



**Guidance for the Submission and Conduct of Clinical Trials (CT)
with Medicinal Products**

NOTE: The English translations of Austrian legal documents are not authorized and therefore not legally binding. The original, legally binding, German text passages are included in the text for your reference.

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I. Prerequisites for the conduct of a Clinical Trial

I. 1 Required components of the Application

according to § 40 Austrian Medicinal Products Act (AMG):

- the EudraCT Application Form (see <https://eudract.ema.europa.eu>) and
- the documents required according to EudraLex Volume 10 CT-1, reflected in the “L_ I211_List of documentation required” see the English BASG website: www.basg.gv.at “Medicines” – “Before Authorization” – “Clinical Trials”

The EudraCT application form (in PDF and XML) and the documents required for the assessment need to be submitted electronically on a data medium (e.g. CD). The application should be sent to the BASG together with a covering letter by mail to the address in section I.2. To facilitate the processing the BASG welcomes the additional submission of a print-out of the EudraCT application form.

Documents that require a signature need to be signed electronically or manually signed and scanned.

Folders on the data medium should have the following structure:

- „1_General information“
contains e.g. the covering letter and the EudraCT application form in PDF and XML
- „2_Protocol“
contains e.g. the current version of the protocol, the synopsis and the signature pages
- „3_IB“
contains the Investigator’s Brochure according to ICH GCP and CT-1
- „4_IMPDP“
contains the full IMPD, simplified IMPD or SmPC according to CT-1 and all other relevant manufacturing information
- „5_Additional information“
contains e.g. the Patient Information, the summary of the Paediatric Investigation Plan or the summary of Scientific Advice

The EudraCT form should be completed in English with the exception of contact information on Austrian sponsors, legal representatives, request for the competent authority, the study sites and clinical investigators (e.g. Departments of University Clinics etc.). These fields are essential to the technical processing and the referencing of applications and should therefore be comprehensively and consistently completed. The sponsor is responsible for the accuracy and completeness of the information provided in the application form.



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Informed Consent Forms (ICFs) are evaluated exclusively by the Ethics Committees. The Austrian Competent Authority welcomes ICF templates for information only as part of the initial Clinical Trial Application package. The Austrian Competent Authority does not require notification about any amendments to ICFs nor about the EC approval of such ICF amendments. If substantial amendments to the protocol or the investigator's brochure lead to an amendment of the ICF, only submission of the updated protocol/IB amendment is required.

I. 2 Address

Clinical Trial Applications should be addressed to the Austrian Competent Authority, the Federal Office for Safety in Health Care (Bundesamt für Sicherheit im Gesundheitswesen, BASG) under the following address:

Austrian Federal Office for Safety in Health Care (BASG)

Austrian Agency for Health and Food Safety (AGES)

Institute Surveillance (INS), Department for Clinical Trials (CLTR)

Traisengasse 5; A-1200 Vienna; Austria

I. 3 Confirmation of receipt

An automatic confirmation of receipt by e-mail is associated with the following procedures:

- initial application
- substantial and non-substantial amendment
- development safety update report (DSUR)
- declaration of end of trial

Other submissions sent to the authority will not be confirmed automatically.

Note: All correspondence with the applicant will be sent exclusively to the address indicated in the application form under C.1. Keeping this information updated lies within the responsibility of the applicant.

I. 4 Opinion by an ethics committee:

The initiation of a clinical trial requires a positive opinion of the ethics committee (EC) concerned.

- Opinion of one Austrian lead-ethics committee is sufficient for **multicentre** trials (§ 41b AMG)
- Opinion of a local ethics committee is sufficient for mononational **monocentric** trials

The application to the ethics committee can be submitted prior to or simultaneously with the application to the BASG, but **not** following thereafter. The date of submission needs to be stated in the cover letter as well as in the application form (section H). If already available at the time of



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submission to the BASG, the vote of the ethics committee (EC) should be included in the clinical trial dossier.

For further information, the applicant is referred to the website of the Forum of Austrian Ethics committees (www.ethikkommissionen.at). Should the EC not come to a positive conclusion on the trial (i.e. a **negative vote**) the clinical trial application will be refused by BASG. Alternatively the applicant has the possibility, after consulting with the BASG, to withdraw the application.

I. 5 Batch release (“Chargenfreigabe”)

Medicinal products whose manufacture involves the use of human blood or plasma, as well as immunological medicinal products need to obtain batch release. According to § 26 (1) AMG, applications need to be submitted to

Austrian Federal Office for Safety in Health Care (BASG)

Austrian Agency for Health and Food Safety (AGES)

Institute OMCL (official medicines control laboratory)

Possingergasse 38, 1160 Vienna

E-Mail: chargen@ages.at

For further information see: www.basg.gv.at → OMCL → Formulare → F_L036-CFG-Antrag.docx

The quality assessment of clinical trial applications includes the evaluation for suitability of the methods (and limits) chosen for batch release purposes. In cases where changes to the batch release methods or parameters are intended, these need to be submitted in form of a substantial amendment to the BASG.

If the Investigational Medicinal Products (IMPs) are blood products § 26 (1) AMG, the following is to be considered:

a) Import of IMPs from outside the European Economic Area (produced outside the EEA, § 12 AWEG 2010) that fulfil the definition of a blood product (according to § 2 para 2 AWEG 2010):

The approval of an application for marketability is contingent on the submission of either documentation of batch release in Austria or alternatively, batch release by an EU-OMCL and notification of the Austrian OMCL.



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b) Shipment of IMPs within the European Economic Area (produced in a EEA country; § 14 AWEG 2010):

A shipment notification should be associated with the documentation of batch release in Austria or alternatively, batch release by an EU-OMCL and notification of the Austrian OMCL. These documents are legally required for shipment.

I. 6 Studies following additional legal frameworks:

I.6.1 Clinical trials with Advanced Therapies (ATMPs)

The principal dossier requirements for clinical trials with ATMPs are the same as those for clinical trials with non-AMTPs unless otherwise indicated in this guidance document.

For investigational products that are obtained through the donation of human tissues or cells the Tissue Safety Act applies (Gewebesicherheitsgesetzes, GSG). In those cases documented approval as tissue donation site (Gewebeentnahmeeinrichtung) according to § 19 GSG is required in the dossier. For further information please see the FAQ: www.basg.gv.at/arzneimittel/gewebe/faq/

I.6.2 Official ruling by the Federal Ministry of Health according to the GMO Act

Additional requirements apply to clinical trials with gene therapy medicinal products (GTMPs) and trials involving genetically modified organisms (GMOs). In these cases, the Austrian Gene technology Act, BGBl. Nr. 510/1994 § 4 Z 3 as well as §§ 74 to 79, need to be taken into account and the trial dossier needs to be submitted (ideally in parallel) to the BASG and to the Federal Ministry of Health (Bundesministerium für Gesundheit, BMG).

Applicants are advised that the Austrian Gene Technology Act refers to the following definition of gene therapy which differs from the definition in the Austrian medicinal products Act:

§ 4 Z 24 GTG: Somatic gene therapy for humans: The targeted introduction of isolated, nucleic acids, in somatic cells in humans, leading to the expression of the introduced nucleic acids, or the application of ex vivo genetically modified somatic cells or tissues to humans. A person treated with a somatic gene therapy is not considered a GMO

§ 4 Z 24 GTG: „Somatische Gentherapie am Menschen: Anwendung der gezielten Einbringung isolierter exprimierbarer Nukleinsäuren in somatische Zellen im Menschen, die zur Expression der eingebrachten Nukleinsäuren führt, oder die Anwendung derart außerhalb des menschlichen Organismus gentechnisch veränderter somatischer Zellen oder Zellverbände am Menschen. Ein mit einer somatischen Gentherapie behandelter Mensch gilt nicht als GVO.“



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Information concerning the rules of procedure for the submission of clinical trial dossiers according to the Gene technology Act is available for download on the following webpage: www.gentechnik.gv.at

A somatic gene therapy in human subjects may according to § 75 GTG only be initiated after the approval of the trial by the Austrian Competent Authority BASG and the Federal Ministry of Health (BMG) by a medical doctor in a hospital. The application for approval of the gene therapy clinical trial needs to be submitted to the BMG by the clinical director of the hospital involved and the coordinating physician.

Please be advised to utilize the EudraCT Number as Reference when communicating with both agencies.

In summary, clinical trials with ATMPs require the following documentation before initiation:

- a positive vote by the ethics committee
- the notification of approval by the Austrian Competent Authority
- the notification of approval by the Federal Ministry of Health, should the requirements of the Gene technology Act apply to the investigational medicinal product(s).

I.6.3 Clinical trials according to the Austrian Medicinal Devices Act

(Medizinproduktegesetz MPG, § 40 BGBl Nr. 657/1996 as amended)

See guidance: www.basg.gv.at –“Medical Devices” – “Clinical Trials”

I.6.4 Clinical trials conducted according to both the AMG and MPG legislations (“combined clinical trials”):

In the case of a combined study, a clinical trial application form according to the AMG and a separate application form according to the MPG are to be submitted to the address in section 0. If this submission occurs simultaneously to the BASG the fee will consist of the fee for the submission of an MPG study plus 35 percent of the fee for AMG trial submission. It is therefore essential that combined clinical trials are clearly indicated as such in the cover letter.



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II. Fees

Fees apply to initial clinical trial applications and substantial amendments. Current fees are published on the BASG Website at www.basg.gv.at/en/about-us/fees/. Fees are generally linked to index price adjustments.

Commercial clinical trials:

3,000 € for clinical trials Phase I-III

1,503 € for clinical trials Phase IV

500 € for substantial amendments

Non-commercial clinical trials:

600 € for clinical trials Phase I-III

300 € for clinical trials Phase IV

No fee for substantial amendments

A non-commercial trial is a trial where the raw data remain the exclusive property of the academic sponsor and no access is granted to third parties.

See 0 for medical device/medicinal product legislation combination trials

Changed fees for substantial amendments also apply to ongoing clinical trials initiated prior to the new fee structure.

Per default the invoice will be made out to the name/address of the applicant (section C of the EudraCT form). In case other arrangements are desired, the cover letter needs to contain contact details on the addressee of the invoice and the person/organization responsible for payment to the BASG.

III. Assessment by the Austrian Competent Authority

Note: All correspondence with the applicant will be sent exclusively to the address indicated in the application form under C.1. Keeping this information updated lies within the responsibility of the applicant.

III.1 Formal completeness:

The clinical trial application has to be submitted in proper ("valid") form by the sponsor. The assessment of formal completeness of the application is the first action taken by the CA.



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For a initially complete submission the validation date is the date of receipt of the submission. Should the application be incomplete, additionally required information will be requested by phone or e-mail. The dossier is then considered complete ("validated") upon receipt of the requested information or the required formal corrections (xml).

The validation date is the "clock start" for the 35 (calendar-)day scientific assessment period and is noted in the confirmation of formal completeness, which is sent to the sponsor (or named representative) by e-mail.

III.2 Timeframes:

The date of formal validation defines the start of the scientific assessment period. The clinical trial application can be considered as approved if the BASG has not communicated an objection within 35 days after this date (silent approval) or if the decision on the procedure has been published earlier than 35 days on the BASG website (see 0) .

Exception: Clinical trial applications with ATMPs need to be approved by written notification by BASG within the 90 day period stated on the confirmation of formal completeness. Should the engagement of an advisory board be required, the stated period is extended by a further 90 days. Alternatively, when the assessment is completed before the legal timeline, the receipt of the official communication or publication on the BASG Website indicates the decision of the BASG on the clinical trial submission.

Scientific assessment

Scientific assessment starts after the confirmation of the formal completeness. Scientific questions and requests for additional information (e.g. concerning the IMPD) may arise in this phase of the application procedure. Major deficiencies will be communicated to the applicant in a deficiency letter (see III.4.3).

III.3 BASG actions

Note: All correspondence with the applicant will be sent exclusively to the address indicated in the application form under C.1. Points 4.1, 4.2 and 4.3 are not applicable for clinical trials with Advanced Therapy Medicinal Products (ATMPs).

III.4.1 Non-interdiction/Silent approval

A clinical trial application is considered approved, if formal completeness has been confirmed, the ethics committee concerned has come to a positive opinion and either no objections have been raised by the BASG within the noted 35 calendar days or a decision by the BASG has been published on the BASG webpage within less than 35 days. The list of decisions can be found on the following website:



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<https://abstimmungen.basg.gv.at/abstimmung> → „Abstimmungen“. To search for a given procedure, the procedure number needs to be entered into the field „Betrachtungsobjekt“.

The screenshot shows the BASG-Abstimmungen website interface. At the top, it displays the logo and name of the Bundesamt für Sicherheit im Gesundheitswesen (BASG) and the AGES Medizinmarktaufsicht. Below this, there is a search bar and a results section. The results section shows a table with the following columns: Verfahrensnummer, Genehmigt am, Art, Typ, Ergebnis, Betrachtungsobjekt, Zulassungsnummer, and Inhaber. The 'Betrachtungsobjekt' column is highlighted with a red box. Below the table, it says 'No data to display.'

There is not requirement to wait for the publication on the BASG website, if 35 days have passed and, the other way round, if a decision has been published on the BASG website there is no need to await the end of the 35 day timeline.

In this case, the sponsor will **not** receive a written notification of approval by BASG.

III.4.2 Voluntary Harmonisation Procedure, VHP

Clinical trials or amendments that have already been assessed in the framework of the Voluntary Harmonization Procedure, VHP will undergo expedited review after confirmation of formal completeness, focusing on potential conditions and commitments imposed during the VHP. As outlined above in 0, the decision of the BASG will be published on the website, aiming to keep the timeline of ten days for initial applications and seven days for substantial amendments. The sponsor will not receive an additional written notification of approval by BASG.

III.4.3 Deficiency letter by the BASG according to § 45 Abs. 3 AVG

Should a dossier not fulfil the legal or scientific requirements the objections and information lacking will be communicated to the applicant in a deficiency letter. The letter will be sent via e-mail exclusively to the address indicated in the application form under C.1.

The sponsor then has the opportunity to amend the dossier (normally once) within a reasonable timeframe agreed upon by the agency and the sponsor. A single extension of the set timeframe can be requested. Should the sponsor fail to submit required information or to clarify questions, the clinical trial application will be rejected by official notification according to 0.

The AMG does not foresee a legal timeframe for assessment of a response to deficiencies. In case the response is complete and well structured and raised deficiencies are fully covered, review is usually completed within a week.



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If deficiencies have been appropriately addressed this will be communicated to applicants per e-mail. Subsequently, the clinical trial will follow the process described in 0, i.e. publication on the BASG website. A written notification will **not** be sent to the sponsor by BASG.

III.4.4 Interdiction according to § 40 para. 3 AMG

Should the sponsor fail to amend the clinical trial dossier according to the letter of deficiencies, the BASG will communicate the interdiction of the clinical trial by official notification to the sponsor or named representative.

III.4.5 Interdiction according to § 40 para. 4 AMG

Should the EC come to a negative conclusion on a clinical trial application, the BASG will communicate the interdiction by official notification to the sponsor or named representative.

III.4.6 Official ruling by the BASG according to § 40 para. 6 AMG

Applicable to Advanced Therapies.

IV. Amendments

Should it become necessary to amend the initial trial dossier the classification of whether the change is to be considered as substantial or non-substantial according to EudraLex, Volume 10 Chapter I lies within the responsibility of the applicant (see CT-1 document, point 114).

All amendments should be accompanied by a cover letter stating

- the classification as substantial or non-substantial amendment
for which clinical trial(s) the amendment is submitted (EudraCT number)

IV.1 Substantial Amendments

Both the BASG and the ethics committee concerned have to be notified of substantial (having an effect on the safety of trial participants) amendments according to § 37a AMG. The application should contain a covering letter describing the planned changes, the "Substantial Amendment Notification Form", the summary of changes and the changed documents of the dossier. The "Substantial Amendment Notification Form" can be found in Chapter 1 Eudralex Volume 10.

The "Substantial Amendment Notification Form" and the documents required for the assessment shall be submitted electronically on a data medium (e.g. CD). Documents that require a signature need to be signed electronically or submitted as scan of with a manual signature. The amendment application should be sent to the BASG together with a covering letter by e-mail to the address in section I.2. To



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facilitate the processing the BASG welcomes the additional submission of a print-out of the EudraCT application form.

Changed documents of the dossier (protocol, IB, IMPD) need to be submitted in a clean and a track-change version. Furthermore, changes need to be summarized and justified in a separate section/document ("summary of changes"). In case of changes to the EudraCT application form, a new PDF and XML version is to be submitted.

Similar to the initial application, amendments are subject to silent approval after 35 days. **The automatic confirmation of receipt stipulates the target date (start of the 35 day period).** There is no communication on the formal completeness of the amendment application. An explicit authorisation by the BASG before the expiration of the 35-day period (see 0 and 0) is also possible for amendment (e.g. for the VHP).

Exception: Substantial amendments for clinical trials with ATMPs need to be approved by written notification by BASG.

See "L_I219_Classification of Amendments for Clinical Trials with Medicinal Products according to the Austrian Medicinal Products Act (AMG)" for classification guidance

<http://www.basg.gv.at/en/medicines/before-authorisation/clinical-trials/>

IV.2 Urgent Safety Measures

Urgent safety measures may be taken without prior notification to the national competent authority. Examples of urgent safety measures are a temporary halt or additional monitoring measures are implemented to ensure the safety of the clinical trial participants.

However, the sponsor must inform *ex post* the national competent authority and the Ethics Committee concerned of the new events, the measures taken and the plan for further action as soon as possible. Where the initial contact is by telephone, for reasons of traceability, this should be followed up by e-mail and followed by a written report.

Finally, information and changed documents need to be submitted as substantial amendment according to IV.2. It needs to be highlighted in the amendment application form that the submission relates to already implemented safety measures.

IV.3 Temporary Halt and Restart of a Trial

A temporary halt is an unplanned stoppage of the trial not envisaged in the approved protocol and where there is an intention to resume activities. A temporary halt can be a substantial amendment



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(IV.1) or part of an urgent safety measure (IV.2). In this case, the notification of the temporary halt of a trial should be made immediately and, at the latest within 15 days.

The reasons and scope, e.g. stopping recruitment or interrupting treatment of subjects already included, should be clearly explained.

The restart of the trial should be treated as a substantial amendment and contain justification that it is safe to restart the trial.

If the sponsor decides not to recommence a temporarily halted trial he should notify the national competent authority within 15 days of his decision. This also applies when recruitment is not restarted, but treatment of already recruited participants continues.

IV.4 Non-substantial Amendments:

According to CT-1, sponsors are not required to submit non-substantial amendments to the Competent Authority or the EC. Non-substantial changes should be documented and appended to a (later) substantial amendment.

There is no application form for non-substantial amendments. The application form for substantial amendments should not be used for non-substantial amendments and may lead to classification as "substantial". Should the sponsor wish to report the non-substantial amendment, an informal notification can be submitted to the BASG electronically on a data medium (e.g. CD) together with a covering letter by mail to the address in section I.2.

If non-substantial amendments induce changes in the application form, an updated electronic version (e.g. CD) of the xml File needs to be submitted to the BASG to ensure up-to-date information.

Changes to the protocol regarding additional safety measures for the participants required by the ethics committee can be submitted in the form of a non-substantial amendment (exception). The updated protocol needs to be submitted to the CA.

Changed versions of the informed consent form do not need to be submitted to the BASG.

IV.5 Notifications not related to a clinical trial:

Notifications without reference to a clinical trial cannot be processed by the IT system. Sponsors and applicants are therefore alerted to the need to submit notifications with a cover letter linking the submission to a BASG reference number and detailing the nature and reason of the submission.



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V. Reporting obligations to the Competent Authority during a clinical trial

V.1 Reporting of suspected unexpected serious adverse reactions, SUSAR, § 41e AMG

V.1.1 SUSAR criteria

- The adverse reaction has to be serious
- Causality between adverse reaction and investigational medicinal product has to be suspected
- The adverse reaction has to be unexpected. The definition of “unexpectedness” is based on the reference safety information (RSI)

V.1.2 Reference Safety Information (RSI)

For new clinical trial applications:

When submitting a clinical trial application the reference safety information (RSI) should be, when applicable, within the Summary of Product Characteristics (SmPC) or within the Investigators Brochure (IB). If the RSI is within IB it should be a clearly identified separate section. This section should include a list of expected adverse reactions, e.g. in the form of a table, where all related adverse events (i.e. adverse reactions) are listed by nature and severity including frequency (see CT1 section 2.3. (32.), CT3 section 7.2.3.2. (51 to 53)). If different indications are being investigated for the investigational medicinal product (IMP), separate tables of expected adverse reactions by indication might be applicable to avoid misinterpretation, e.g. oncologic indications and immune mediated diseases. If RSI is within the SmPC, the list of expected adverse reactions is contained in section 4.8 Undesirable Effects. Please note that relevant safety information may also be contained in other sections, for further details please see EudraLex Volume 2C, http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm. If the IMP has a marketing authorization (MA) in several Member States concerned with different SmPCs, the sponsor should justify its selection of the most appropriate SmPC, with reference to subject safety, as the RSI (see CT3 section 7.2.3.2. (54)). In cases where the IB is used as the RSI (rather than the SmPC) for IMPs with MA any differences between the list of expected adverse reactions in the IB and the SmPC should be highlighted and justified. The applicant should indicate in the cover letter where the RSI is located.



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For ongoing clinical trials:

If the RSI is within the IB for an investigational medicinal product and there is not yet a clearly identified separate section to this effect, where all related adverse events (i.e. adverse reactions) are included e.g. in the form of a table (see above), we expect this to be implemented within your next (regular) IB update. The applicant should indicate in the cover letter where the RSI is located.

Changes to the RSI during a clinical trial:

When submitting a (substantial) amendment to an ongoing clinical trial, e.g. an IB update, the applicant should indicate in the cover letter if the RSI is updated. Where changes are proposed these should be clearly indicated using a Track Changes table.

Any change to an RSI is considered a substantial amendment and requires to be justified with supportive data. It is recommended to update the RSI, if necessary, in alignment with the annual period for a development safety update report (DSUR). If the date of RSI update is aligned this way the DSUR can act in part as justification for the RSI changes. In case your RSI is updated prior to the end of the reporting period of the DSUR a detailed justification by data is expected.

V.1.3 Reporting obligations

Sponsors are obliged to report SUSARs which occur within a given clinical trial in Austria or abroad § 41 (e) AMG. Reporting obligations do not apply to SUSARs which occur in clinical trials with the same investigational medicinal product but which have not been submitted in Austria.

V.1.4 Reporting Timelines

- The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authority and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days
- All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor

Note: Reporting obligations for SUSARs to the Austrian Competent Authority start once all prerequisites for the conduct of the trial are met (i.e. positive vote by the EC and silent approval by the competent authority). Reporting obligations end with the termination of the clinical trial in Austria



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provided that the national termination of the trial has been communicated to the agency (by informal notification).

V.1.5 Reporting procedure:

The preferred method is the electronic reporting in E2B-Format. Prerequisite for electronic reporting is the submission of the following form: "Ansuchen um Befreiung von der Meldungsverpflichtung über schwerwiegende Nebenwirkungen gemäß § 41e AMG an das Bundesamt für Sicherheit im Gesundheitswesen (BASG)" (see www.basg.gv.at → Formulare → Klinische Prüfung/).

Subsequently, report should be send directly to the the Pharmacovigilance Database of the European Medicines Agency (EudraVigilance-Clinical Trial Module) and not to BASG. Receipt will therefore be confirmed by the EV-Database and not the BASG.

This approach fulfills the legal reporting obligations according to § 41e of the Austrian Medicines Act. No further reporting to BASG, as described in the previous paragraph will then be required. Reporting obligations to ethics committees or other authorities involved are not affected by this procedure.

If electronic reporting to Eudravigilance is impossible, then SUSARs reports should be sent in paper (together with supporting documentation on CD, if necessary) to the address listed in section 0.

Only one method of reporting must be chosen for a given SUSAR, dual-reporting must be avoided. In case of technical problems during E2B submission, SUSARs are to be reported according to the requirements of the EMA and the BASG to both agencies.

V.2 Submission of the annual safety report

The Sponsor is required to submit annual reports to the BASG and the EC concerned, according to the "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use".

The required format for the annual safety report is the "development safety update report, DSUR". For content and structure of the DSUR please refer to the ICH guideline E2F „Note for guidance on development safety update reports" (EudraLex Volume 10, Chapter II). Further information can be found on the ICH homepage Homepage (www.ich.org → Work Products → ICH guidelines → Efficacy guidelines → Clinical Safety → E2F Development Safety Update Report). A Q&A document is available on the website of the Heads of Medicines Agencies (HMA) (<http://www.hma.eu/human.html> → Working Groups → Clinical Trials Facilitation Group).

The DSUR and the supporting documentation (e.g. appendices or tables) should be submitted electronically on a data medium (e.g. CD) and sent to the BASG together with a covering letter by mail to the address in section I.2.



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V.3 Annual update of the Investigator's Brochure (IB)

According to Article 8 of the Directive 2005/28/EC it is the sponsors responsibility to annually validate and update the Investigators Brochure. The update of the IB *per se* is not considered as a substantial amendment and therefore does not need to be submitted to the BASG.

The definition of a substantial amendment is however fulfilled, if new results included in the IB update (might) affect the safety and the physical and mental integrity of the clinical trial participants or show an impact on the scientific integrity of the Study. This could be the case even in the case of an unchanged Risk-Benefit-assessment.

VI. End of Trial

VI.1 End of trial according to the protocol

According to point 4.2 of the "Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1, 30.3.2010)", the sponsor has to make an end of trial declaration when the complete trial has ended in all Member States/third countries concerned.

For the declaration of the global end of the trial the "Declaration of the End of Trial" form should be submitted electronically on a data medium (e.g. CD) and sent to the BASG together with a covering letter by mail to the address in section I.2.

Consequently there are two options for the applicant from the BASG perspective:

1. Reporting of the global end of trial only: In this case, the procedure remains active until the end of trial is notified and all reporting obligations remain (SUSARs, ASR, etc.)
2. Informal communication of the National End of Trial on a data medium (e.g. CD) to the BASG together with a covering letter by mail, followed later by the declaration of the global End of Trial: In this case, the procedure is closed with the National End of Trial and only the provisions for the final study report remain.

The National end-of-trial is usually considered as the last visit of the last patient in Austria.



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IV.2 Premature termination of the clinical trial

According to § 32 para 1 Z 5 AMG (as amended) the sponsor is obliged to report the premature termination of the clinical trial in Austria to the BASG and the EC within a timeframe of 15 days clearly stating all reasons for the termination.

VII. Reporting obligations to the NCA after the conduct of the trial

According to § 32 Para.1 Z 10 AMG (as amended) and the CT-1 document the sponsor needs to assure the completion of a final study report on the clinical trial within a maximum of one year after the final (international) completion of the study and make it available on request.

Since July 21st 2014 sponsors are required to upload the final study report for Clinical Trials in the EudraCT database. This obligation arises from Directive 2001/20/EC and the Regulation (EC) No 1901/2006 on medicinal products for paediatric use. Posting the final study report fulfills the reporting requirement to the National Competent Authority. Final study reports will be made available to the public via the EU Clinical Trials Registry.

Posting of final study reports is compulsory for all Clinical Trials. Their publication is done automatically according to published rules (all authorized Clinical Trials except phase I studies in the adult population).

VII.1 Clinical Trials that ended on July 21st 2014 or thereafter:

The final study report needs to be uploaded within 12 months of the global end of trial for non-paediatric trials and within 6 months of the end of trial for Paediatric trials. Final reports for Paediatric trials that are not part of article 46 of Regulation (EC) No 1901/2006 can be given the 12 month timeline, if scientifically justified.

VII.2 Clinical Trials that ended on July 21st 2013 or thereafter and before July 21st 2014:

For all trials the final study report needs to be uploaded within 12 months after the finalisation of the programming (July 21st 2015).

VII.3 Clinical Trials that ended before July 21st 2013:

For Paediatric trials within the scope of article 41 (1) or article 46 of Regulation (EC) No 1901/2006 a timeline of 12 months (July 21st 2015) after the finalisation of the programming applies. The final study report for non-paediatric trials and other paediatric trials needs to be uploaded within 24 months (July 21st 2016) after the finalisation of the programming.



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Format of the final study report

- The “Full data set” is mandatory for Clinical trials which ended on July 21st 2014 or thereafter.
- A summary report (publication, synopsis according to ICH E3,...) is sufficient for paediatric trials conducted before Regulation (EC) No 1901/2006 entered into force (article 45).
- Either the full data set or a summary report is acceptable for clinical trials that ended more than a year before July 21st 2014.

The full data set comprises all required fields of the EudraCT database for the final study report and comprises information on the study, the study participants, endpoints and adverse events. A detailed listing can be found in chapter V of EudraLex Volume 10.

Further information for posting of results is available

- on the EudraCT Public Website (<https://eudract.ema.europa.eu/document.html>)
 - „Result related documentation“
 - „Training on EudraCT Results“
- in the Commission Guidance document in EudraLex Volume 10, Chapter V and
- in the FAQ section of the BASG website

VIII. Labelling of Investigational Medicinal Products (IMPs)

Labelling requirements for investigational medicinal products are laid out in the Kennzeichnungsverordnung 2008, the translation of the requirements of the GMP Annex 13 (Volume 4 - EudraLex) into National Law.

According to § 32 (1) 7 AMG the sponsor needs to provide “the appropriately characterised and labelled investigational medicinal product, which was manufactured under a license according to § 62 AMBO (Arzneimittelbetriebsordnung), or, for IMPs not manufactured in Austria, which has been manufactured according to internationally accepted standards, according to paragraph 3”

The applicant is referred to the English original text of Annex 13 (Volume 4 – EudraLex):

(<http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-4/>)

In the following is the relevant citation of the Austrian legislation, **Kennzeichnungsverordnung 2008**:

§ 50. (1) Der Sponsor einer klinischen Prüfung hat sicherzustellen, dass die Kennzeichnung der Prüfpräparate einen ausreichenden Schutz der betroffenen Personen bietet, die



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Rückverfolgbarkeit und die Identifizierung des Arzneimittels und der Prüfung ermöglicht und eine ordnungsgemäße Verwendung des Arzneimittels gewährleistet.

(2) Prüfpräparate dürfen außer in den Fällen nach den Abs. 3 und 4 oder in sonstigen begründeten Fällen nur in den Verkehr gebracht werden, wenn auf den Primärverpackungen und, soweit verwendet, auf der Außenverpackung in gut lesbarer Schrift, allgemein verständlich in deutscher Sprache und auf dauerhafte Weise angegeben sind:

- 1. Name oder Firma und Anschrift des Sponsors,*
- 2. Telefonnummer des Sponsors, sofern die Telefonnummern nicht in einem Begleitdokument aufgeführt sind, das dem Prüfungsteilnehmer auszuhändigen ist,*
- 3. Bezeichnung und Stärke des Prüfpräparates,*
- 4. Chargenbezeichnung mit der Abkürzung „Ch.-B“ oder Code-Nummer der Prüfung, BGBl. II - Ausgegeben am 28. Mai 2008 - Nr. 174 9 von 10*
- 5. Darreichungsform,*
- 6. Inhalt nach Gewicht, Volumen oder Stückzahl,*
- 7. Art der Anwendung,*
- 8. Dosierungsanleitung mit Einzel- oder Tagesgaben oder diesbezüglicher Verweis auf ein Begleitdokument oder die Anweisung eines Prüfers,*
- 9. Dauer der Verwendbarkeit (Verfalldatum mit dem Hinweis „verwendbar bis“ bzw. eine geeignete Abkürzung im Sinne des § 20 oder soweit die Art des Prüfpräparates dies erlaubt, Datum der Nachtestung) unter Angabe von Monat und Jahr,*
- 10. Prüfplancode, der die Identifizierung der klinischen Prüfung, der Prüfstelle, des Prüfers und des Sponsors ermöglicht, sofern nicht in einem Begleitdokument enthalten, das dem Prüfungsteilnehmer ausgehändigt werden kann,*
- 11. von der europäischen Datenbank vergebene EudraCT-Nummer, sofern diese nicht in einem Begleitdokument enthalten ist,*
- 12. Identifizierungscode der betroffenen Person, und, sofern erforderlich, Kennzeichnung der Einnahmesequenz, sofern nicht in einem Begleitdokument enthalten, das der betroffenen Person ausgehändigt werden kann,*
- 13. Hinweis, dass das Arzneimittel zur klinischen Prüfung bestimmt ist,*
- 14. Aufbewahrungs- oder Lagerungshinweise, sofern dies in der Genehmigung für die klinische Prüfung vorgesehen ist,*
- 15. Hinweis, dass das Prüfpräparat außer Reich- und Sichtweite von Kindern aufbewahrt werden soll, sofern das Prüfpräparat dazu bestimmt ist, der betroffenen Person ausgehändigt zu werden, und*



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16. besondere Vorsichtsmaßnahmen für die Beseitigung von nicht verwendeten Prüfpräparaten oder sonstige besondere Vorsichtsmaßnahmen, um Gefahren für die Gesundheit nicht betroffener Personen und die Umwelt zu vermeiden, oder Angaben für die Rückgabe. Wenn Primärverpackung und Außenverpackung fest verbunden sind, ist die Kennzeichnung auf der Außenverpackung ausreichend. Die Angabe nach Z 3 kann im Fall einer Verblindung der Prüfpräparate entfallen oder auf geeignete Weise verschlüsselt werden.

(3) Sofern Primärverpackung und Außenverpackung des Prüfpräparates dauernd zusammengehalten werden sollen und die Außenverpackung Angaben gemäß Abs. 2 aufweist, muss die Primärverpackung mindestens die Angaben nach Abs. 2 Z 1, 3, 4, 5, 6, 7, 10 und 12 aufweisen, die Angabe nach Abs. 2 Z 7 kann bei festen oralen Darreichungsformen entfallen.

(4) Bei Primärverpackungen von nicht mehr als 10 ml Volumen und bei Ampullen brauchen die Angaben nach Abs. 2 nur auf den Außenverpackungen gemacht zu werden, jedoch müssen sich auf den Primärverpackungen und den Ampullen mindestens die Angaben nach Abs. 2 Z 1, 3, 4, 7, 10 und 12 befinden.

(5) Angaben nach Abs. 2, die zusätzlich in einer anderen Sprache wiedergegeben werden, müssen in beiden Sprachversionen inhaltsgleich sein. Weitere Angaben sind zulässig, sofern sie mit der Verwendung des Prüfpräparates in Zusammenhang stehen, für die gesundheitliche Aufklärung wichtig sind und den Angaben nach Abs. 2 nicht widersprechen.

(6) Wenn die Dauer der Verwendbarkeit nachträglich verlängert werden soll, ist ein zusätzliches Etikett auf der Primärverpackung und, soweit verwendet, auf der Außenverpackung anzubringen, das das neue Verfalldatum oder das Datum der Nachtestung sowie die Chargenbezeichnung aufweist. Mit dem Etikett kann das frühere Datum, nicht aber die bereits vorhandene Chargenbezeichnung überdeckt werden.

(7) Sofern es sich bei Prüfpräparaten um zugelassene oder registrierte Arzneyspezialitäten handelt, die ohne zusätzliche Herstellungsmaßnahmen zur Verwendung in der klinischen Prüfung bestimmt sind, kann auf besondere Kennzeichnungen auf der Primärverpackung und Außenverpackung nach den Abs. 2 bis 6 verzichtet werden, soweit es das Konzept der klinischen Prüfung erlaubt. Angaben nach Abs. 1 können auch in einem Begleitdokument aufgeführt werden.



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Special requirements for labelling for Tissues and Cells are described in 2006/86/EG Appendix II, section E (see Annex).

For genetically modified organisms (GMOs), additional requirements apply, outlined in § 62a of the Gene Technology Act: GMOs that are used in closed systems, released or used for scientific reasons including clinical trials need to be labeled as such on the label or in accompanying documentation.

§ 62a GTG: „GVO, die für Arbeiten mit GVO im geschlossenen System, für eine Freisetzung oder für wissenschaftliche Zwecke einschließlich klinischer Prüfung bereitgestellt werden, müssen auf einem Etikett oder in einem Begleitdokument als GVO gekennzeichnet sein.“

IX. Import of IMPs

As stated in § 6 (2) of the Austrian Medicinal Products Import Act (AWEG 2010, BGBl I Nr. 79/2010, as amended) the shipment of medicinal products within the European economic area (EEA) for clinical or non-clinical trials or clinical experimentation does not require a notification of distribution.

Similarly, medicinal products for these purposes which are licensed in Switzerland or were manufactured there do not require a notification of distribution.

The text is applicable to the shipment of blood products which are used as medicinal products in clinical or non-clinical trials (§ 14 Abs. 8 AWEG 2010).

Under the provision that they have been released by an EU Qualified Person, the ruling applies to medicinal products manufactured outside the EEA.

IMPs which contain addictive or psychotropic substances

An import license by the Ministry of Health (BMG) is required for medicinal products and blood products which contain addictive or psychotropic substances, independently of AWEG 2010 requirements, country of origin or license status. Therefore an application for an import license according to the addictive substance legislation is to be directed to the BMG (<http://www.bmg.gv.at/>).



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X. Contact

Further questions can be addressed to the following e-mail addresses:

- All questions regarding clinical trials → clinicaltrials@ages.at
- Compassionate Use → compassionate-use@ages.at
- Non-interventional studies → nis@ages.at
- Questions on
- Clinical trials with medical devices
 - Tissue banks or tissue safety
 - Shipment/Importation of IMPs
 - Labelling of IMPs
 - Handling of IMPs
 - Archiving → inspektionen@ages.at

XI References

XI.1 Websites

BASG/AGES

www.basg.gv.at

www.ages.at

BASG/AGES Frequently asked questions (FAQs)

www.basg.gv.at/arzneimittel/faq/klinische-pruefung/

Federal Ministry of Health, Bundesministerium für Gesundheit

www.bmg.gv.at

EudraCT-Website

www.eudract.ema.europa.eu

European Legislation (EudraLex)

http://ec.europa.eu/health/documents/eudralex/index_en.htm

European Medicines Agency

www.ema.europa.eu

Ethics committees in Austria

www.ethikkommissionen.at

Forum of Austrian ethics committees

www.meduni-graz.at/ethikkommission/Forum/index.htm

International Conference on Harmonisation (ICH)

www.ich.org



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XI.2 Laws and guidance

- Arzneimittelgesetz - AMG; BGBl Nr. 185/1983 (as amended)
- Arzneimittel-Betriebsordnung 2009 - AMBO 2009; BGBl. II Nr. 324/2008 (as amended)
- Kennzeichnungsverordnung 2008; BGBl. II Nr. 174/2008 (as amended)
- Arzneiwareneinfuhrgesetz 2010 - AWEG 2010; BGBl. I Nr. 79/2010 (as amended)
- Verordnung des Bundesamtes für Sicherheit im Gesundheitswesen über den Gebührentarif gemäß Gesundheits- und Ernährungssicherheitsgesetzes (as amended)
www.basg.gv.at/en/about-us/fees
- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (CT-1)
- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (CT-3)
- Gewebesicherheitsgesetz - GSG; BGBl. I Nr. 49/2008 (as amended)
- Gentechnikgesetz - GTG; BGBl. Nr. 510/1994 (as amended)

XI.3 Guidance for ATMPs

EudraLex

http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/index_en.htm

- Volume 4 Annex 2 (GMP) „Manufacture of Biological Medicinal Products for Human Use“
- Volume 10, Chapter 5 (GCP) „Detailed Guideline on Good Clinical Practice Specific to Advanced Therapy Medicinal Products“

European Medicines Agency

www.ema.europa.eu/ → Human regulatory → Scientific guidelines → Multidisciplinary

- Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products, CHMP/SWP/28367/07
- Reflection paper on classification of advanced therapy medicinal products, EMA/CAT/600280/2010
- Human cell-based medicinal products, CHMP/410869/06
- Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products, EMEA/149995/2008



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- Reflection paper on *in-vitro* cultured chondrocyte containing products for cartilage repair of the knee, EMA/CAT/CPWP/568181/2009
- Guideline on Xenogeneic Cell-Based Medicinal Products, EMEA/CHMP/CPWP/83508/2009
- Non-clinical studies required before first clinical use of gene therapy medicinal products, CHMP/GTWP/125459/06
- Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products, CHMP/GTWP/125491/06
- Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors, EMEA/273974/05
- Development and Manufacture of Lentiviral Vectors, CHMP/BWP/2458/03
- Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products CPMP/BWP/3088/99
- Note for Guidance on Virus Validation Studies: The design, contribution and interpretation of studies validating the inactivation and removal of viruses, CPMP/BWP/268/95
- Please follow this link for ATMP specific EMA Guidelines
www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000298.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800862bd

International Society for Stem Cell Research

Guideline for the Clinical Translation of Stem Cells

(www.isscr.org/home/publications/ClinTransGuide)



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XII. Annexes

XII.1 Presentation of pre-clinical data

The applicant is asked to provide clear tables summarizing relevant data concerning the following issues: type of study (acute or chronic toxicity studies, carcinogenicity studies), animal species/strain, study ID, GLP-status, duration of animal dosing, route of administration, number and gender of animals per group, substance, dose selection, NOAEL and major findings, respectively.

In addition, severity and clinical relevance as well as safety margins as compared to the planned dose in humans and time to recovery should be a matter of discussion.

An exemplary table reporting preclinical data is depicted below:

	Study ID/ Duration GLP	Species/strain Sex Number/Group	Dose (mg/kg) Route	NOAEL mg/kg/day	Major findings
Repeated-dose toxicity study	No. XXX 4 weeks yes	Rat SD 10M/10F	0 0.1 0.3 0.75 <u>S.C.</u>	< 0.1	> 0.1: ↓ in urine volume > 0.75: 1M and 1F died

XII.2 Definitions for clinical trials with Advanced Therapy Medicinal Products (ATMPs)

Advanced Therapy Medicinal Products (ATMPs) include Gene therapy medicinal products and somatic cell therapy medicinal products as defined in Annex I Part IV to Directive 2001/83/EC, and tissue engineered products according to Article 2 Paragraph 1b of the Regulation 1394/2007 on Advanced Therapy Medicinal Products.

While the “Reflection paper on classification of advanced therapy medicinal products” (EMA/CAT/600280/2010) provides helpful details, the legal definitions are found in the above cited documents.



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Somatic cell therapy medicinal product

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

- (a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;
- (b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

Gene therapy medicinal product

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

- (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;
- (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

'Tissue engineered product'

means a product that:

- contains or consists of engineered cells or tissues, and
- is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices. Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.



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XII.3 Cell based Therapies (Somatic Cell Therapy, Tissue Engineering)

Donor Testing

Requirements for cellbased products are in accordance to those for blood products and are laid down in Directive 2006/17/EC. These requirements are applicable independently of whether the ensuing medicinal product is intended for autologous or allogeneic use.

In the following the minimal required tests are cited from Directive 2006/17/EC:

HIV 1 and 2	Anti-HIV-1,2
Hepatitis B	HBsAg, Anti HBc
Hepatitis C	Anti-HCV-Ab
Syphilis	See 1.4 (below)

1.2. HTLV-I antibody testing must be performed for donors living in, or originating from, high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas.

1.3. When anti-HBc is positive and HBsAg is negative, further investigations are necessary with a risk assessment to determine eligibility for clinical use.

1.4. A validated testing algorithm must be applied to exclude the presence of active infection with *Treponema pallidum*. A non-reactive test, specific or non-specific, can allow tissues and cells to be released. When a non-specific test is performed, a reactive result will not prevent procurement or release if a specific Treponema confirmatory test is non-reactive. A donor whose specimen tests reactive on a Treponema-specific test will require a thorough risk assessment to determine eligibility for clinical use.

1.5. In certain circumstances, additional testing may be required depending on the donor's history and the characteristics of the tissue or cells donated (e.g. RhD, HLA, malaria, CMV, toxoplasma, EBV, *Trypanosoma cruzi*).

Traceability

The requirements for traceability are defined in Article 15 of the Regulation for Advanced Therapy Medicinal Products:

1. The holder of a marketing authorisation for an advanced therapy medicinal product shall establish and maintain a system ensuring that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used.



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2. The hospital, institution or private practice where the advanced therapy medicinal product is used shall establish and maintain a system for patient and product traceability. That system shall contain sufficient detail to allow linking of each product to the patient who received it and vice versa.
3. Where an advanced therapy medicinal product contains human cells or tissues, the marketing authorisation holder, as well as the hospital, institution or private practice where the product is used, shall ensure that the traceability systems established in accordance with paragraphs 1 and 2 of this Article are complementary to, and compatible with, the requirements laid down in Articles 8 and 14 of Directive 2004/23/EC as regards human cells and tissues other than blood cells, and Articles 14 and 24 f Directive 2002/98/EC as regards human blood cells.
4. The marketing authorisation holder shall keep the data referred to in paragraph 1 for a minimum of 30 years after the expiry date of the product, or longer if required by the Commission as a term of the marketing authorisation.

Drug product Testing

Overall test requirements for cell based products result from the two essential requirements of donor-testing and drug product testing. The latter with a specific focus on the absence of infectious material. In the case of investigational medicinal products for autologous use there is no need to repeat the tests for blood-borne pathogens which are required at donation, however the absence of microbial contamination needs to be demonstrated, see *Guideline for Human Cell Based Medicinal Products*. The absence of microbial contamination in the drug product needs to be guaranteed, however should pose time restrictions be encountered due to the nature of the product or the manufacturing process, the required tests can also be conducted prior to batch release.

Cell based medicinal products do not fall under the scope of ICH Q5A "Guideline on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Product Derived from Cell Lines in of human or animal origin", however, its principles should be considered.

Final Labelling for Distribution (DIR/2006/86/EC) Annex II, Part E and F)

1. The primary tissue/cell container must provide:
 - (a) type of tissues and cells, identification number or code of the tissue/cells, and lot or batch number where applicable;
 - (b) identification of the tissue establishment;
 - (c) expiry date;
 - (d) in the case of autologous donation, this has to be specified (for autologous use only) and the donor/recipient has to be identified;
 - (e) in the case of directed donations - the label must identify the intended recipient;



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- (f) when tissues and cells are known to be positive for a relevant infectious disease marker, it must be marked as:
BIOLOGICAL HAZARD.

If any of the information under points (d) and (e) above cannot be included on the primary container label, it must be provided on a separate sheet accompanying the primary container. This sheet must be packaged with the primary container in a manner that ensures that they remain together.

2. The following information must be provided either on the label or in accompanying documentation:
1. description (definition) and, if relevant, dimensions of the tissue or cell product;
 2. morphology and functional data where relevant;
 3. date of distribution of the tissue/cells;
 4. biological determinations carried out on the donor and results;
 5. storage recommendations;
 6. instructions for opening the container, package, and any required manipulation/reconstitution;
 7. expiry dates after opening/manipulation;
 8. instructions for reporting serious adverse reactions and/or events as set out in Articles 5 to 6;
 9. presence of potential harmful residues (e.g. antibiotics, ethylene oxide etc).

External Labelling of the Shipping Container

For transport, the primary container must be placed in a shipping container that must be labelled with at least the following information:

- (a) identification of the originating tissue establishment, including an address and phone number;
- (b) identification of the organisation responsible for human application of destination, including address and phone number;
- (c) a statement that the package contains human tissue/cells and **HANDLE WITH CARE**;
- (d) where living cells are required for the function of the graft, such as stem cells gametes and embryos, the following must be added:
'DO NOT IRRADIATE';
- (e) recommended transport conditions (e.g. keep cool, in upright position, etc.);
- (f) safety instructions/method of cooling (when applicable).