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# Clinical Trials with ATMPs in Europe
# Getting Started

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# Disclaimer

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- **EMA**: “The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.”

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# Essential Differences

## Regional differences

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### EU – NCAs and EMA

- Tracking via the clinical trial (EUDRA-CT)
- GMP certificate/inspection required for phase I
- CT approval is National remit, based on EU legislation
- Trials could be in different MSs – prior to CTR no continuity
- CTR → sharing assessment reports

### USA - FDA

- Tracking via the substance (IND number)
- No initial GMP certificate required
- FDA remit, US legislation
- IND linked to review-team
- Database of previous assessments

# Update

## Where are we now?

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- The Clinical Trials Regulation (CTR) has been finalized and was published on April 16th 2014
- The practical application is awaiting the „go-live“ of the EU portal
- The EU portal has been delayed to 2020
- Various Guidance documents have been updated or newly written
- GMOs framework is under discussion → following presentations
- CAT and CTFG representatives have been working on the Guideline for Investigational ATMPs since the beginning of 2016

# Official Publication

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http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_158_R_0001&from=EN

Official Journal of the European Union

L 158

English edition

Legislation

Volume 57

27 May 2014

Contents

I *Legislative acts*

REGULATIONS

★ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (1) 1

Text is final!
Need for additional guidance, where the legislation cannot be sufficiently detailed

# Clinical Trials with ATMPs

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## My personal take …

- Pre-requisites for the conduct of a CT – product perspective
- Regulatory check – applicable legislation
- Procedural check – current processes and impact of CT Regulation
- Quality dossier

# Prerequisites

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## Product Requirement Document (PRD)

- Organized list of product attributes and features created .. to establish consensus about product design requirements (performance, safety, quality) incorporating the following aspects
- PRD used as reference throughout development and lifecycle
- PRD identifies relevant market and user requirements and links them to a clear set of verifiable technical requirements ... This is essential for rigorous, controlled product development, providing a framework against which product specifications can be developed

→ provides the "pitch" (CT submission) and internal reference for your product

Bioprocess International Feb 2007, pp 22-31

# Prerequisites

## Classification and risk analysis

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- The classification of the product should be considered in the PRD, e.g. somatic cell therapy, tissue engineered product or gene therapy, potentially combined
  - Optional CAT classification procedure

- As outlined in the ATMP Regulation, an initial risk analysis should be conducted based on existing knowledge of the type of product and its intended use to determine the extent of quality, non-clinical and clinical data to be included in the MAA, in accordance with the scientific guidelines … ← impacts on CTs
  - GL on the risk-based approach EMA/CAT/CPWP/686637/2011

# Regulatory check

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## Medicines legislation and …

- Are human starting materials involved → Tissues and cells legislation
  - Donation, procurement, testing – Dir/2004/23/EC, Dir/2006/17/EC
  - Cells imported from 3rd countries – Dir/2015/ 566/EC
  - Transfer of information to GMP manufacturer
- Viral vectors → GMO legislation
  - Impacts on manufacturing site, trial sites and approval procedure
- Medical device legislation
  - Combined ATMP (integral device) → technical requirements
  - Delivery device (non integral)
  - Specialized devices during surgery
- In-vitro diagnostic regulation – companion diagnostic
- Data protection regulation

# Drug/device CTs

## Consequences of potential „hard“ Brexit

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| | Medicinal product legislation | Medical device legislation |
|---|---|---|
| **First submission of CTs** | UK companies can no longer function as legal representatives or be responsible for QM release for 3rd country sponsors | UK companies can no longer function as legal representatives for 3rd country sponsors |
| **Ongoing CTs** | Substantial Amendments are required to switch legal representatives or QM release for 3rd country sponsors from UK to EU resident organizations<br><br>No substantial AMD, if the switch from UK QP to EU QP occurs within the same company. | Substantial Amendments are required to switch legal representatives for 3rd country sponsors from UK to EU resident organizations |
| **IMPs** | IMPs manufactured or licensed in the UK or have to demonstrate complicance with EU GMP and require relase by EU QP; The SmPC will be accepted (ICH Region). | If the CE-Certificate by UK manufacturers /Notified Bodies is no more valid, the products will be considered as non-CE marked and the clinical investigation likely will require approval and a full dossier (depending on detailed setting) |

# Procedural check

## Conducting the CT

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- Familiarize yourself with the submission process and timelines in the MSs where you want to conduct your CT, particularily for GMOs
  - ec.europa.eu/health/human-use/advanced-therapies/gmo_investiganional_en
  - NCAs: Local guidance documents; innovation office
- Consider the required sequence of submissions and dossier content
- Consider VHP procedure – ends with CT Regulation
- If you are submitting soon – consider the impact of the CT regulation
  - Will your trial be completed before the projected go-live?
  - If not – consider transition requirements early → Q&A document
    ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

# How to find relevant documents

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## EudraLex Volume 10

English EN

European Commission > Live, work, travel in the EU > Public Health >

Vol 10: Clinical Trials

### EudraLex - Volume 10 - Clinical trials guidelines

Volume 10 of the publication "The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials.

- Set of documents applicable to clinical trials authorised under Directive 2001/20/EC
- Set of documents applicable to clinical trials that will be authorised under Regulation EU No 536/2014, once it becomes applicable

**https://ec.europa.eu/health/documents/eudralex/vol-10_en**

# EU No 536/2014 documents

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## Updated documents

**Chapter I**

- Guidance to be added at a later stage

**Chapter III – Quality**

- GL on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (revision 1 – **2017**)
- GL on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (Revision 1 - **2017**)
- Auxiliary medicinal products in clinical trials (rev. 2, **2017**)

# EU No 536/2014 documents

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## Updated documents

**Chapter IV – Inspections**

- Guidance for the conduct of good clinical practice inspections (**2017**)
  - Annexes I, II, III, IV, VI, VII
- Guidance for the preparation of good clinical practice inspections (**2017**)
- Guidance for the preparation of good clinical practice inspection reports and communication of inspection findings (**2017**)
- Guidance for coordination of GCP inspections requested in the context of marketing authorisation applications for mutual recognition and decentralised procedures and cooperation between Member States (**2018**)

# EU No 536/2014 documents

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## Updated documents

### Chapter V - Additional documents

- Draft - **Questions and Answers Document** - Regulation (EU) 536/2014 – Version 1 (**2018**) .

  Updated progressively

- Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products - EMEA/CHMP/SWP/28367/07 Rev. 1 (**2017**)
- Guideline for GCP - ICH E6(R2) - EMA/CHMP/ICH/135/1995 (2016)
- Risk proportionate approaches in CTs (**2017**)
- Summaries of CT Results for Laypersons (version 2 - **2018**)
- Ethical considerations for CTs on medicinal products conducted with minors (**2017**)
- Detailed guidelines on GCP specific to ATMPs – (**Update ongoing**)
- Recommendation on the content of the trial master file and archiving – (**Update ongoing**)

# Strategic thinking

## Simple truths

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- Your trial data can only  be considered as reproducible, if the investigational product is sufficiently characterized

- If you want to accelerate your development, you need to accelerate your manufacturing process development and product characterization

- If your trial is supposed to provide pivotal data, the IMP in this trial needs to be mature → Insufficient quality control jeopardizes the use of the data for MAA

# Quality Dossier

## Outlook on iATMP Guidance

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- Content:
  - Multidisciplinary guideline for all iATMPs (SC, TE, GT)
  - Quality, preclinical and clinical guidance
  - Considering device aspects

- Focus on requirements for first-in-human and exploratory studies

- Quality data in the IMPD are expected to reflect increasing knowledge and experience during product development
  e.g. difference between exploratory and pivotal studies

# Points to consider

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## Active substance

- Focus of CT approval is the safety of subjects enrolled in the trial!
- Where iATMP production is continuous and the active substance cannot be separated from the drug product (DP), it is sufficient to provide information only once in Drug Substance (DS) section
- The IMPD is not set in stone. Specifications and acceptance criteria need to be reviewed and, where appropriate, adjusted to the respective stage of development; same applies to in-process controls
- Progressively increasing stability data are expected

# ATIMP

## Describing the active substance

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- Cell-based investigational ATMPs (CBiATMP):
  description of active substance, including information on the cell composition; structural components to be described that are part of the active substance, e.g. where cells are grown into sheets or combined with matrices/scaffolds.

- Gene Therapy investigational ATMPs (GTiATMPs):
  description including diagrammatic representation of the construct; provision of therapeutic sequence(s), junction regions and regulatory elements, and sequences added for targeting, regulation or expression of the construct

# General properties (1)

## .. and Mechanism of action (MoA)

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- The proposed mechanism of action should be described →it forms the basis for active substance control including biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect)
- Claimed activities should be reflected at least in characterization studies and in release specifications unless otherwise justified

- CB IMPs: origin of the cells, processing technique (e.g. reprogramming, genetic modification, activation) and test results of the manipulated starting material

# General properties (2)

## .. and Mechanism of action (MoA)

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GT IMP vector as starting material:

Same level of information as active substance, GMP principles, no Masterfile concept

- Vector design, development genetics (origin applicable, history and biological characteristics of the parental virus or bacterium); full sequence for plasmid DNA
- Avoid antibiotic resistance genes (or other elements used for selection)
- Data on control and stability of the vector and therapeutic sequence(s) during development to be provided; ensure fidelity of replication systems. Provide evidence on sequence correctness and maintenance

# Manufacturing process/process controls

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## General

- Step-by-step description
- Identify critical steps
- Identify intermediate products
- Identify relevant process parameters, in-process controls (IPCs) and acceptance criteria
- Early phase IPC testing to focus at minimum on safety aspects
- No “alternative” manufacturing steps without justification and supportive data

→ To be regularly revisited during development

# Raw materials

## PharmEur Chapter 5.2.12

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**Raw materials of biological origin for the production of cell-based and gene therapy medicinal products:**

- .. applies to the following classes of raw materials
  - sera and serum replacements;
  - recombinant proteins, i.e. growth factors, cytokines, hormones, enzymes and mAbs
  - proteins extracted from biological material, i.e. enzymes and polyclonal Abs
  - vectors
- .. other classes of biological raw materials, where appropriate
- Out of scope: Medical devices, plastics and chemically synthesised raw materials, i.e basal media, synthetic peptides/ polynucleotides

# Starting materials

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## Producer/packaging cell lines

- identity, purity, cell number, viability, strain characterization, genotyping/phenotyping, verification of the plasmid/transgenic/ helper sequence structure (e.g. restriction analysis or sequencing), genetic stability, copy number, identity and integrity of the introduced sequences
- Testing for adventitious viruses according to ICH Topic Q5A and EP 5.1.7, including tests for contaminating and endogenous viruses
- Absence of bacterial and fungal contamination, mycoplasma and spiroplasma (insect cells). Electron microscopy of insect cells unless otherwise justified
- Descriptions of design, construction, production and banking system

# Process evaluation/validation

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## During development

- Documented evidence that the manufacturing process can consistently produce a result within specific parameters
- Appropriate monitoring and control measures expected, but not validation; higher demands for pivotal studies
- Emphasis on the validation of aseptic process and quality and control of starting/ raw materials. Validation of aseptic manufacturing conditions prior to First-in-Human CTs.
- Provide summaries of characterization and verification studies, not reports (EMA/CHMP/BWP/187338/2014)
- Characterization/evaluation/validation with surrogate materials - GMP Guide on ATMPs; consider representativeness
- Describe approach if concurrent validation is foreseen

# Characterization

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## Potency

- The assay should be based on the intended biological effect which should ideally be related to the clinical response. Surrogate potency methods can be considered, need to be justified
- Development of a suitable potency assay to be started ASAP, preferably when material for first CT is produced, should be validated prior to pivotal CTs unless otherwise justified

- GTiATMP: The intended action of regulating, repairing, replacing, adding or deleting a genetic sequence should be demonstrated. The in vitro biological activity of all transgene(s) and any other expressed sequences should be investigated

# Control of active substance

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## Specifications

- Early acceptance criteria are inherently preliminary → ongoing review
- Specifications need to be meaningful (MoA) and quantitative
- Tests/defined acceptance criteria for **quantity, identity, purity and biological activity**. Upper limits for impurities (safety considerations)
- 'record' or 'report results' is **not** a specification – anything permissive – task of agency to evaluate safety
- Additional tests not sufficiently mature for specifications → can be included without pre-defined limits, results in batch analyses
- If certain release tests cannot be performed on DS or DP, only on key intermediates and/or as in-process tests, this needs to be justified
- **GTiATMP**: genetic identity + integrity – therap. sequence + vector

# Integral devices

## Drug substance

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- Cell-based medicinal products may incorporate structural components as starting materials which independently are medical devices or active implantable medical devices → should meet essential requirements on medical devices as per current legislation → information to be provided in IMPD

- Cell-based medicinal products may also incorporate structural components which are not identical to, or used in the same way as in a medical device → to be appropriately characterised and evaluated for suitability for intended use

# You want do develop an ATMP?

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## … keep in mind …

- Know your product/MoA/dose
- Product requirement document
- Know the regulatory requirements
- Determine data requirements according to risk-based approach
- Build analytic panel early including ..
- … potency assay
- Design trial to increase product knowledge

- Finally … consider the market

# Thank you for your attention
# Questions?