk management systems“. An RMP template can be found in the corresponding EMA guideline („Guidance on format of the risk management plan (RMP) in the EU–integrated format“). If an RMP has been submitted to, or approved by, the EMA, this should be forwarded to Swissmedic. Updates/changes to the RMP should be submitted both in “track changes” mode and as a finalised version. The RMP for a medicinal product, which presents the risk aspects of the product, the planned pharmacovigilance activities and risk minimisation measures, is part of the authorisation dossier (Module 1). The evaluation of the documentation is an integral part of the authorisation decision. The purpose of the RMP is to describe known and suspected potential risk aspects at the time of authorisation, and to establish strategies on how these can be characterised in future and countered in a risk minimisation approach. Swissmedic has published RMP summaries of authorised medicinal products since November 2015. Based on the publicly accessible RMP summaries, interested professionals and lay people can obtain information about the specific measures that have been arranged for the future characterisation and minimisation of risks for the corresponding medicinal product. The RMP summaries supplement the publicly accessible information for healthcare professionals and patient information texts and are linked to the corresponding medicinal product via the Swissmedic product information platform (AIPS at www.swissmedicinfo.ch). For further information, see guidance document „MU103_10_001e_WL Guidance document RMP ICH E2E Information for submission of RMP HMV4“.

Labelling

The requirements for the labelling of TP/GT/GMO should respect the EU Regulation[2], the Labelling standards of cellular therapy products[3], and the Swiss Medicinal Products Authorisation *Ordinance (AMZV),* Appendices 1, 3, 4 and 5.1[4].

More detailed general information on the product and patient information can be found on the Swissmedic website → Services and Lists → Documents and Forms → Transplant products → Authorisations TpP/GT/GMO → Product information and packaging TPO4 in the guidance document „ZL000_00_027e_WL Guidance document Product information for human medicinal products HMV4“ and in the templates „ZL000_00_041e_VL Product information for human medicinal products HMV4“ and „ZL000_00_042e_VL Patient information for human medicinal products HMV4“. The medicinal product information texts must include the references to the corresponding texts in Modules 2, 3, 4 and 5. Statements made in the medicinal product information must be scientifically justified and proved. Suitable references are study reports, publications, or other scientific documentation. References to study reports, publications, other scientific documentation, a summary or an overview must always cite the corresponding page number. Example: *Study xyz, Binder 3, page 736. Or Binder 2, Reference 38: Müller et al, title etc., page 13.*

[2] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

[3] Ashford P., et.al. (2007) Standards for the Terminology and Labelling of Cellular Therapy Products. Transfusion, Vol. 47, pp. 1319-1327

[4] SR 812.212.22: Ordinance of the Swiss Agency for Therapeutic Products on the requirements for the authorisation of medicinal products, Annexes 1, 3, 4 and 5.1

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A simple reference to the firm's internal Core Data Sheet (CDS) or the Company CDS (CCDS) or the Summary of Product Characteristics (SmPC) is not permitted, since these are not scientific references. References must not be removed while the application is in progress. All changes compared to the last approved version must be clearly marked as such. The marking must be shown in the manuscripts throughout the entire application process. Changes must be marked/highlighted using Word's "Track Changes" function. No other forms of marking/highlighting will be accepted.

Product information / SmPCs (text drafts, 1 copy, only applies to paper-based submissions)
The product information must additionally be submitted as a Word file. Standardised product information must be drawn up for experts and health professionals and must be included in the packaging of the TP/GT/GMO. The draft must be submitted with the authorisation application. If the TP/GT/GMO has already been authorised in other countries, or submitted to the relevant authorities, the product information texts submitted to the relevant authorities or approved by the relevant authorities must be submitted and – if not already in German, French, Italian or English – translated. SmPCs that have already been approved or any available draft SmPCs must also be submitted.

Patient information (text drafts, 1 copy, only applies to paper-based submissions)
The patient information must additionally be submitted as a Word file. Although TP/GT/GMO are normally only administered by specialised physicians and it is their responsibility to provide comprehensive information to the patients who will be treated with them, it can be useful to have separate patient information for certain products. This is usually requested in connection with a List of Questions (LoQ) or a preliminary decision. It must be submitted only with the reply to the LoQ or the preliminary decision. If corresponding drafts are already available, these must be submitted with the authorisation application.

Packaging elements (drafts, 1 copy, only applies to paper-based submissions)
The packaging elements must additionally be submitted as a Word file (text drafts, 1 copy for paper-based submissions). All draft texts for the packaging elements (primary and secondary packaging) must be submitted with the authorisation application (for paper-based submissions). Colour laser print-outs in original format can be submitted instead of original prints of packaging (folding cartons, labels, sachets, etc.). In addition, packaging should be submitted on a data carrier as a single file with searchable text (OCR). Paper copies are not required when making a submission in eCTD format. Users of the Swissmedic eGov Portal do not need to submit an additional electronic data carrier for the packaging. Detailed general requirements relating to packaging elements can be found on the Swissmedic website → Services and Lists → Documents and Forms → Transplant products → Authorisations TpP/GT/GVO → Product Information and packaging TPO4 in the guidance document „ZL000_00_021e_WL Guidance document Packaging for human medicinal products HMV4".

Decisions by foreign authorities
Assessment Reports by foreign authorities with comparable medicinal product control systems (according to the list published on the Swissmedic website) and the company's replies must be submitted in Module 1. If new Assessment Reports become available during the review period, these must be submitted in connection with the reply to a LoQ/preliminary decision. If final Assessment Reports by foreign authorities with comparable medicinal product control systems exist (according to the list published on the Swissmedic website) but are not enclosed with the application, the reasons for omitting them must be stated in the cover letter.

Paediatric Investigation Plan
For authorisation applications for a human medicinal product with stated indications pursuant to Article 11 TPA or for an important medicinal product for rare diseases (orphan drug) that contains at least one new active substance, paediatric investigation plans pursuant to Article 54a TPA must be

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submitted. The requirements are based on the guidance document „ZL000_00_023e_WL Guidance document Paediatric Investigation Plan HMV4“.

Information on GCP inspections
A completed EMA GCP inspections template must be submitted for all application types whose documentation includes clinical trials (including bioequivalence trials).

For further information on formal requirements see guidance document „ZL000_00_020e_WL Guidance document Formal requirements HMV4“.

6 Requirements for Module 2

Module 2 is a general introduction regarding the TP/GT/GMO. It should contain an overview of the product, the indications, pharmaceutical form and modes of action, and on the available documentation on its quality and nonclinical and clinical characteristics. If the CTD is submitted in paper format an overall list of contents (Module 2.1) must be submitted as a separate document with indications of page and binder numbers, in a sufficient degree of detail (1 copy). In the case of electronic submission, a corresponding overall list of contents with the corresponding links to the sections should be included.
The summaries/overviews (2.3 to 2.7) must contain sufficient references to the corresponding documentation (Module 3-5), showing with the corresponding page and binder numbers. In the case of electronic submission, appropriate links must be included. For further details on the table of contents and binder labelling for paper-based submissions and referencing, see guidance document „ZL000_00_020e_WL Guidance document Formal requirements HMV4“ chapters 2.6.1 and 2.6.2.

Quality section (Module 2.3)
Module 2.3 must contain a short but critical summary drawn up by an expert. Key data should if possible be summarised in tables and graphics.
The critical summary should provide the reviewer with an overview of all parts of Module 3. It should above all discuss critical aspects and refer to relevant data submitted in Module 3.

Nonclinical section (Modules 2.4 and 2.6)
Module 2.4 must contain a short but critical summary, drawn up by an expert, of the experimental and bibliographic data on pharmacodynamics, pharmacokinetics and toxicology as per ICH M4S, as well as a risk assessment as a separate document. The scientific rationale with regard to the necessary nonclinical evaluation, the animal models used and the selection of the studies carried out must be justified. All safety-relevant points must be addressed and discussed. Trials not carried out (see Module 4) must be justified in the summary. In addition, a risk evaluation regarding the use of the TP/GT/GMO must be carried out. Relevant nonclinical data submitted with Module 3 (e.g. studies on biological activity) must be referred to. The status of the GLP quality system for preclinical studies must be indicated.
In addition, a critical assessment of the safety relevance of new excipients plus potential impurities should be provided and, where necessary, supported by experimental trials.
A Nonclinical Summary Written and Tabulated Summaries (Module 2.6) according to ICH M4S should be submitted. Module 2.6 must contain a comprehensive summary of all studies carried out (pharmacodynamics, pharmacokinetics and toxicology). This must be completed by a summary in table form, from which the GLP status can be seen.

Clinical section (Modules 2.5 and 2.7)
Module 2.5 must contain information on the clinical development, with the main clinical events, in the form of a critical summary.
A risk/benefit assessment based on nonclinical and clinical experience that takes all possible risks into account must be submitted, including in comparison with similar products.

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This must include a critical analysis regarding the design and results of the clinical trials which support the intended clinical use of the product, plus an analysis of the resulting restrictions regarding control group, patient population, end point and concomitant therapies during the trials, etc.
The Overview of Safety should – among other aspects – address the long-term safety aspects and planned measures to minimise any adverse reactions. Key data should if possible be summarised in tables and graphics.
Module 2.7 must contain a comprehensive summary of all clinical trials carried out. It must be completed by a summary in table form. The Summary of Clinical Safety should include, among other aspects, post-marketing data (if applicable).

7 Requirements for Module 3

The composition and presentation of the documentation relating to the pharmaceutical quality of a medicinal product with a new active substance (Module 3) should be in accordance with Article 3 TPLRO. Relevant ICH guidelines, for example The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality-M4Q, as well as other guidelines and specification documents listed in chapter 7, should be taken into consideration.
Differing dosages of the same pharmaceutical form should be submitted in the same binder. Since the quality of the starting materials for TP/GT/GMO can vary considerably, the focus of quality assurance for the products is well-documented, irreproachable quality of these starting materials plus a reproducible, validated manufacturing process. Information must be submitted on the clinical and serological compatibility of the donor, by tissue and cell type (autogenous, allogeneic or xenogenous), tests carried out and the requirements for the said tests, on the histological, microbiological and virological quality of the harvested starting materials and their traceability (e.g. identification number, donor centre, etc.).
Regarding quality, the same requirements apply to all TP/GT/GMO, independently of whether they are of autogenous, allogeneic or xenogenous origin.
The following sections address specific aspects that must be taken into account in this section.

Active substance
General information
All starting materials, additives and auxiliary materials used in the manufacturing process for TP/GT/GMO (e.g. tissues, cells or cell bank systems) must be documented. For the active substance, the type of the in-vitro or *ex vitro* cell transformation (growth, differentiation, selection by antibodies, etc.) must be described. The grade of cell differentiation in comparison to the starting material must also be specified. All medical devices or biological materials (e.g. matrix or capsules) in the culture medium or manufacturing additives contained in the matrix (growth factors, cytokines, antibodies, medicinal products) and auxiliary materials must be listed and documented to the greatest possible extent (information on CE certification or reference to a pharmacopoeia).

All manufacturing and control processes must be documented, and in particular the critical manufacturing steps. In addition, intermediate and final storage must be described. The traceability of substance groups and quality parameters, from the starting material to the finished product, is of particular importance.

Manufacturing (active substance)
- Complete address of all firms involved in the manufacturing (e.g. all manufacturing steps, supplies, control, packaging, etc.), including available proof of quality
- Detailed description of the process (diagram of all manufacturing steps, including intermediate products and products added), plus list of controls, including the specifications following the individual manufacturing steps (details for cell banks)
- Description of the active substance
- Reproducibility
- Description of the manufacturing premises, including monitoring thereof

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- Identification of the critical manufacturing steps
- Description of all manufacturing additives and auxiliary substances used to manufacture the finished product and intermediate products
- Description of all equipment used (cell incubator, microscope, etc.) or materials (cell culture containers) used during the manufacturing of the intermediate and finished product
- Type of harvesting (aseptic, non-sterile, etc.), method (operation, apheresis, etc.), address of the entity carrying this out
- Description of validation and/or evaluation trials (trial plans, results, analysis) plus the selection of critical control steps and limits for critical manufacturing steps (e.g. cell culture, cell culture harvest, cleaning and modification)
- Shelf life
- Summary of modifications to the manufacturing process that took place during development and the resulting conclusions if nonclinical and clinical trials were carried out prior to the modifications, and justification of why the results obtained were not affected by the modifications

Description

- Type of cells and cell cultures
- Origin (autogenous, allogeneic or xenogenous) of the cells (for animal starting materials, the country of origin), and type of starting material (tissue, organs or biological fluids)
- Type of harvesting and preparation of the cells
- Storage of the cells prior to further processing
- Type of manipulation or processing of the cells and physiological function of the cells constituting the active substance
- Efficacy (biological activity)
- Medical devices and biological materials used (proof in the form of certificates)
- Batch size (number of cells, size of constructs, etc.)
- Specific requirements for materials of human and non-human origin (albumin, immunoglobulin, growth factors, etc.) to reduce animal spongiform encephalopathy
- Analysis methods to identify the cells or tissues (phenotype and genotype markers)
- Purity (number of cells with the selected markers in the active substance), impurities (in connection with the product or its manufacturing)
- Other characteristics required to describe the active substance
- Viral harmlessness (in accordance with Directive 2006/17/EC5) of the starting materials and the individual manufacturing steps
- Tumorigenicity, mutagenicity of the selected additives (e.g. cytokines, growth factors, etc.) and senescence of the starting materials
- Specifications, analytical methods, qualifications and validations carried out
- Analysis certificates for reference substances used
- Master cell bank and working cell bank
- Procedures in the case of bacterial or yeast contamination within the framework of the manufacturing process (type of decontamination) and result achieved

Controls

- Diagram for each manufacturing step showing the analysis methods and specifications
- Controls of donors, starting materials, other raw materials and of auxiliary materials
- Controls of medical devices or biological materials (certificate of the medical devices)
- Controls and specifications of the critical steps and the intermediate products
- Description and validation of the analysis methods (in-process and end-product controls)
- Microbiological cell or tissue tests (e.g. endotoxins, bacteria, yeasts and mycoplasms)

[5] Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

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- Virological detection tests in starting materials and active substances
- Proof of cell vitality (percentage or absolute number of cells)
- Specifications including justification for critical parameters of the cell culture e.g. cell vitality, cell density, purity, cell culture time, number of passages, etc.) or other cell manipulations
- Procedure if results are out of specification (OoS values), e.g. microbiological contamination of the finished product
- Execution and documentation (batch record) of the batch analysis (end and intermediate products)
- Identification and specification limits for residues of manufacturing substances in the finished product

Culture media
- Specifications and analysis methods regarding identity, content, purity, shelf life, use and other quality criteria such as identification of non-human components to reduce animal spongiform encephalopathies (if applicable, reference to the corresponding monograph)
- Analysis certificate

Control of the intermediate products
- Specifications, analysis methods (incl. validation documents), testing frequency
- Cell bank system

Conservation and transport
- Description of the packaging (including starting materials, manufacturing additives, kits, etc.), labelling
- Defined procedure for the intermediate storage of the active substance (e.g. cryoconservation)
- Conditions for the storage of the finished product
- Conditions for the transport of the finished product
- Diagram of the transport procedures

Directive 2004/23/EC, amended by Directives 2006/17/EC and 2006/86/EC on the traceability of starting materials and additives, must be consulted[6].
- Coding system
- Labelling
- Procedure

Stability
- Summary of the stability studies, conclusions, and stability protocols used
- Results of the stability studies, including the analytical procedures used and their specifications, and validations of the analytical procedures used
- Data on stability and validation reports

Finished product
Description and composition
- Complete qualitative and quantitative composition
- Formulation of the finished product (e.g. suspension, cell construct, combination of medical device and cells)
- Composition of the formulation(s) used for the clinical trials, if these are different from the finished product applied for
- Data on the choice of all relevant analysis methods and other documents (e.g. precision of the dosage)

[6] Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

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- Labelling of the finished product
- Traceability of the finished product

Pharmaceutical development of the product
Justification for:
- The composition (e.g. biocompatibility with the medical device)
- Choice of the dosage form
- Function of the manufacturing additives and auxiliary materials used
- The primary and secondary containers

Manufacturing method for the finished product
- Manufacturing process (documented manufacturing instructions)
- Description of the manufacturing process with flow diagram (including packaging process, details of manufacturing site and if applicable, manufacturers involved in the various manufacturing steps)
- Data regarding transplant products from the same batch (handling methods, traceability)
- Details of finished product controls (specifications, analysis methods, testing frequency)
- Details of the in-process controls (specifications, analysis methods and testing frequency)
- Risk evaluation for the individual manufacturing steps (if applicable, corresponding validation plan / validation report)
- Sublethal irradiation
- Validation and qualification of the manufacturing process

The finished product must be tested for microbial contamination (bacteria and fungi). The said microbiological test must in principle correspond to a pharmacopoeia monograph. The procedure in the case that a contaminated finished product is administered to a patient must be described. The following must be examined: identity of the Master Cell Bank (MCB) or Working Cell Bank (WCB), the finished product, the purity (e.g. residues of manufacturing additives, pyrogenicity, endotoxins, efficacy and vitality).

Controls of components other than the active substance(s)
- Manufacturing additives, auxiliary materials, biological materials, medical devices, etc.
- Certificates of conformity, manufacturing certificates

Controls of the finished product
- Specification and derivation
- Description and validation of the analytical control procedure
- Batch analysis

Conservation, transport and traceability
Description of the packaging (labelling and precise description of all elements including in the packaging, and in particular those used to administer the product).

Primary container
- Description (with construction diagram), specifications, integrity data and feasibility studies (microbiological leak testing)
- Conditions for storing the finished product (duration and temperature allowed, conditions after opening the container)
- Documents proving the harmlessness of the materials used, (e.g. CE certification, endotoxins, etc.)

Secondary container
- Description (with construction diagram), specifications, integrity data and feasibility studies

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- Conditions for storing the finished product (duration and temperature allowed, conditions after opening the container)
- Validation of the transport
- Transport conditions
- Traceability

Stability
- Summary of the stability studies and conclusions
- Stability data

Annexes to Module 3
- Manufacturing sites, including for the equipment (e.g. flow diagram of the manufacturing process(es), detailed material and personnel flow)
- Information (e.g. statement of harmlessness, cleaning / decontamination processes, study results on the viral safety of biological materials) to prevent / control non-viral (e.g. bacteria, mycoplasms) and/or viral-contaminated substances)
- Information on cell / tissue banks (e.g. certificates)
- Information on non-cellular components used (e.g. biological or inert matrices/ carrier materials, medical devices)

8 Requirements for Module 4

The documentation on the pharmacological and toxicological studies of a medicinal product with a new active substance (Module 4) should be compiled in accordance with Article 4 TPLRO and must reflect the latest scientific and technological findings. The presentation must conform to ICH M4S analogously.
When implementing the studies, the relevant ICH guidelines and other guidelines listed in chapter 8 should be taken into consideration. Safety-relevant studies must be performed in conformity with GLP.
Data on the sections for primary and secondary pharmacodynamics, safety pharmacology, pharmacokinetics and toxicology must in principle be submitted. Studies on safety pharmacology and on toxicology must be carried out with respect for GLP. All divergences from the above-mentioned series of standard preclinical tests must be justified. The nonclinical evaluation includes not only the active substance components but also critical auxiliary materials and impurities caused by the manufacturing process. The product used for the nonclinical evaluation must be identical with the TP/GT/GMO applied for or its manufacturing must be comparable with the product used in the clinical trials and submitted for authorisation. All investigations regarding nonclinical aspects must have been carried out with relevant animal models, and the choice of animal model must be justified. The clinically relevant dosages, routes of administration, treatment plan and treatment duration must be taken into account in the nonclinical investigations. The conducted studies must include sufficient information to enable a definitive risk assessment of its use in humans to be conducted. The corresponding ICH guidelines and the guidelines of the EMA and/or US FDA should be taken into account in the planning of the preclinical studies. The various studies should all be submitted as individual reports. Cited bibliographic references should all be submitted electronically as PDFs.

Pharmacodynamics
The pharmacodynamics studies should prove the scientific rationale for the TP/GT/GMO and its efficacy (proof of principle, proof of concept). In addition to *in vivo* and/or *in vitro* studies on efficacy, pharmacodynamic interactions of the transplanted cells or administered gene therapy products (viral vectors, plasmids) with the surrounding tissue and non-cellular elements (in the sense of secondary pharmacological interactions) must be studied. The pharmacodynamics studies should also be used as the basis for defining the initial dose in clinical trials, the planned treatment regimen and the duration of treatment.

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Safety pharmacology
Depending on the type of product, the effects on the central venous, cardiovascular or respiratory system must be investigated (case-by-case basis). Should the transplanted cells secrete active substances (growth factors, hormones), targeted studies to investigate the safety pharmacological effects thereof must be carried out. The safety pharmaceutical investigations can also be carried out within the framework of toxicology studies. If safety pharmaceutical preclinical studies are not carried out, product-specific reasons must be given.

Pharmacokinetics
Conventional regulatory ADME studies are not expected. The pharmacokinetic investigations relating to TP should contain *in vivo* studies on biodistribution, migration behaviour and survival capacity. In addition, data on cell viability, proliferation, degree of differentiation and functioning duration must be submitted. As regards GT/GMO, depending on the specific product, data on biodistribution, persistence, clearance, latency, mobilisation and shedding are expected. The risk of germline transmission of gene transfer vectors and the risk of integration of vector DNA sequence in the genome of cells in target tissue should also be investigated (see also under Toxicology). The studies should be conducted with clinically relevant administration routes and at dosages with adequate safety margins relative to the clinically relevant doses. Particularly for studies investigating shedding, early, intermediate and late time points should be included in the evaluation.

Toxicology
GLP-compliant studies are expected for the toxicology evaluation. Whether toxicology studies must be carried out depends on the type of the TP/GT/GMO in question (case-by-case basis), and must be in accordance with its clinical use. The evaluation of toxicology in relevant animal models must be carried out with a product that is identical with the product applied for, or that is comparable in terms of the cellular and non-cellular components and the manufacturing process. Proof of the comparability must be provided. Local effects (e.g. inflammations, effects caused by secreted substances), systemic effects on the immune system (e.g. induction of autoimmunity) and long-term toxicological effects (local, systemic) must be evaluated. Depending on the product and type of therapeutic use, studies on the potential for cell transformation should also be submitted (tumorigenicity). The duration of the toxicology studies should be justified and is based partly on the site and duration of efficacy. Specifically for GT products, the potential toxicity of the therapeutic transgene should be subjected to a risk-based evaluation. For GT/GMO products, the potential for the integration of vector genome in the target cells should be investigated (evaluation of insertional mutagenesis, analysis of insertion sites). Depending on the product type, indication and target population in each case, risk-based studies should be conducted to investigate reproductive and developmental toxicity. This applies in particular to viral products capable of replication.

9 Requirements for Module 5

The documentation regarding the clinical investigations relating to a medicinal product with a new active substance (Module 5) should be compiled in accordance with Articles 5 and 6 TPLRO. The presentation of the clinical data is described in ICH Guideline “The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy-M4E (Clinical Overview and Clinical Summary of Module 2, Module 5: Clinical Study Reports)”.
The study reports for (the applicant's own) clinical trials conducted for the application should be drafted according to ICH E3 Guideline “Structure and Content of Clinical Study Reports”.
The studies must be carried out in accordance with GCP guidelines. Other guidelines issued by the ICH and the guidelines listed in chapter 8 should also be taken into account.
Published works (offprints) should as a rule be enclosed separately, with corresponding references in the summary and in the original documentation. Since every TP/GT/GMO constitutes a „new active substance“, the company applying for an authorisation should carry out its own studies with the proposed product on the proposed indications and dosages.

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Data on the following points must be submitted:

Pharmacodynamics
The pharmacodynamic characteristics must be known, and depending on the intended function in the body, it must be possible to prove them by means of appropriate measures. The proof of principle may be based on nonclinical studies or previous clinical experiences with the product. Information regarding the method of action must be provided (e.g. immunology, compensation for cell deficit, colonisation of a tissue).

Pharmacokinetics
In general, information on proliferation/differentiation, biodistribution or cell migration and their function during the expected lifetime must be submitted. If no conventional pharmacokinetics (ADME) studies are submitted, this must be justified accordingly.

Dose finding studies
The selected dose must be in line with the potency of the product. The dosage applied for, for a corresponding indication, must be based on nonclinical studies and quality results, and present the minimum effective, optimum, and maximum safe dose for various types of use in the entire therapeutic spectrum.

Clinical efficacy
The clinical data must be collected within the framework of trials carried out in compliance with GCP, and prove the efficacy for the indication and dosage applied for. Any therapeutic alternatives with the same indication that are already available must be taken into consideration in this respect. When analysing efficacy, the entire therapeutic environment must be evaluated and also taken into consideration (e.g. including surgery or other concomitant therapies, both medicinal and non-medicinal).
The trial product must be manufactured using the same process as the product applied for. Statistical analysis of the data and findings from the trial are essential for the overall evaluation of efficacy and safety. In order to provide proof of efficacy and safety for products with long-term effects, a follow-up over a sufficiently long period must be planned.

Safety
A risk analysis based on clinical data must be submitted. In order to be able to define the safety profile of the product, all data on quality and nonclinical aspects, clinical data collected for the product to date, plus information on a comparable product should be taken into consideration. All possible risk factors should be considered: for example the risk of immunogenicity or tumour genesis caused by a neoplastic transformation of the host cells and those of the product should be evaluated on a nonclinical, case-by-case basis.
In addition, the risk throughout the whole time that the product is used (e.g. including during surgery) plus the significance of other therapies should be taken into consideration. A risk profile according to the level of manipulation of the cells should be established. Furthermore, potential negative effects such as the possible consequences of a large concentration of cells on a small surface, a vascular occlusion or a secretion of pharmacologically active substances should be taken into consideration.

Long-term effects
The long-term effects, the survival of the transplant product in the host tissue, interactions between the transplanted cells and the surrounding tissues, the adherence of the product to the underlying tissue, migration of the cells, or dislocation are important aspects with regard to efficacy but also to safety, and must therefore be taken into consideration and presented in accordance with appropriate methods. The specific requirements depend on the product and must be assessed on a case-by-case basis.

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For products containing a matrix (medical devices), the requirements relating to medical devices must also be respected. The characteristics, performance, biocompatibility and cell interactions with the host tissue or with the cells of the product must be described.

Pharmacovigilance planning
Reference should be made to the publication in the Swissmedic Journal (05/2006) regarding „ICH-Guideline and Pharmacovigilance Planning (E2E): Implementation in Switzerland“. The pharmacovigilance plans and safety specifications can be either submitted as stand-alone documents or integrated within the CTD. A separate document is preferable.

Documents to be submitted after authorisation has been granted:
RMP summaries
An RMP Summary must be submitted for all authorisation applications (see also chapter 5). **The submission of the RMP Summary is a requirement that is specified after the application has been approved.**
The RMP Summary should be submitted, in English, to Swissmedic as a separate document (for format and content see the document „Guidance on format of the risk-management plan in the European Union part VI: Summary of activities in the risk-management plan by product“) with a cover letter (not a separate application) up to 60 calendar days after approval of the authorisation application (submission via Swissmedic Portal: delivery type „communication“, CD by post or eCTD). A translation into the Swiss national languages is not envisaged. The publication language is English, and the company is responsible for ensuring that the text is correct. When drafting the summary, ensure that it is complete (list all risks and risk minimisation measures) and easily comprehensible. The RMP Summary will be checked by Swissmedic and, provided there is no cause for complaint, published on the Swissmedic website with a link to AIPS. No separate correspondence is conducted with the marketing authorisation holder. In the event of a complaint, the marketing authorisation holder will be contacted. Updates to RMP summaries: If RMP Updates are required during the life cycle of the medicinal product (see chapter 7), the RMP Summary should also be updated. The above-mentioned requirements relating to form and content apply to these updates. The RMP Updates should be submitted together with the PSUR/PBRERs. For detailed information, see „MU103_10_001e_WL Guidance document RMP/ICH E2E Information for submission of RMP HMV4“ on the Swissmedic website → Human medicines → Market surveillance → Risk Management (PSURs, PV Planning, RMP summaries).

PSUR
Once a product has been authorised, Periodic Safety Update Reports (PSURs) must be submitted at yearly intervals. Accordingly, explanations concerning the PSURs can be found in the guidance document „MU103_10_002e_WL Guidance document Information on PSUR PBRER submission HMV4“ on the Swissmedic website → Human medicines → Market surveillance → Risk Management (PSURs, PV Planning, RMP summaries). If you have any questions please contact us on the following phone number +41 (0)58 462 02 43. The PSUR (if applicable as a new eCTD sequence), together with the corresponding form „I-314.AA.01-A11e_Form PSUR PBRER TpP/GT/GMO“, should be sent to the following address: Swissmedic, Schweizerisches Heilmittelinstitut, Einheit Transplantate, Hallerstrasse 7, 3012 Bern, or can be submitted via the Portal. The form is available on the Swissmedic website → Human medicines → Special categories → Transplant products → Documents and Forms → Biovigilance TpP/GT/GMO.

Biovigilance
A patient monitoring system with a corresponding action plan must be drawn up. Since the products in question are new and their risks are not all known, all adverse effects, and not only those that are severe, must be reported to Swissmedic. This includes events that have occurred during the harvesting, application and preparation of the products. For products containing GMO, this also applies to the inadvertent release of the product into the environment or transmission to other humans or

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animals. More comprehensive information on reports relating to TpP/GT/GMO can be found on the Swissmedic website → Human medicines → Special categories → Transplant products → Documents and Forms → Biovigilance TpP/GT/GMO.

The reports should be sent, using a CIOMS form and/or the form „I-314.AA.01-A03e Form Report of an Adverse Drug Reaction to a TpP/GT/GMO“, to the following address: biovigilance@swissmedic.ch.

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ANHANG I

Non-exhaustive list of transplants that are not considered to be „transplant products“ (in accordance with Annex 1 of the EU Regulation 1394/2007 of 13 November 2007).

Type of transplant	Preparation, conservation (examples)
Organs	Kidneys, heart, liver, etc.
Musculoskeletal tissue	
Bones: major transplants, femoral head	untreated deep frozen, freeze dried, sterilised by irradiation, aseptically washed (after bone marrow depletion)
Osteochondral transplants and menisci	untreated deep frozen meniscus, cryoconserved, sterilised by irradiation, freeze dried
Fascia lata or other fascia	untreated deep frozen, freeze dried, sterilised, cryoconserved, aseptically washed
Ligaments and tendons	untreated deep frozen, aseptically washed, cryoconserved, sterilised by irradiation, freeze dried
Cartilage	untreated, deep frozen, sterilised, deep frozen washed, cryoconserved
Skin	untreated fresh, cryoconserved, glycerol conserved, glycerol conserved sterilised, air dried/lyophilised, air dried/lyophilised sterilised
Amniotic membrane	untreated fresh, cryoconserved, glycerol conserved, glycerol conserved sterilised, air dried/lyophilised, air dried/lyophilised sterilised
Cardiovascular tissue	
Heart valves, heart vessels, heart arteries, heart veins	untreated fresh, cryoconserved
Pericardium	untreated fresh, cryoconserved, sterilised by irradiation
Eye tissue	
Cornea	untreated fresh, stored in culture medium, stored in Optisol
Sclera	Deep frozen

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