GOOD MANUFACTURING PRACTICES

FOR ADVANCED THERAPY MEDICINAL PRODUCTS

Joline Ingels

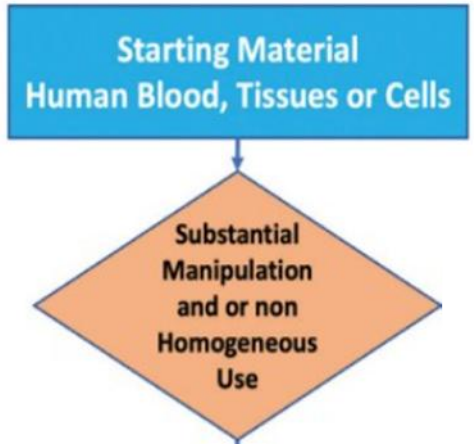
Head of Production

Cell and Gene therapy unit UZGent (CellGENTherapies)

GHENT UNIVERSITY

UZ GENT

ATMP regulation versus tissues and cell regulation



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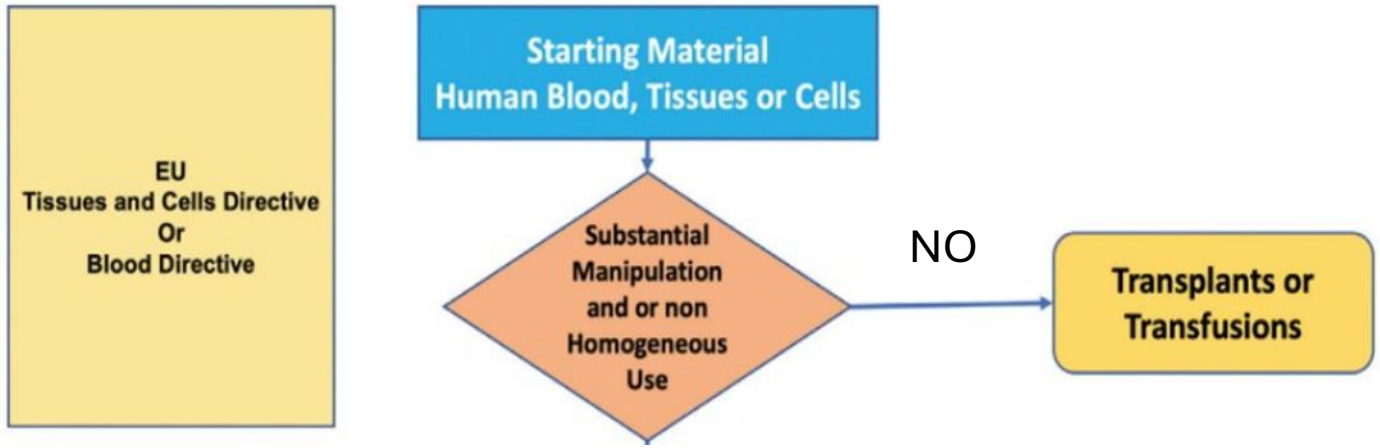

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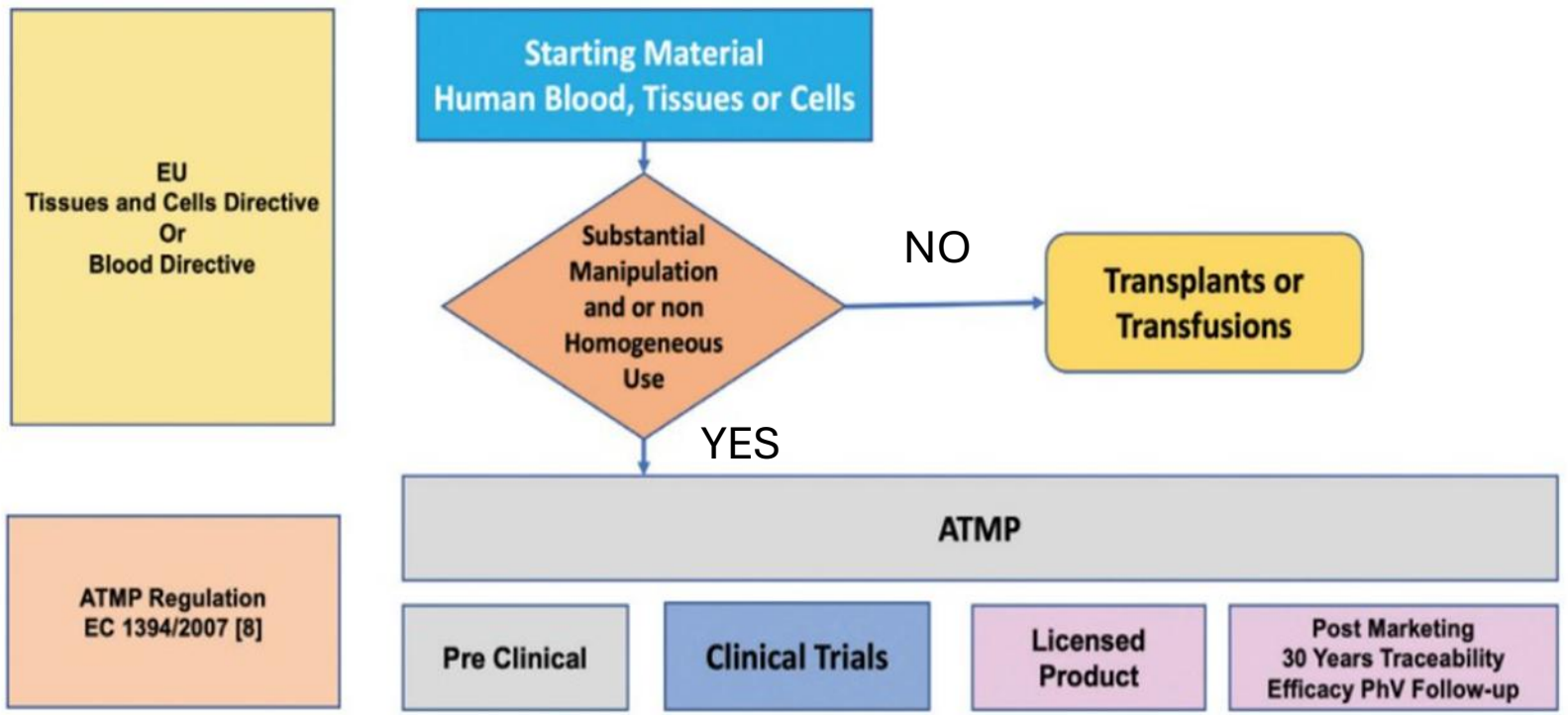

ATMP regulation versus tissues and cell regulation

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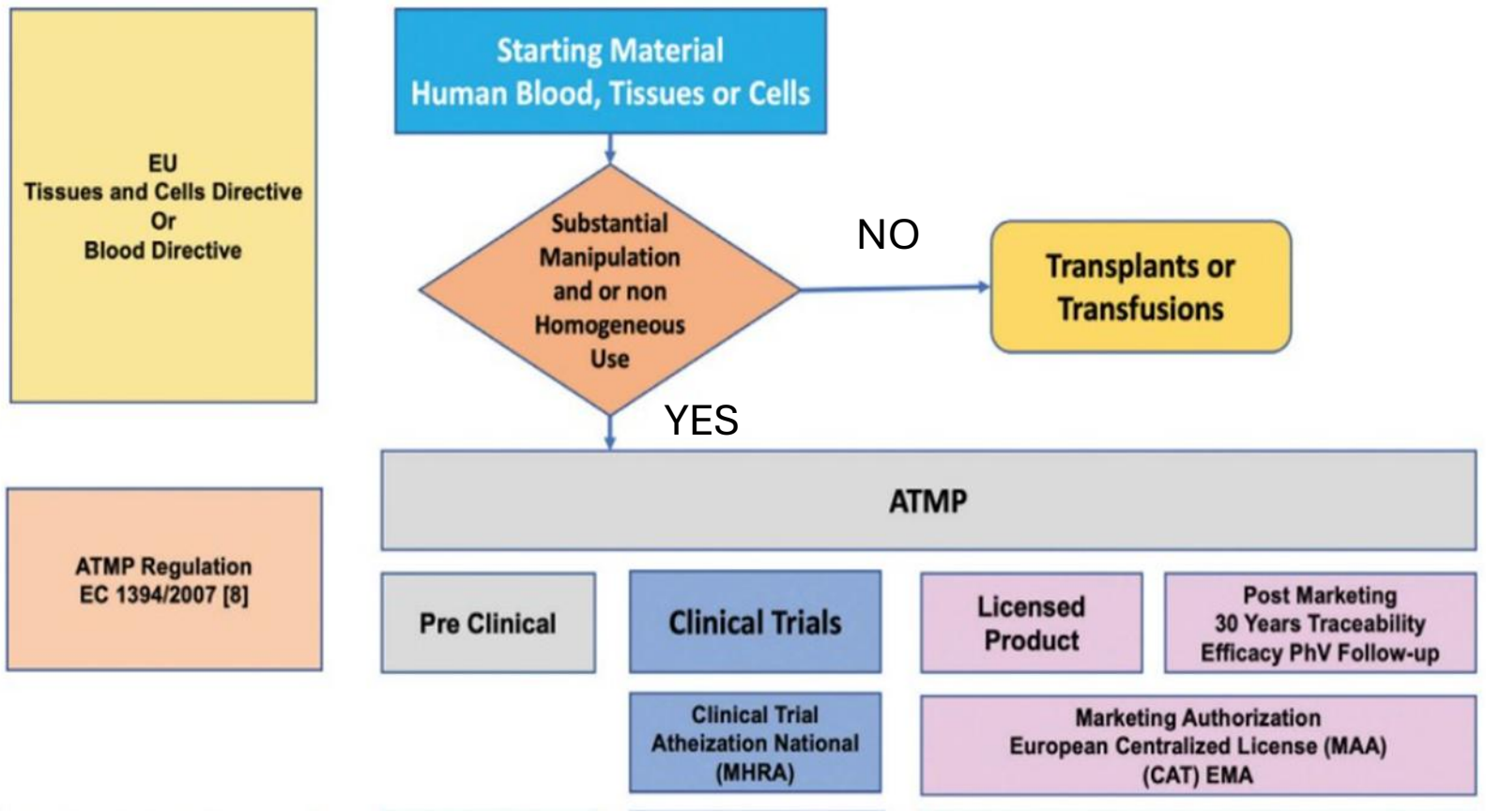

Advanced therapy medicinal products (ATMP)

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Gene Therapy

Somatic Cell Therapy

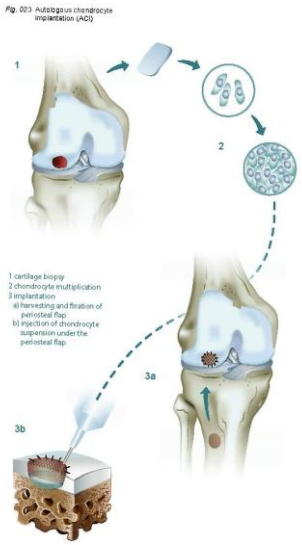
Tissue Engineering

Combined ATMP

Cell based gene therapy

casgevy
(exagamglogene autotemcel)
suspension for IV infusion

HOLOCLAR®
Ex vivo expanded autologous human corneal epithelial cells containing stem cells



ATMP manufacturing workflow

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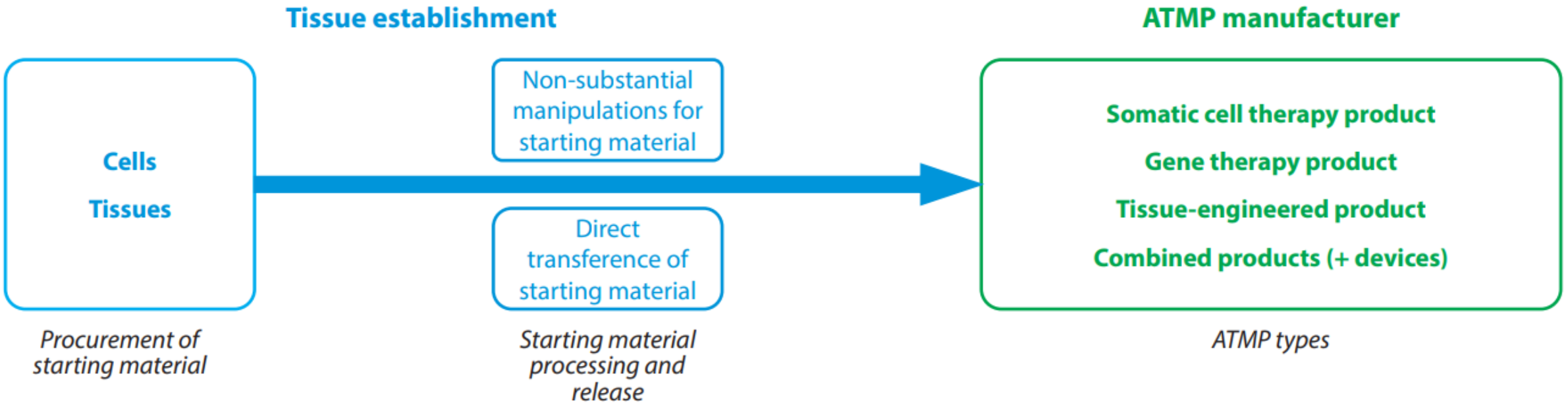

Guide to the quality and safety of tissues and cells for human application. EDQM 5th Edition 2022.

GMP guidelines: EudraLex – Volume 4

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European Commission

EN Search

Public Health

Home > Medicinal products > Eudralex > EudraLex - Volume 4

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

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Introduction

Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively.

TO ENSURE QUALITY, SAFETY, EFFICACY OF THE MEDICINAL PRODUCT

ATMP manufacturing workflow

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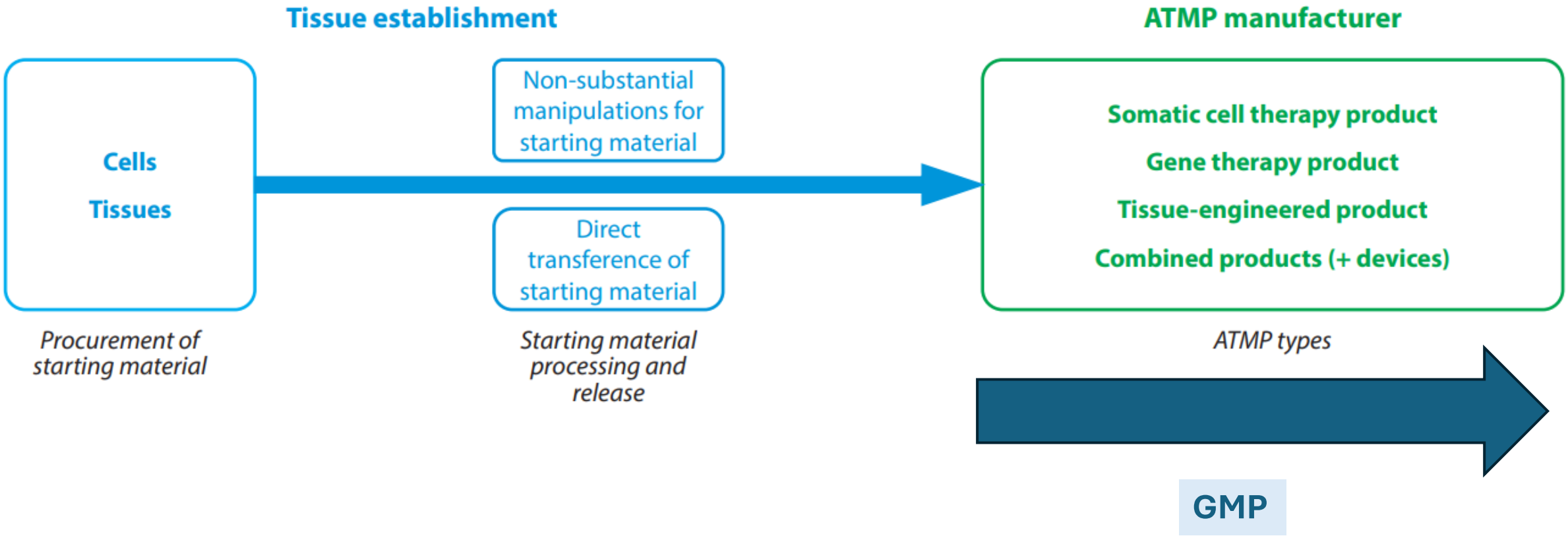

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GMP guidelines: EudraLex – Volume 4

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Part I - Basic Requirements for Medicinal Products

Part II - Basic Requirements for Active Substances used as Starting Materials

Part III - GMP related documents

Annexes

Glossary

Part IV - GMP requirements for Advanced Therapy Medicinal Products

Other documents related to GMP and GDP

Latest updates

Documents

Part I - Basic Requirements for Medicinal Products

- Chapter 1 - Pharmaceutical Quality System (into operation since 31 January 2013)
- Chapter 2 - Personnel (into operation since 16 February 2014)
- Chapter 3 - Premise and Equipment (into operation since 1 March 2015)
  - See transitional arrangement for toxicological evaluation on page 1 of Chapter 3
  - Previous version
- Chapter 4 - Documentation (January 2011)
- Chapter 5 - Production (into operation since 1 March 2015)
  - See transitional arrangement for toxicological evaluation on pages 1-2 of Chapter 5
  - Previous version
- Chapter 6 - Quality Control (into operation since 1 October 2014)
- Chapter 7 - Outsourced activities (into operation since 31 January 2013)
- Chapter 8 - Complaints and Product Recall (into operation since 1 March 2015)
- Chapter 9 - Self Inspection

GMP guidelines for ATMPs: Eudralex Volume 4 Part IV

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Part I - Basic Requirements for Medicinal Products

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Other documents related to GMP and GDP

Latest updates

Documents

Part IV - GMP requirements for Advanced Therapy Medicinal Products

- Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

1. Highly variable starting materials
2. Complex manufacturing processes
3. Small batches
4. Short shelf life

➔ EMPHASIS ON A RISK- BASED APPROACH

GMP guidelines: EudraLex – Volume 4

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European Commission

EN Search

Public Health

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EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

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GOOD MANUFACTURING PRACTICE GMP CERTIFIED

COMPLIANCE CHECKED BY NATIONAL COMPETENT AUTHORITY

famhp federal agency for medicines and health products

Organisation of a GMP facility

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Management

Organisation of a GMP facility

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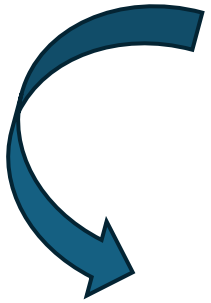
Management



Makes sure that…

Head of production

➔ manufacturing is done in accordance with the SOPs and IMPD/manufacturing authorisation

➔ Premises and equipment are qualified and maintained

➔ Personnel is trained

Organisation of a GMP facility

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Management

Makes sure that...

Head of production	Quality control responsible
➔ manufacturing is done in accordance with the SOPs and IMPD/manufacturing authorisation	➔ Supervises all quality control procedures
➔ Premises and equipment are qualified and maintained	➔ Premises and equipment where quality controls are carried out are appropriate and maintained
➔ Personnel is trained	➔ Personnel is trained

Organisation of a GMP facility

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Management

Makes sure that...

Head of production	Quality control responsible	Qualified person
➔ manufacturing is done in accordance with the SOPs and IMPD/manufacturing authorisation	➔ Supervises all quality control procedures	➔ Each batch has been manufactured and checked in compliance clinical trial/marketing authorisation and all other relevant regulatory requirements, including GMP
➔ Premises and equipment are qualified and maintained	➔ Premises and equipment where quality controls are carried out are appropriate and maintained	➔ Certification of the finished product batch
➔ Personnel is trained	➔ Personnel is trained	

Organisation of a GMP facility

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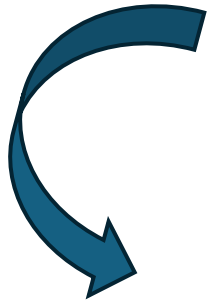

Ensures....

Management

Head of production

- ➔ manufacturing is done in accordance with the SOPs and IMPD/manufacturing authorisation
- ➔ Premises and equipment are qualified and maintained
- ➔ Personnel is trained

Quality control responsible

- ➔ Supervises all quality control procedures
- ➔ Premises and equipment where quality controls are carried out are appropriate and maintained
- ➔ Personnel is trained

Qualified person

- ➔ Each batch has been manufactured and checked in compliance clinical trial/marketing authorisation and all other relevant regulatory requirements, including GMP
- ➔ Certification of the finished product batch

INDEPENDENCY OF QUALITY CONTROL ACTIVITIES FROM THE PRODUCTION ACTIVITIES

Aseptic processing of ATMPs: cleanroom requirements

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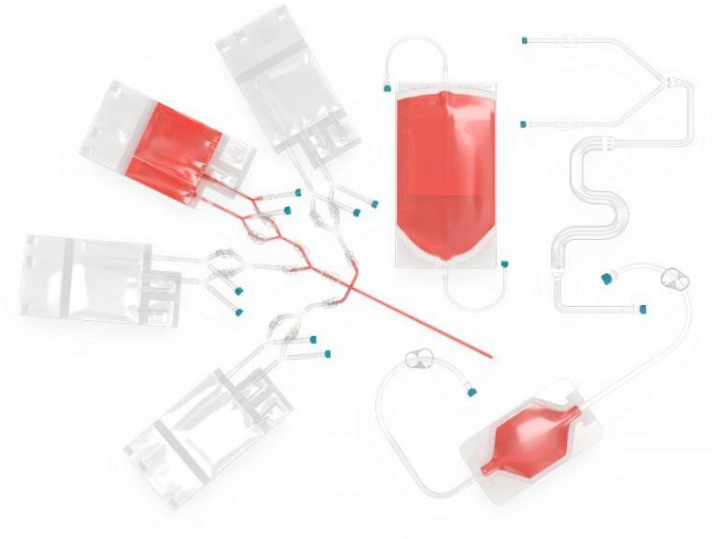
If no terminal sterilization is possible -> ASEPTIC PROCESSING

Production in closed system, isolator → **Grade D**



Aseptic processing of ATMPs: cleanroom requirements

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If no terminal sterilization is possible -> ASEPTIC PROCESSING

Production in open system → **Grade A in grade B background**

Operating in a grade B clean room: gowning

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Operating in a grade B clean room: gowning

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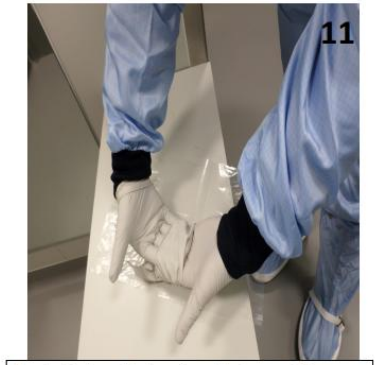
Desinfecteer je handen. Open de verpakking van de wasbare steriele overall. Hou de oranje lus aan je rechter hand, de witte lus aan je linker hand. Haal de overall uit de verpakking

Breng je armen in de mouwen. Linker arm aan de kant van de witte lus, rechter arm aan de kant van oranje lus. Trek de overall over je hoofd



Operating in a grade B clean room: gowning qualification

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Operating in a grade B clean room: gowning qualification

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Operating in a grade B clean room: gowning qualification

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Operating in a grade B clean room: gowning qualification

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Operating in a grade B clean room: gowning qualification

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Operating in a grade B clean room: gowning qualification

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Each operator should be qualified for gowning initially and periodically.

An operator failing the gowning qualification cannot enter grade B!

Operating in a grade B clean room

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Viable and non-viable particle monitoring during critical aseptic process steps

Operating in a grade B clean room

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Viable and non-viable particle monitoring during critical aseptic process steps

Finger prints after critical aseptic process steps

Operating in a grade B clean room

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Line clearance

LOKAAL 158	Line clearance
Lokaal	**Inhoud:** ☑ Conform ☐ niet conform iTask nr. : **Netheid:** ☑ OK ☐ niet OK iTask nr. :
Werktafels	**Inhoud:** ☑ Conform ☐ niet conform iTask nr. : **Netheid:** ☑ OK ☐ niet OK iTask nr. ::
LAF-kast	**Inhoud:** ☑ Conform ☐ niet conform iTask nr. : **Netheid:** ☑ OK ☐ niet OK iTask nr. :

Line cleaning

2. Aan het einde van de productie

Datum en uur	
☑ Rest van de goederen verwijderd ☑ Alle documenten verwijderd ☑ MVK-kast, toestellen en lokalen gereinigd ☑ Preventief onderhoud van de toestellen door de gebruiker uitgevoerd volgens het onderhoudsboek ☑ Studiespecifieke toestellen verwijderd ☑ Lijnopruiming – reiniging geregistreerd in logboek van het lokaal	
Trigram/paraf uitvoerder	

Validation of aseptic processing

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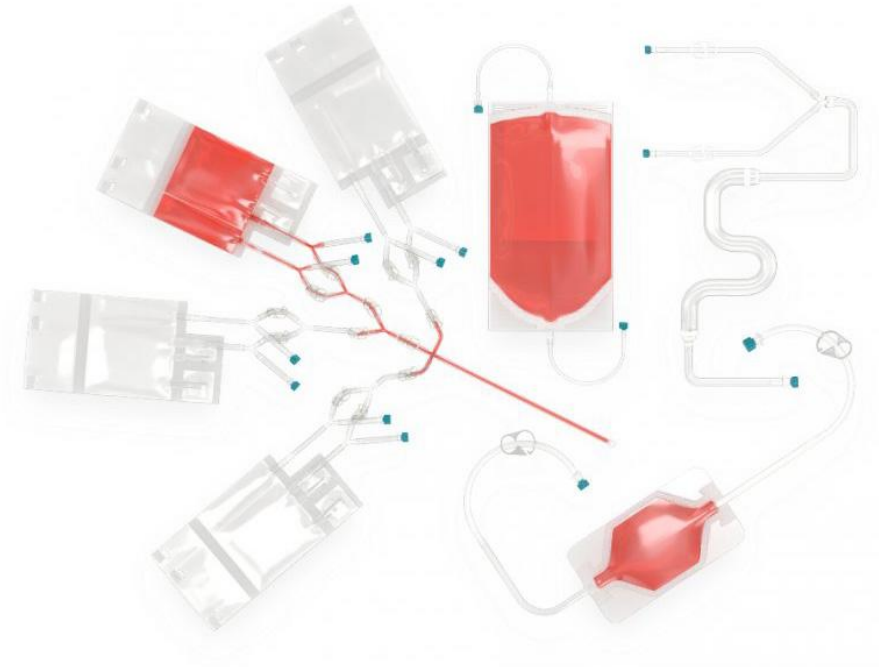
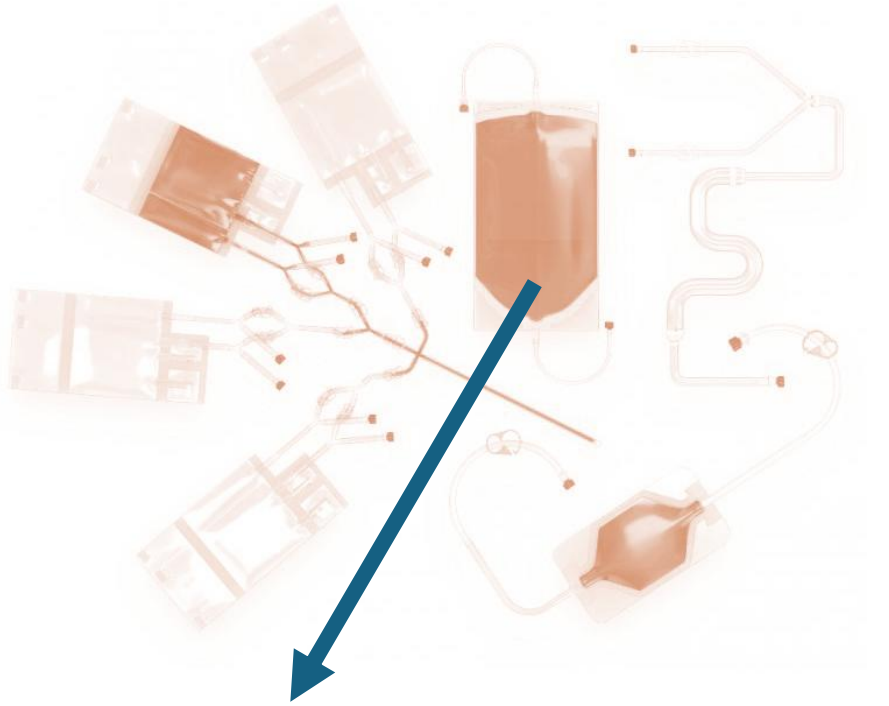
Actual production proces



Aseptic process simulation



Microbial growth medium

Validation of aseptic processing

Inspection of ‘finished product’ and ‘waste’ for microbial contamination

Validation of aseptic processing

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Inspection of ‘finished product’ and ‘waste’ for microbial contamination

Growth promotion test of culture medium

Validation of aseptic processing

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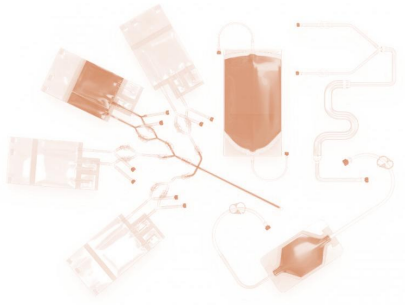

Validation run
X 3

Initial
qualification

Validation of aseptic processing

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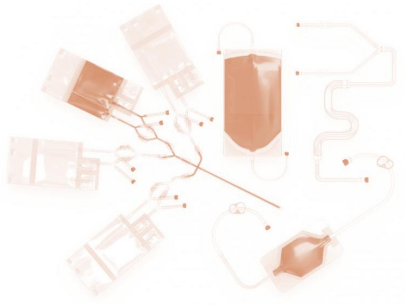
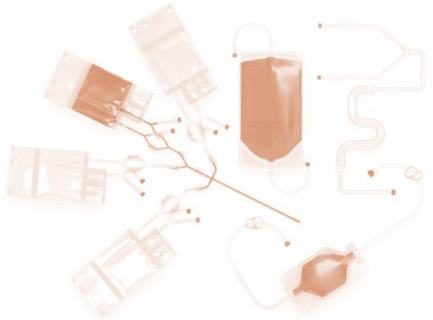




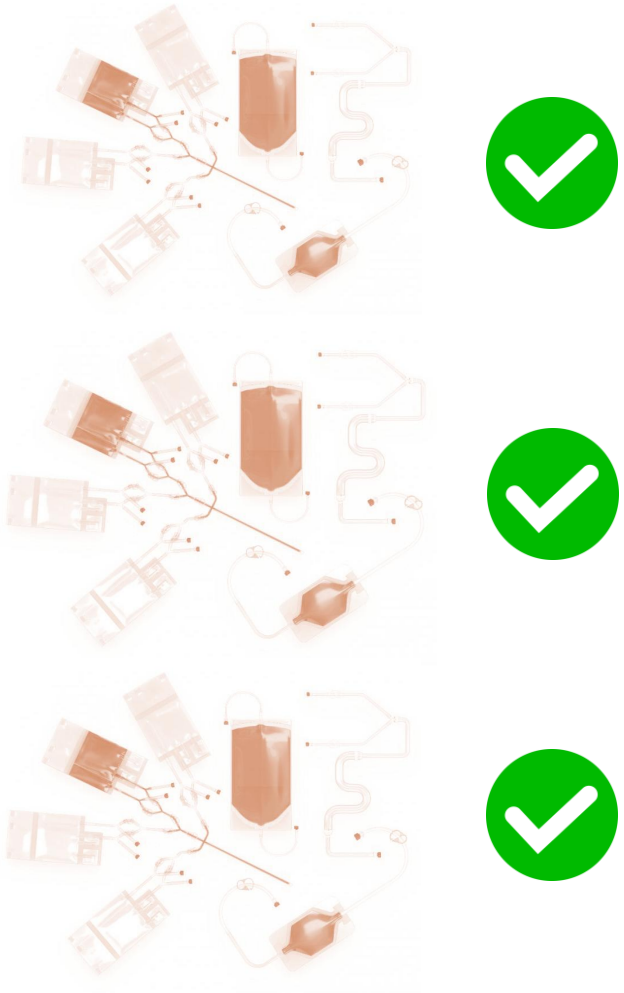
Validation run
X 3

Initial
qualification

Validation of aseptic processing

CellGENTherapies

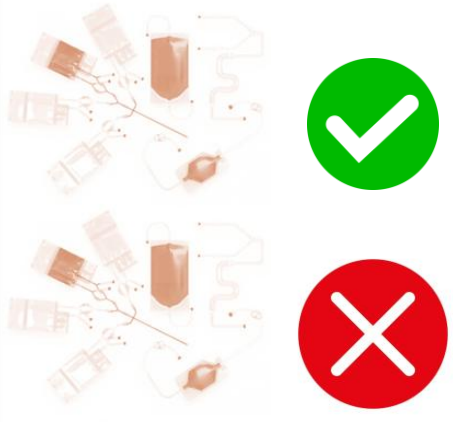
Validation run
X 3



Initial
qualification

Validation of aseptic processing

CellGENTherapies



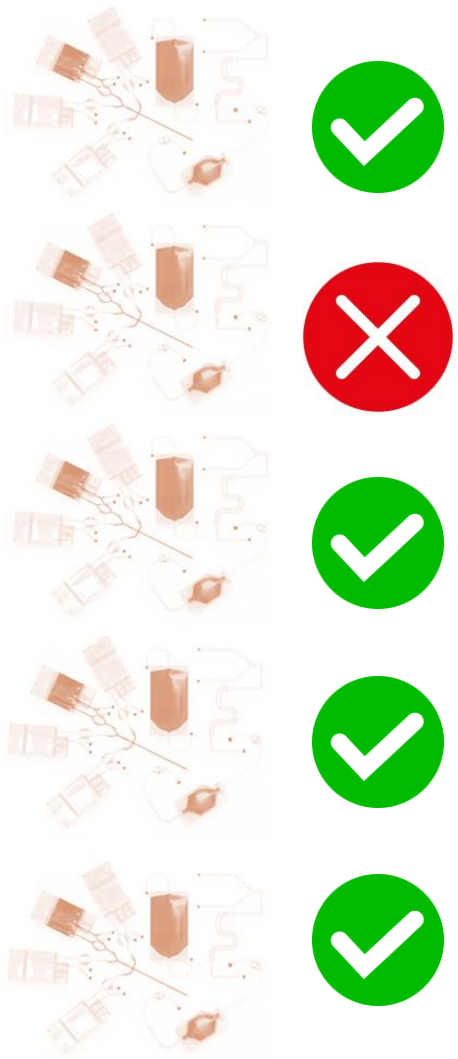
Validation run
X 3

Initial
qualification

Validation of aseptic processing

CellGENTherapies

Validation run
X 3

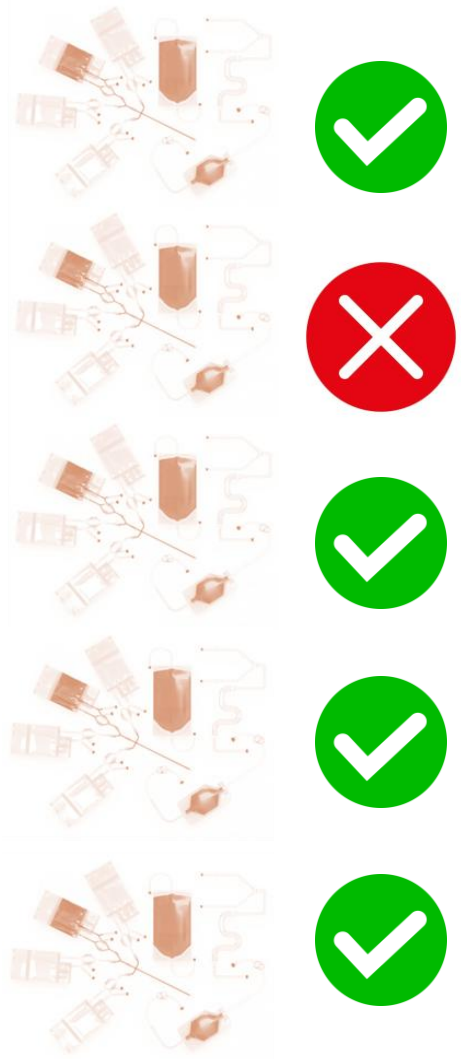


Initial
qualification

Validation of aseptic processing

CellGENTherapies

Validation run
X 3



Initial qualification

Repeat periodically

Quality control

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Safety-related quality attributes

Sterility

Endotoxins

Mycoplasma

Should be performed according to European Pharmacopoeia

Other quality attributes

Identity

Purity/ impurities

Content

Potency

Mostly product-specific assays

Quality control

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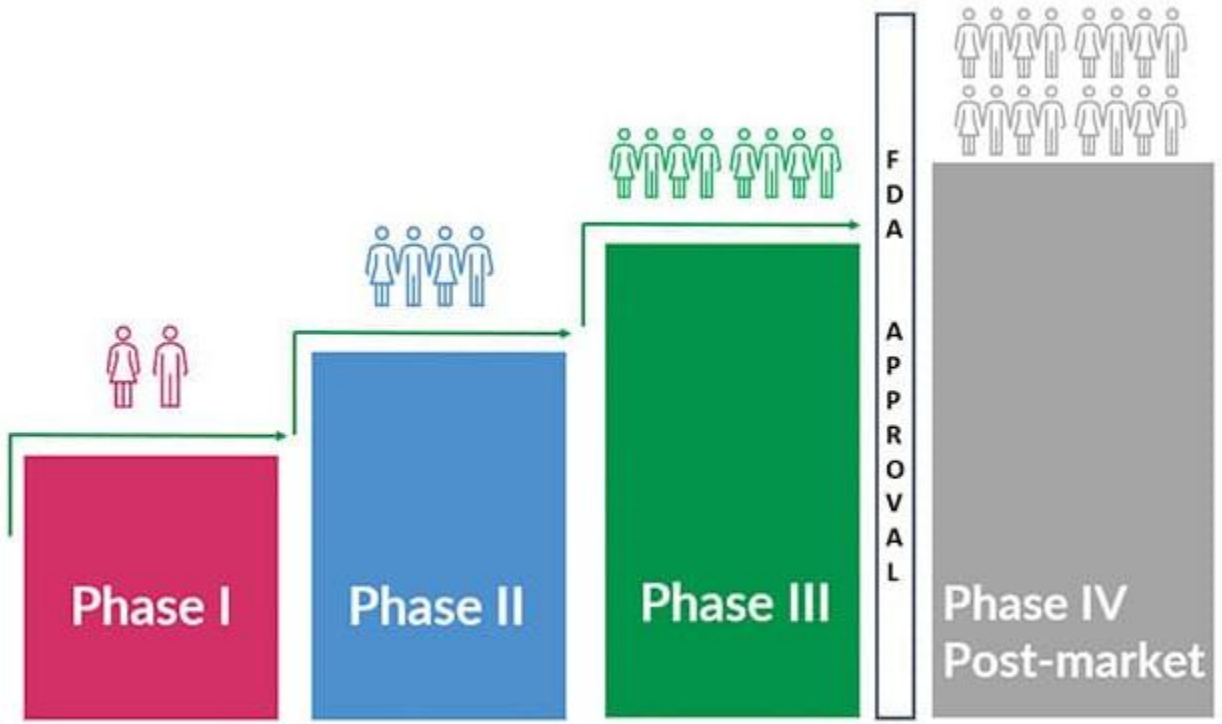

Validation level

For iATMPs, the level of validation should grow together with the development phase and the criticality of the test results

Quality control and batch certification

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Certificate of Analysis CTU3 Cell Therapy – MIDRIX

Product	☒ MIDRIX$^{4\text{-LUNG}}$ ☐ MIDRIX^{NEO}
Productiedatum	24/APR/2020
Vervaldatum	OKT/2020
Batchsize	~~123~~ VIALS 121 (SF) HABE, 14 MEI 2020.

Klei
Batchnr.:
180705-DC-20042020
ETK

QC-Parameter	Specificaties	Resultaat	Conform?
Steriliteit MNC-A	Negatief	Negatief	conform
Mycoplasma test supernatant MDDCs	Negatief	Negatief	conform
Steriliteit supernatant MDDCs	Negatief	Negatief	conform
Visuele controle van de vials	- Onbeschadigd - Gesloten - Wit opaque gekleurde inhoud	OK	conform
Endotoxines finale IMP	< 125 EU/mL	93,4 EU/ml	conform
Steriliteit finale IMP:	Negatief	Negatief	conform
Viable cell count finale IMP	> 3*10^6/vial	5,06 x 10^6	conform
Identiteit finale IMP: - CD11c+HLADR+ - DC fenotype: o rMFI CD14 o rMFI CCR7 o rMFI CD86, rMFI CD83, rMFI CD70, rMFI CD40	>70% NA >10 2 van de 4 >10	99,52 % NA 22,07 OK	conform
Onzuiverheden finale IMP	CD3, CD56, CD19 < 10%	0,03 %	conform
IP10 productie	Positief	OK	conform

Quality control and batch certification

CellGENTherapies

Certificate of Analysis CTU3 Cell Therapy – MIDRIX

Product	☒ MIDRIX$^{4\text{-LUNG}}$ ☐ MIDRIX^{NEO}
Productiedatum	24/APR/2020
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QC-Parameter	Specificaties	Resultaat	Conform?
Steriliteit MNC-A	Negatief	Negatief	conform
Mycoplasma test supernatant MDDCs	Negatief	Negatief	conform
Steriliteit supernatant MDDCs	Negatief	Negatief	conform
Visuele controle van de vials	- Onbeschadigd - Gesloten - Wit opaque gekleurde inhoud	OK	conform
Endotoxines finale IMP	< 125 EU/mL	93,4 EU/ml	conform
Steriliteit finale IMP:	Negatief	Negatief	conform
Viable cell count finale IMP	> 3*10^6/vial	5,06 x 10^6	conform
Identiteit finale IMP: - CD11c+HLADR+ - DC fenotype: o rMFI CD14 o rMFI CCR7 o rMFI CD86, rMFI CD83, rMFI CD70, rMFI CD40	>70% NA >10 2 van de 4 >10	99,52 % NA 22,07 OK	conform
Onzuiverheden finale IMP	CD3, CD56, CD19 < 10%	0,13 %	conform
IP10 productie	Positief	OK	conform

Batch Certificate

Product Name	MIDRIX-CTRL
Eudra CT number	2018-004665-14
Protocol number	MIDRIX^4-LUNG, Phase 1a, version 2.1
Strength	2 x 10^6 cells/vial
Dosage form	Vial for i.d. injection, 100 µl
Package size	N/A
Batch size	11 vials
Batch number	180706-DC-21092020
Date of manufacture/ packaging	25/sep/2020
Expiry date	Maa/2021
Manufacturer and address	University Hospital Ghent, GMP Unit 3 Cell Therapy, Corneel Heymanslaan 10, 9000 Gent
Manufacturing authorization number	1940 IMP

Deviations/Investigations-numbers that apply to this lot of Drug product are mentioned below:

Deviation/Investigation Number	Resolution
N/A	N/A

I hereby certify that this batch of product has been manufactured/packaged at the above mentioned site in compliance with the current Good Manufacturing Practice, the Product Specification File and the requirements of Article 13.3 of Directive 2001/20/EC .

Clinical trial application

CellGENTherapies

- EudraCT-number
- Favourable opinion of:
  - Ethics committee
  - Relevant Authority (FAMHP)
- Content of the application
  - Cover letter
  - Clinical trial application form
  - Clinical trial protocol
  - Investigator's brochure
  - **Documents related to compliance with GMP**
  - **IMP dossier (IMPD)**
  - Non-IMP used in the trial
  - Other documents

Federal Agency For Medicines And Health Products

CERTIFICATE NUMBER: ***BE/GMP/2021/064***

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER [1, 2]

Part 1

Issued following an inspection in accordance with

The competent authority of Belgium confirms the following:
The manufacturer: ***Universitair Ziekenhuis Gent***
Site address: ***GMP Unit Cell Therapy (Unit 3), P3 verdieping 2, Corneel Heymanslaan 10, Gent, 9000, Belgium***

Has been inspected under the national inspection programme in connection with manufacturing authorisation no. ***1940 IMP*** in accordance with Art. 13 of Directive 2001/20/EC.

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2021-05-19 00:00:00.0***, it is considered that it complies with:

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. Updates to restrictions or clarifying remarks can be identified through the EudraGMDP website (http://eudragmdp.ema.europa.eu/).
This certificate is valid only when presented with all pages and both Parts 1 and 2.
The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

[1] *The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, shall also be required for imports coming from third countries into a Member State.*

[2] *Guidance on the interpretation of this template can be found in the Interpretation of the Union format for GMP certificate.*

[3] *These requirements fulfil the GMP recommendations of WHO.*

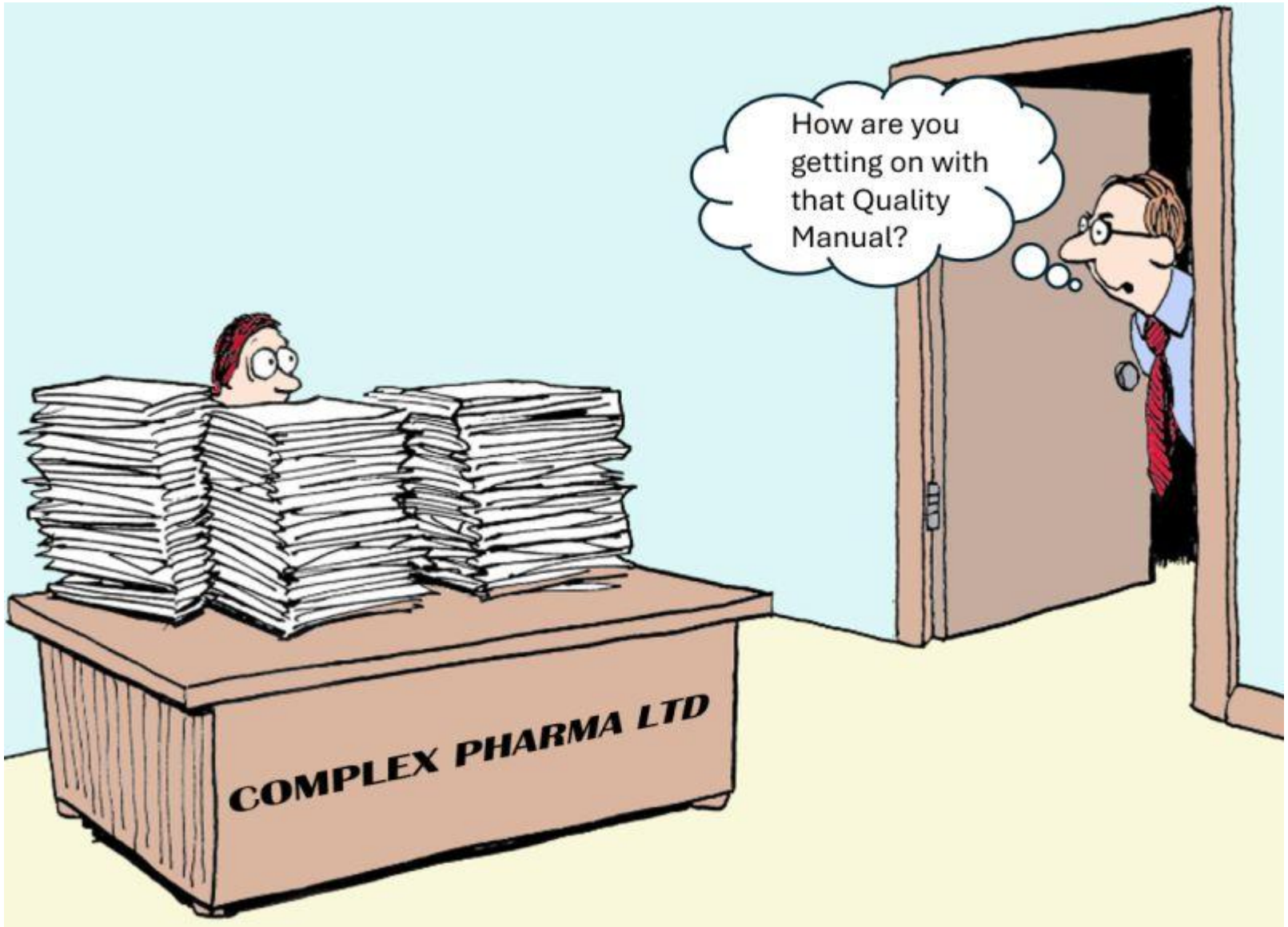
EudraGMP

Part 2

1 MANUFACTURING OPERATIONS	
1.1	**Sterile products**
	1.1.1 Aseptically prepared (processing operations for the following dosage forms)
	1.1.1.1 Large volume liquids
	1.1.1.4 Small volume liquids
	1.1.3 Batch certification
1.3	**Biological medicinal products (list of product types)**
	1.3.1 Biological medicinal products (list of product types)
	1.3.1.2 Immunological products
	1.3.1.3 Cell therapy products
	1.3.1.4 Gene therapy products
	1.3.1.5 Biotechnology products
	1.3.2 Batch Certification (list of product types)
	1.3.2.2 Immunological products
	1.3.2.3 Cell therapy products
	1.3.2.4 Gene therapy products
	1.3.2.5 Biotechnology products
1.5	**Packaging**
	1.5.2 Secondary packaging
1.6	**Quality control testing**
	1.6.1 Microbiological: sterility
	1.6.2 Microbiological: non-sterility
	1.6.3 Chemical/Physical
	1.6.4 Biological

Clarifying remarks (for public users)

1.1.1.1, 1.1.1.4 and 1.1.3 limited to ATIMP's 1.3.1.2 and 1.3.2.2 limited to ATIMP's


How are you getting on with that Quality Manual?
COMPLEX PHARMA LTD

History of CellGENTherapies

- **Established with expertise coming from the Bank of Hematopoietic Stem Cells UZGent**

➔ **<u>Key expertise in quality system, infrastructure, and cell processing</u>**

- **Established in 2014**
- Licensed producer of investigational ATMPs
- **2016: first iATMP produced under GMP conditions**

The hematopoietic stem cell processing team which was key in the establishment of the GMP facility

UZ GENT UNIVERSITEIT GENT

The team

Advisory Board

Director
Prof. Dr. B. Vandekerckhove

Head of Production
J. Ingels, PhD

Qualified Person
Apr. L. De la Mane

Quality assurance
N. Lootens

Saskia De Smet
Valerie Redant, PhD
Bo Coppens
Ing. Pascal Vandermeulen
Sofie Leyman
Viviane Van De Steene

Ryma Addoun
Eva Van Houtte
Jits Vandewiele

Business developers
Tim Desmet, PhD
Katrien Vanhonacker

Mission

To facilitate moving research “from bench to bedside” by providing expertise, equipment and a licensed facility for the production of cell and gene therapeutics for early phase clinical trials.

Since 2016

CellGENTherapies

Technology transfer

We start from your research protocols and translate them towards GMP-compliant protocols. Additionally, Ghent University licenses technology in the field of gene and cell therapy.

Quality testing

We have our own in-house quality laboratory and additionally work with recognized external analytical service providers.

Writing of IMPDs

We write investigational medicinal product dossiers and interact with the regulatory body.

Manufacturing of iATMP

We make products for clinical studies. We specialize in small and personalized batches, in a variety of technologies.

View our iATMP list

CellGENTherapies

Technology transfer | Manufacturing of iATMP | Writing of IMPDs | Quality testing

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