Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of Advanced Therapy Products (CGTPs/ATMPs)

John Geigert, Ph.D., RAC, President
BioPharmaceutical Quality Solutions
3533 Corte Esperanza Carlsbad, CA 92009 USA
+1-760-943-0198 BPQS@aol.com

Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of Advanced Therapy Products

Course Goal

The Challenge for Advanced Therapy Medicines

Because of the diverse and evolving manufacturing processes for these living medicinal products (gene and cellular therapies), no single set of GMP & Quality Principles will fit all!

There isn't a simple GMP & Quality System playbook, yet!

A Solution

Focus not just on a list of what to do or what not to do, but instead consider how to apply a risk-based, patient-safe approach, for the actions to be taken

Who is John Geigert, Ph.D., RAC?

"If you are humble, nothing will touch you, neither praise nor disgrace, because you know what you are"
Mother Teresa, Missionaries of Charity in Calcutta India, 1910-1997

- *40+ years experience in Chemistry, Manufacturing & Control (CMC) strategies for the clinical development/commercialization of biologics (recombinant proteins, monoclonal antibodies, gene therapies, cellular therapies)*
- *Senior CMC Expert and Vice President Quality in the industry (Cetus, Immunex, IDEC Pharmaceuticals)*
- *Past Chair PDA Biopharmaceutical Advisory Board*
- *20 years as an independent CMC regulatory compliance consultant to the biopharmaceutical industry*

3

Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of Advanced Therapy Products

Course Outline

1. ***Overview of the CGTP Landscape***
   Discussion of the increasing diversity of these advance therapy medicines; introduction to the regulatory authority systems in place to regulate these evolving manufacturing processes and products
2. ***Advanced Therapy Product GMP and Quality Risk Consequences***
   Adapting knowledge from established regulatory guidances and experiences (e.g., mAbs, recombinant viral vaccines, etc.), and what minefields might occur if improperly adapted
3. ***Regulatory Authority Expectations During Clinical Development***
   Understanding the regulatory guidance for ATMPs that currently exists, and why those guidances stress the necessity of a risk-based control approach to GMPs and Quality Principles during clinical development
4. ***Industry Practice in Applying the Risk-Based Principles to ATMPs***
   Applying Quality by Design (QbD) and Quality Risk Management (QRM) to ATMPs; PDA Technical Report 81 on Cell-Based Therapy Control Strategy

(Continuous presentation over the 6 hours of instruction) *(Please ask your questions)*

4

Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of Advanced Therapy Products

Course Outline

1. Overview of the Cell & Gene Therapy Landscape

- ***Discussion of the increasing diversity of these advanced therapy medicines***
- ***Introduction to the regulatory authority systems in place to regulate these evolving manufacturing processes and products***

5

Biologic Medicinal Product Landscape

(~300 FDA-licensed)

Vaccines for Infectious Diseases

Live, Attenuated/ Inactivated, Killed/ Subunit Vaccines

Genetically Engineered Live Viral Vaccines (Dengvaxia for Dengue; Ervebo for Ebola; COVID-19)

Human Plasma-Derived Proteins

Blood clotting proteins/ Immunoglobulins

Genetically Engineered Proteins

Recombinant Proteins (100+)

Monoclonal Antibodies (100+)

Cell & Gene Therapy Products

Recombinant Live Viruses

Genetically Modified Live Cells

Cellular Therapy

Many lessons learned on CMC risk management from here that can be applied to CGTPs

But there are some CMC minefields due to differences

(more on this later)

6

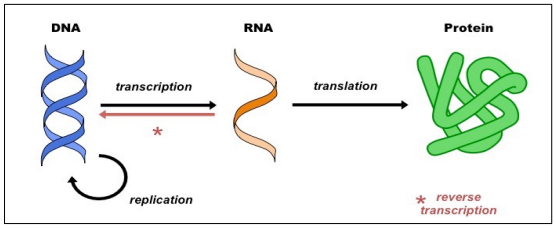
The Majority of Biologic Medicinal Medicines Today Are:

Non-Living, Recombinant Proteins/mAbs

Gene inserted into a living microorganism (e.g., E. coli, CHO), to produce a protein medicine

Production in a Bioreactor – recombinant protein/mAb

Central Dogma of Molecular Biology



Harvest, purify, formulate, fill

Administration of recombinant protein/mAb to patients to treat the medical problem/disease

(e.g., human insulin, Factor VIII, mAbs for cancer therapy)

7

The Majority of Biologic Medicinal Medicines in the Future Might Be:

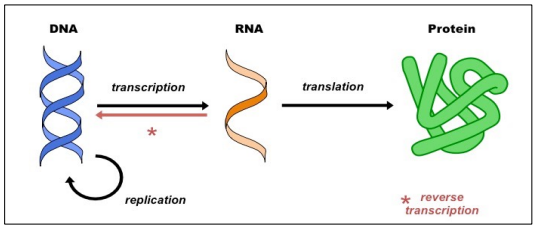
Living, Genetically Modified Viruses/Cells and Living Cells

Gene inserted into a living human to fix a defective genetic capability or add a new genetic capability

In vivo – gene transfer directly into human patient
Ex vivo – gene transfer into human cells, then into patient

The patient produces the desired gene product (protein), in situ to fix a faulty human gene(s) or add a new gene(s)

Central Dogma of Molecular Biology



Patient/Donor-sourced cells

Significant manipulation of cells

Administration of cells to patient(s)

Autologous – same
Allogeneic – many

8

Regulatory authorities predict CGTPs to grow significantly!

Assessing the current pipeline and trends in incoming INDs, FDA views this as an inflection point in cell and gene therapy technology and innovation. As such, FDA attempts to project the volume of cell-based or directly administered gene therapy products in development and gaining approval in coming years:

- Currently 800+ active INDs
- Anticipate receipt of 200+ new INDs per year by 2020
- Predict approval of 10-12 cell and gene therapy products per year by 2025

Note: this is the same annual market approval rate for new mAbs today!

Drawing an analogy to the platforms for humanizing antibodies that accelerated the mainstreaming of human monoclonal antibody drugs in the late 1990's, FDA credits the advent of safe and effective vectors (e.g., AAV vectors) for the delivery of gene therapy products as enabling this progress.

To accommodate these increases, CBER is expanding its review group dedicated to reviewing these applications, with the hope of adding about 50 additional clinical reviewers to the CBER Office of Tissues and Advanced Therapies (OTAT).

Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies January 15, 2019

9

Most large biologic companies have jumped in; many by acquisition!

GILEAD — *Yescarta, Tecartus* — Kite, A GILEAD Company — *~$12 billion*

NOVARTIS — *Kymriah* — *Zolgensma* — avexis — *~$9 billion*

Roche — *Luxturna* — Spark THERAPEUTICS — *~$5 billion*

Bristol-Myers Squibb — Celgene "Committed to improving the lives of patients worldwide" — *Zynteglo, Abecma, Breyanzi* — bluebirdbio "recode for life" — JUNO THERAPEUTICS — *~$74 billion*

janssen — BAYER — astellas — AMGEN — Biogen — Takeda

Lonza — FUJIFILM Diosynth biotechnologies — ThermoFisher SCIENTIFIC — Catalent BIOLOGICS

10

Advanced Therapies
3 groups

EU ATMPs	USA CGTPs
Gene Therapy Medicines	Gene Therapy Medicines
Somatic-Cell Therapy Medicines	Cellular Therapy Medicines
Tissue-Engineered Medicines	Tissue Engineered Medicines

Cell & Gene Therapy Products (CGTPs) = Advanced Therapy Medicinal Products (ATMPs) = Advanced Therapy Medicines

11

Advanced therapies are … Gene Therapy Medicines

(a) 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;

AND

(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 therapies work by inserting 'recombinant' genes into the human body to:

- ***Replace** a disease-causing gene with a healthy copy of the gene (gene restoration)*
- ***Inactivate** a disease-causing gene that is not functioning properly (gene inhibition/disabling)*
- ***Addition** of a new or modified gene into the body to help treat a disease (gene addition)*

In vivo – gene transfer directly into human
Ex vivo – gene transfer into human cells, then into human

12

Gene Therapy (IN VIVO) Medicines are slowly starting to hit the market …

Pre-2017	market approved
• Glybera (VISION – lipoprotein lipase protein restoration – virus gene insertion)	EMA (2012) (market withdrawn 2017)
• Imlygic (MELANOMA – GM-CSF protein addition – virus gene insertion)	FDA/EMA (2015)

2017/2018	market approved
• Luxturna (VISION – RPE-65 protein restoration – virus gene insertion)	FDA/EMA

2019/2020	market approved
• Zolgensma (SPINAL MUSCULAR ATROPHY - Survival motor neuron protein restoration – virus gene insertion)	FDA/EMA

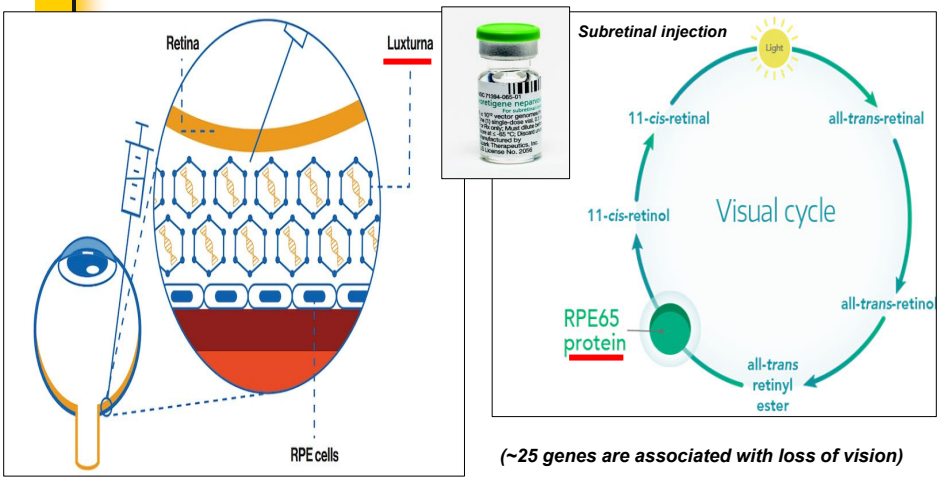
2021/ →	market approved

13

Gene Therapy Medicine: Recombinant Living Virus (for gene insertion)

Spark Therapeutics LUXTERNA

Adeno-associated virus (AAV) vector (with RPE65 gene) to restore gene



(~25 genes are associated with loss of vision)

Virus Gene Inactivation (under clinical study)

CPE 290 gene in the retina inactivates vision – Editas has injected a virus (AAV) containing CRISPR into patients' eyes to shutdown this gene, to restore vision

14

Gene Therapy (EX VIVO) Medicines are hitting the market …

Pre-2017	*market approved*
• *Strimvelis (adenosine deaminase enzyme restoration – hematopoietic stem cell gene insertion)*	*EMA (2016)*
• *Zalmoxis (suicide gene – allogeneic T-cell gene insertion)*	*EMA (2016)*

2017/2018	*market approved*
• *Kymriah (CANCER – CAR T-cell gene insertion)*	*FDA/EMA*
• *Yescarta (CANCER – CAR T-cell gene insertion)*	*FDA/EMA*

2019/2020	*market approval*
• *Zynteglo (β-globin protein restoration – hematopoietic stem cell gene insertion)*	*EMA*
• *Libmeldy (arylsulfatase A (ARSA) enzyme restoration – hematopoietic stem/progenitor cell gene insertion)*	*EMA*
• *Tecartus (CANCER – CAR T-cell gene insertion)*	*FDA/EMA*

2021/ →	*market approval*
• *Breyanzi (CANCER – CAR T-cell gene insertion)*	*FDA*
• *Abecma (CANCER – CAR T-cell gene insertion)*	*FDA*
• *Skysona (cerebral adrenoleukodystrophy protein restoration – hematopoietic stem cell gene insertion)*	*EMA*

15

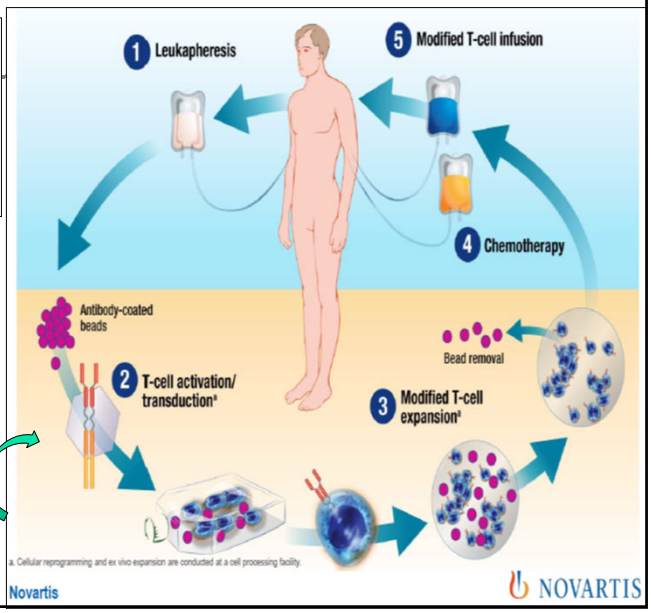
Gene Therapy Medicine: Genetically Modified Living Cells (gene addition)

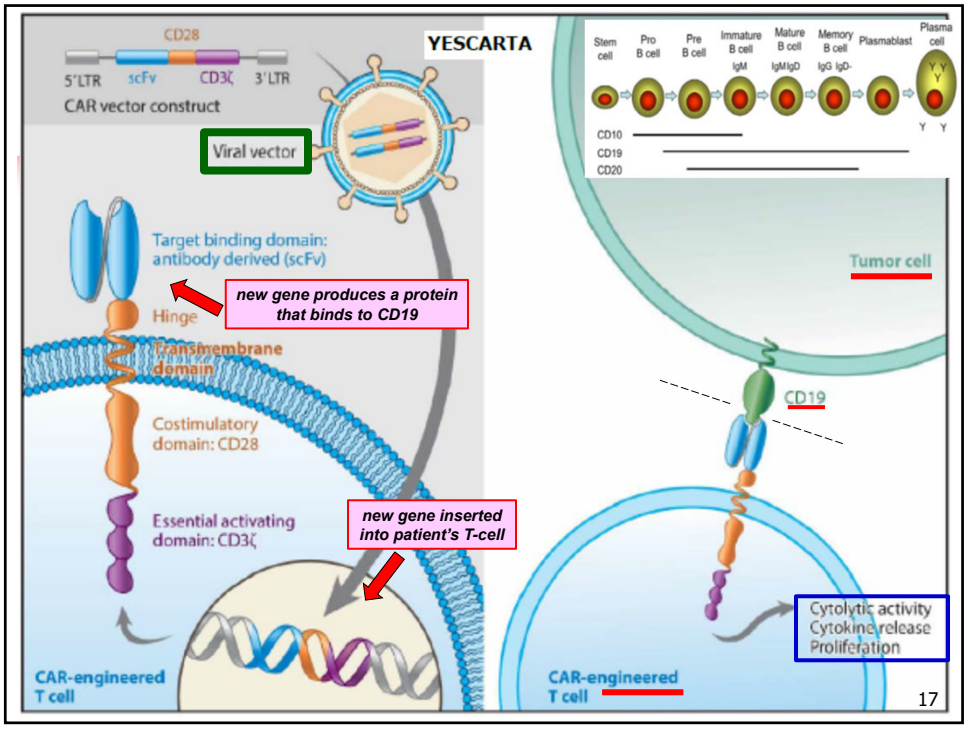
Novartis KYMRIAH
Kite YESCARTA

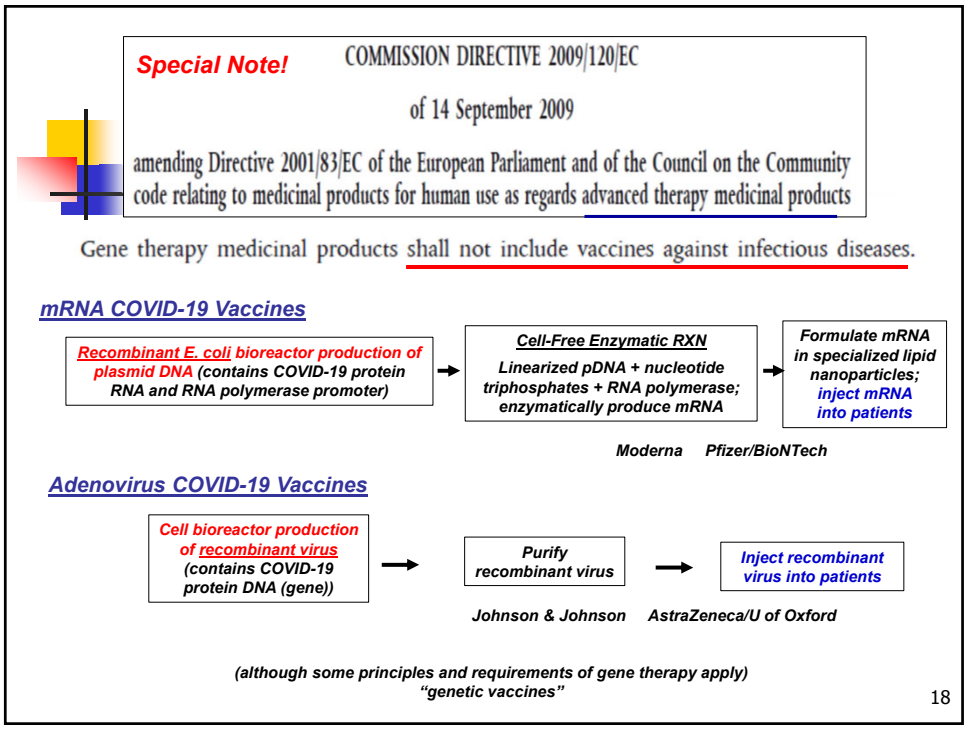
autologous genetically modified T-cells to bind/kill CD19-containing leukemia cells

(CAR – chimeric antigen receptor)

Genetically engineered lentivirus/retrovirus to add a gene to the human T-cells




YESCARTA
CD28
5'LTR
scFv
CD3ζ
3'LTR
CAR vector construct
Viral vector
Target binding domain: antibody derived (scFv)
new gene produces a protein that binds to CD19
Hinge
Transmembrane domain
Costimulatory domain: CD28
Essential activating domain: CD3ζ
new gene inserted into patient's T-cell
CAR-engineered T cell
Stem cell
Pro B cell
Pre B cell
Immature B cell
Mature B cell
Memory B cell
Plasmablast
Plasma cell
IgM
IgM IgD
IgG IgD-
CD10
CD19
CD20
Tumor cell
CD19
Cytolytic activity
Cytokine release
Proliferation
CAR-engineered T cell
17


Special Note!
COMMISSION DIRECTIVE 2009/120/EC
of 14 September 2009
amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products
Gene therapy medicinal products shall not include vaccines against infectious diseases.
mRNA COVID-19 Vaccines
Recombinant E. coli bioreactor production of plasmid DNA (contains COVID-19 protein RNA and RNA polymerase promoter)
Cell-Free Enzymatic RXN
Linearized pDNA + nucleotide triphosphates + RNA polymerase; enzymatically produce mRNA
Formulate mRNA in specialized lipid nanoparticles; inject mRNA into patients
Moderna
Pfizer/BioNTech
Adenovirus COVID-19 Vaccines
Cell bioreactor production of recombinant virus (contains COVID-19 protein DNA (gene))
Purify recombinant virus
Inject recombinant virus into patients
Johnson & Johnson
AstraZeneca/U of Oxford
(although some principles and requirements of gene therapy apply)
"genetic vaccines"
18

Advanced therapies are … Cell Therapy Medicines

(a) contains or consists of cells 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,

FDA: 'more than minimal manipulation'

OR

of cells that are not intended to be used for the same essential function(s) in the recipient and the donor;

FDA: 'not for homologous use'

AND

(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

'Not Substantial Manipulation' is …

- cutting
- grinding
- freezing
- irradiation
- cell separation
- centrifugation

FDA: HCT/P 361 product

'Substantial Manipulation' is …

- Cell expansion by cell culturing
- Differentiation/activation with growth factors
- Enzymatic digestion of tissue to release cells

FDA: HCT/P 351 product (CGTP)

Note: Cell therapy medicines are not biopharmaceuticals (i.e., no genetic engineering), but biologicals

Can be autologous (same patient) or allogeneic (multi-patients) or pluripotent (undifferentiated)

19

Cell Therapy Medicines are slowly starting to hit the market …

Pre-2017	*market approved*
• *Provenge (PROSTATE CANCER – autologous peripheral blood cells activated with rGM-CSF)*	*FDA (2010)/EMA (2013) (EMA market withdrawn 2015)*
• *Laviv (SEVERE WRINKLES – autologous skin fibroblasts)*	*FDA (2011)*

2017/2018	*market approved*
• *Alofisel (PERIANAL FISTULAS – allogeneic mesenchymal adult stem cells from adipose tissue)*	*EMA (2017)*

2019/2020	*market approved*
• *Remestemcel-L (GRAFT-VS-HOST DISEASE- allogeneic mesenchymal adult stem cells from bone marrow)*	*[FDA*]*

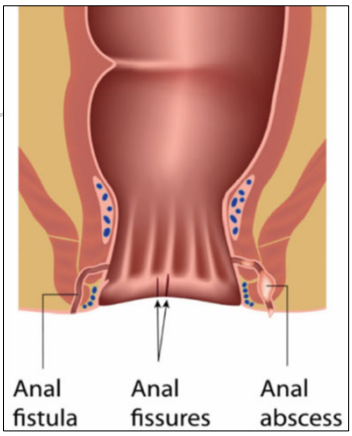
2021/ →	*market approved*

[CRL]*

20

Cell Therapy (allogeneic)

EMA approved 2017 FDA (in Phase 3 clinical)



Alofisel is made up of 'mesenchymal stem cells' from the fat tissue of a donor. To make this medicine, the cells are selected and cultivated in the laboratory to increase their number. When injected into the walls of the fistula, these cells can help to reduce inflammation and support the growth of new tissue. This encourages the fistula to heal and close.

21

Advanced therapies are … Tissue Engineered Products

***(a)** contains or consists of engineered cells or tissues*

AND

***(b)** 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*

Tissue Engineered Products are very slowly starting to hit the market …

	market approved
• *Gintuit (WOUNDS – allogeneic cultured keratinocytes and fibroblasts in bovine collagen sheets)*	*FDA (2012)*
• *Holoclar (CORNEAL SURFACE RESTORATION – autologous epithelial stem cells)*	*EMA (2015)*
• *Spherox (KNEE CARTILAGE – autologous spherical aggregates of chondrocytes)*	*EMA (2017)*
• *MACI (KNEE CARTILAGE – autologous cultured chondrocytes on a porcine collagen matrix)*	*FDA/EMA (2019)*

22

Regulatory Authority Landscape for Advanced Therapies

(EU and USA to be discussed)

(more on this in Section 4)

23

Regulatory Authority Landscape for Advanced Therapies

European Union

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

National Competent Authorities (NCAs) regulate clinical trials

(country-by-country variability: speed of assessment, and time for approval of clinical trials in the different EU countries)

European Medicines Agency (EMA) regulates commercial ATMPs

EUROPEAN MEDICINES AGENCY

Committee for Medicinal Products for Human Use (CHMP)

Committee for Advanced Therapies (CAT)

24

Pathway to Commercialization for ATMPs in EU

Clinical Trial Application (CTA)	→	Marketing Authorisation Application (MAA)
[human clinical studies]		[market approval]
CMC: Investigational Medicinal Product Dossier (IMPD)		CMC: eCTD Module 3
NCA reviewed		EMA mandatory

Committee for Advanced Therapies (CAT)

(classification of ATMPs, scientific advice) (assist CHMP in review for market approval)

25

Regulatory Authority Landscape for Advanced Therapies

USA

Public Health Service (PHS) Act (1944) [2020 amended]

"Biological product is a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings"

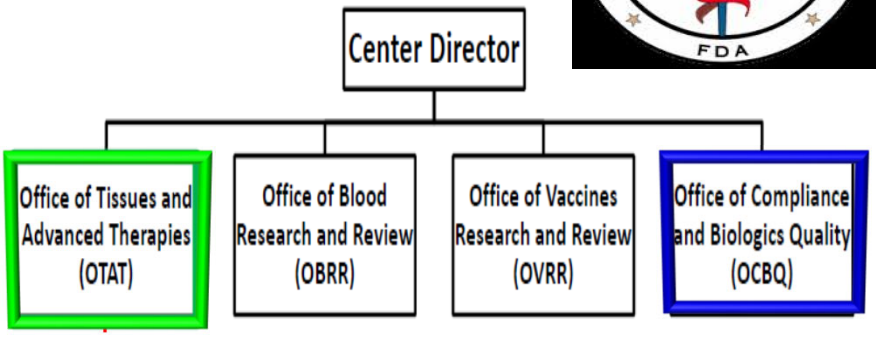
CGTP: CELLULAR & GENE THERAPY PRODUCT
currently under the category of 'analogous products'

Analogous = comparable in certain respects

26

U.S. FDA

CDER **CBER** CDRH



CMC review *GMP review*

Center for Biologics Evaluation & Research (CBER) regulates both clinical and commercial CGTPs

27

PHS Act: Biologic License Application (BLA) Pathway

Investigational New Drug (IND)		*Biologics License Application (BLA)*
21 CFR 312	→	*21 CFR 600-680 + 21 CFR 314*
[human clinical studies]		*[market approval]*
CMC: eCTD Module 3		*CMC: eCTD Module 3*

Food Drug & Cosmetics (FD&C) Act: Chemical Pharmaceuticals/ Peptides

IND → *New Drug Application (NDA)*

28

CONFUSED YET!

ATMP

CAT

substantial manipulation

not same essential function

CGTP

OTAT

more than minimal manipulation

not for homologous use

QUESTIONS??

29

Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of Advanced Therapy Products

Course Outline

2. **Advanced Therapy Product GMP and Quality Risk Consequences**
   - Adapting knowledge from established regulatory guidances and experiences (e.g., mAbs, recombinant viral vaccines, etc.)
   - What minefields might occur if improperly adapted

30

Patients expect their medicines to be safe and efficacious at time of use

Patients cannot check the quality of their medicines

Patients therefore are dependent upon an effective GMP & Quality System!
(facility, process, staff, product – "all doing what is right")

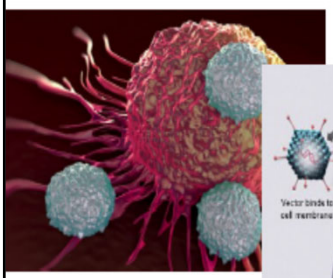
Unsafe or poor quality medicines can harm patients

31

The Regulatory Authority Challenge

Trying to keep pace with the rate of changes in CGTP science and technology, to protect patients!

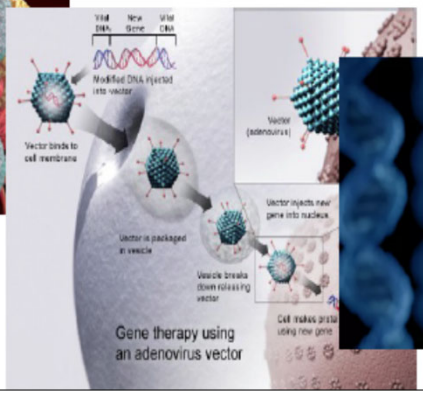
Cell-based Therapeutics



Autologous
Allogeneic

Stem Cells
Progenitor Cells
Differentiated Cells

Gene Therapy Products

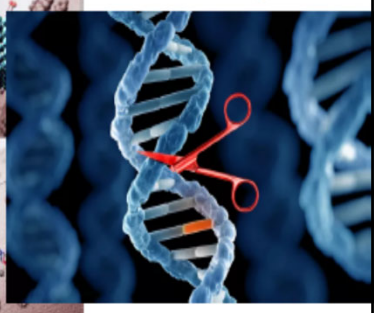


Plasmid Transient Cell Transfection
Virus Transient Cell Transduction
Producer Virus Cells

Adeno-Associated Virus (AAV)
Lentivirus (LV)
Retrovirus (RV)

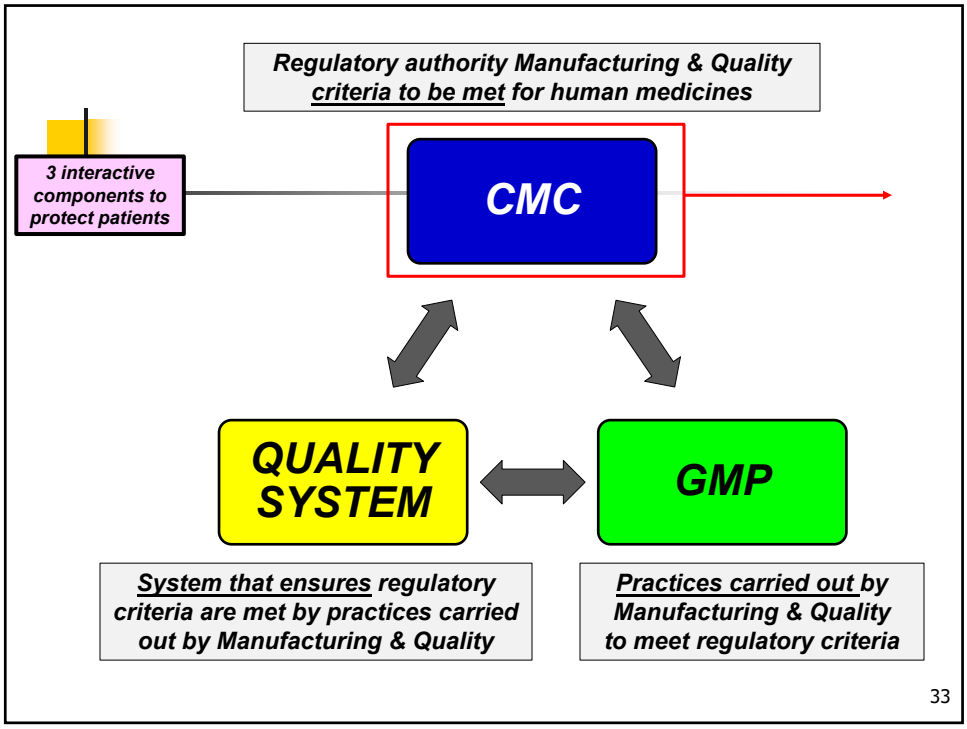
CRISPR-Cas
Zinc Finger Nuclease (ZFN)
TALEN

Gene Editing



In Vivo
Ex Vivo

32



33

EMA CMC Regulatory Guidances for ATMPs

- Guideline on Human Cell-Based Medicinal Products (2008)
- Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products (2017)
- ■ EC Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products (2017)
- Guideline on the Quality, Non-Clinical and Clinical Aspects of Gene Therapy Medicinal Products (2018)
- ■ Guideline on the Quality, Non-Clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials (draft, 2019)
- Q&A – Comparability Considerations for Advanced Therapy Medicinal Products (ATMP) (2019)
- Q&A – The Use of Out-Of-Specification Batches of Authorised Cell/Tissue-based Advanced Therapy Medicinal Products (2019)
- ❖ Guideline on Quality, Non-Clinical and Clinical Aspects of Medicinal Products Containing Genetically Modified Cells (2020)
- EC Good Practice on the Assessment of GMO-related Aspects in the Context of Clinical Trials with Human Cells Genetically Modified by Means of Viral Vectors (2020)
- ❖ Draft Toolbox Guidance on Scientific Elements and Regulatory Tools to Support Quality Data Packages for PRIME Marketing Authorization Applications (2021)
- Q&A – Principles of GMP for the Manufacturing of Starting Materials of Biological Origin Used to Transfer Genetic Material for the Manufacturing of ATMPs (2021)

■ provided in course ❖ recommended reading

34

FDA CMC Regulatory Guidances for CGTPs

- ❖ *Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (IND) (2008)*
- *Guidance for Industry: CGMP for Phase 1 Investigational Drugs (2008)*
- *Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (2011)*
- *Guidance for Industry: Recommendations for Microbial Vectors Used for Gene Therapy (2016)*
- *Draft Guidance for Industry: Chemistry, Manufacturing and Controls Changes to an Approved Application – Certain Biological Products (2017)*
- *Guidance for Industry: Evaluation of Devices Used with Regenerative Medicine Advanced Therapies (2019)*
- ■ *Guidance for Industry: Chemistry, Manufacturing & Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (2020)*
- *Guidance for Industry: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up (2020)*

■ *provided in course* ❖ *recommended reading*

Possible in 2021

- *Considerations for the Development of Human Gene Therapy Products Incorporating Genome Editing*
- *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Therapies*

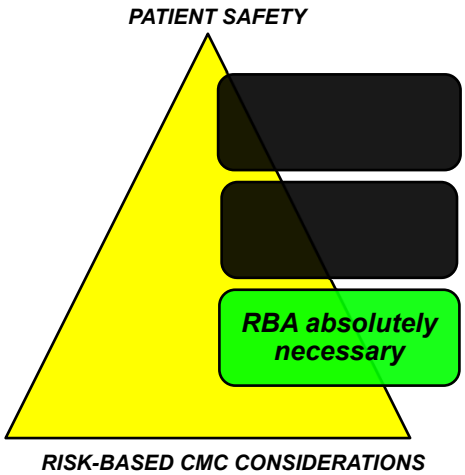
PIC/S

- *Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use (2021)*

(non-binding, informal co-operative arrangement between 53 Regulatory Authorities in the field of GMP)

35

Risk-Based Approach (RBA) for CGTP CMC Regulatory Compliance



36

CMC regulatory compliance is always <u>MANDATORY!</u>

1.1. Scope

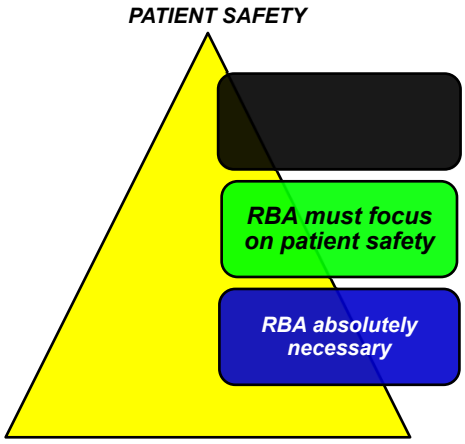
1.10. Compliance with good manufacturing practice ("GMP") is mandatory for all medicinal products that have been granted a marketing authorisation. Likewise, the manufacture of investigational medicinal products must be in accordance with GMP. Advanced therapy medicinal products that are administered to patients under Article 3(7) of Directive 2001/83/EC[1] (so called "hospital exemption") must be manufactured under equivalent quality standards to the manufacturing of advanced therapy medicinal products with a marketing authorisation.

A risk-based approach (RBA) provides the necessary CMC flexibility!

2.13. The risk-based approach ("RBA") is applicable to all type of ATMPS. It applies in an equal fashion to all type of settings. The quality, safety and efficacy attributes of the ATMPs and compliance with GMP should be ensured for all ATMPs, regardless of whether they are developed in a hospital, academic or industrial setting.

2.14. Manufacturers are responsible for the quality of the ATMPs they produce. The risk-based approach permits the manufacturer to design the organisational, technical and structural measures that are put in place to comply with GMP -and thus to ensure quality- according to the specific risks of the product and the manufacturing process. While the risk-based approach brings flexibility, it also implies that the manufacturer is responsible to put in place the control/mitigation measures that are necessary to address the specific risks of the product and of the manufacturing process.

Risk-Based Approach (RBA) for CGTP CMC Regulatory Compliance



39

The risk-based approach is about protecting patients!

In deciding on the appropriate measures to address the identified risks, the priority should be the safety of subjects enrolled in the trial. The Guideline on strategies to identify and mitigate risks for First-in-Human Clinical Trials with Investigational Medicinal Products (Doc. Ref. EMEA/CHMP/SWP/294648/2007) excludes ATMPs but its principles are nevertheless also useful in the design of first-in-human (FIH) trials with advanced therapy investigational medicinal products

An immature quality development may compromise the use of the study in the context of a marketing authorisation application (e.g. if the product has not been adequately characterised). A weak quality system may also compromise the approval of the clinical trial if the safety of trial subjects is at risk.

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

31 January 2019
EMA/CAT/852602/2018

40

2.17. The evaluation of the risks and the effectiveness of the control/mitigation measures should be based on current scientific knowledge and the accumulated experience. Ultimately, this evaluation is linked to the protection of patients.

EUROPEAN COMMISSION

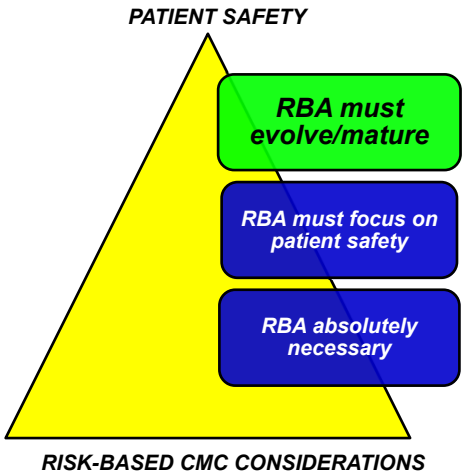
Good Manufacturing Practice for Advanced Therapy Medicinal Products
22.11.2017

Conclusions

- ***A risk-based approach focuses CMC regulatory compliance activities that may affect product quality, safety and/or efficacy (all of which, directly or indirectly, can impact patient safety)***
- ***A risk-based approach attempts to avoid non-value-added activities, and focuses efforts, with the limited resources, on the value-added activities***
- ***A risk-based approach does not mean doing less, but doing the right amount at the right time based upon the understanding of the potential risks to patient safety***
- ***Thus, a risk-based approach actually enhances patient safety in early clinical study phases, especially when product understanding and resources may be limited***

41

Risk-Based Approach (RBA) for CGTP CMC Regulatory Compliance



42

The risk-base approach must evolve/mature!

2.16. When identifying the control/mitigation measures that are most appropriate in each case, the ATMP manufacturer should consider all the potential risks related to the product or the manufacturing process on the basis of all information available, including an assessment of the potential implications for the quality, safety and efficacy profile of the product, as well as other related risks to human health or to the environment. When new information emerges which may affect the risks, an assessment should be made whether the control strategy (*i.e.* the totality of the control and mitigation measures applied) continues to be adequate.

2.22. The quality and safety of the product needs to be ensured from the first stages of development. Nevertheless, it is acknowledged that there is a gradual increase in the knowledge of the product and that the level of effort in the design and implementation of the strategy to ensure quality will step up gradually. It follows that the manufacturing procedures and control methods are expected to become more detailed and refined during the more advanced phases of the clinical trial.

Risk-Based Approach: to manage the "minimum CMC regulatory compliance continuum"

- ***"minimum" – different levels for CMC regulatory compliance at different clinical development stages***
- ***"continuum" – the minimum CMC regulatory compliance level rises as clinical development advances***

"The safety and well-being of trial subjects (be they patients or healthy volunteers) should always be the priority and special consideration should be given to characterising risk and putting in place appropriate strategies to minimise risk."

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

20 July 2017
EMEA/CHMP/SWP/28367/07 Rev. 1

FOCUS

- ***Early clinical stage → patient safety***
- ***Late clinical stage → patient safety + manufacturing process consistency***

Classroom Work Problem

'minimum CMC regulatory compliance continuum'

How is it acknowledged by regulatory authorities during clinical development?

REFERENCE 1

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

REFERENCE 2

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

31 January 2019
EMA/CAT/852602/2018

Read the FDA and/or EMA document: Where in the IND and/or IMPD CMC submission are phrases used such as:

- *'may be limited early in development'*
- *'not required for early stage'*
- *'acknowledged that during early clinical development'*
- *'not required for Phase 1 studies'*
- *'may be adjusted throughout the product development stages'?*

breakout rooms
read, discuss
fill in table

45

'minimum CMC regulatory compliance continuum'

acknowledged by regulatory authorities

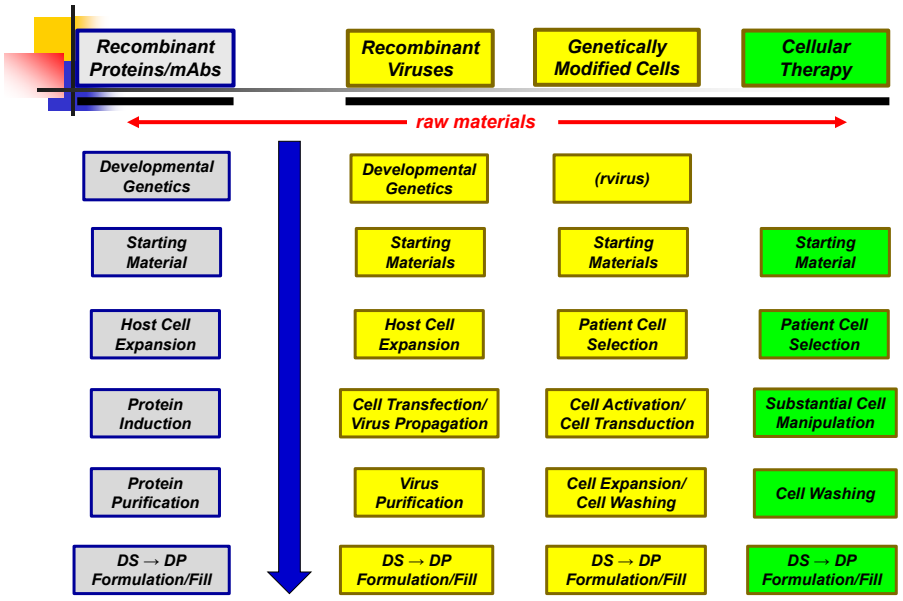
(~20 minutes)

IND/IMPD CMC Section		FDA (Reference 1)	EMA (Reference 2)
S.2.2	Description of Mfg Process and Process Controls		
S.2.4	Control of Critical Steps and Intermediates		
S.2.5	Process Validation and/or Evaluation		
S.4.1	Specification		
S.4.3	Validation of Analytical Procedures		
S.4.5	Justification of Specification		

46

Comparison of Manufacturing Process Flow Diagrams

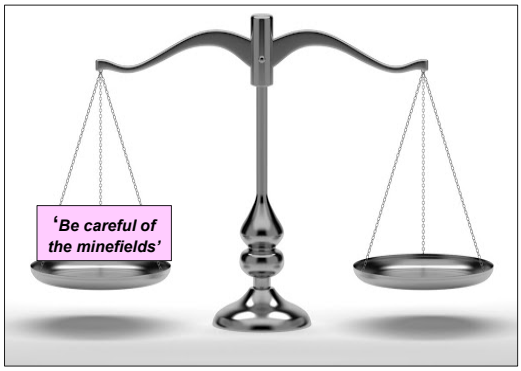
Similarities and Differences



47

Lessons Learned from Across the Biological Industry

True: ***CGTPs living viruses and cells are different in many ways from the vaccine, recombinant protein and mAb biologic medicines***



48

Not All Knowledge Applies Equally Across the Biological Industry

Manufacturing of living medicines (viruses/cells)
versus
Manufacturing of non-living medicines (rproteins/mAbs)

Patient-specific manufacturing batches ('personalized medicine')
versus
Inventory-build batches

Handling of living medicines (impact on genetic capability)
versus
Handling of non-living medicines (impact on potency)

Testing very complex living medicines, with limited analytical/biological tests
versus
Testing of complex proteins, with extensive analytical/biological tests

Intense time pressure on Quality for medicine release to patient

(will discuss these in next section)

49

Classroom Work Problem

'minimum CMC regulatory compliance continuum'

acknowledged by regulatory authorities

IND/IMPD CMC Section		FDA (Reference 1)	EMA (Reference 2)
S.2.2	Description of Manufacturing Process and Process Controls	We acknowledge that information on process controls may be limited early in development and recommend that sponsors provide additional information and updates as product development proceeds.	Critical steps should already be identified for the manufacture of early clinical trial material and adequate acceptance criteria for these critical steps established, for other IPCs, monitoring might be appropriate. During development, as process knowledge is gained, further details of in-process testing should be provided and acceptance criteria reviewed.
S.2.4	Control of Critical Steps and Intermediates	We recommend that you also consider any steps in which in-process tests with acceptance criteria are performed as critical control steps. The Agency acknowledges that this information may be limited in the early phases of development and recommends that sponsors provide additional information and updates as product development proceeds.	Critical steps in the manufacturing process should be identified as appropriate for the stage of development and all available data and acceptance criteria should be provided. It is acknowledged that due to limited data at an early stage of development complete information may not be available.
S.2.5	Process Validation And/or Evaluation	Process validation studies are generally or typically not required for early stage manufacturing, and thus, most original IND submissions will not include process performance qualification. We recommend that you use early stage manufacturing experience to evaluate the need for process improvements and to support process validation studies in the future.	The manufacturing process for ATIMPs is not expected to be validated for early clinical trials but appropriate monitoring and control measures should be implemented to ensure compliance with the requirements in the clinical trial authorisation.

50

IND/IMPD CMC Section		FDA	EMA
S.4.1	Specification	For products in the early stages of clinical development, very few specifications are finalized, and some tests may still be under development.	During early phases of clinical development specification can include wider acceptance criteria based on the current knowledge of the risks. As the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature preliminary and need to be subject to review during development.
S.4.3	Validation of Analytical Procedures	Validation of analytical procedures is usually not required for original IND submissions for Phase 1 studies; however, you should demonstrate that test methods are appropriately controlled.	Validation of analytical procedures during clinical development is an evolving process. An appropriate degree of method qualification should be applied at each stage to demonstrate the methods are suitable for their intended use at that time.
S.4.5	Justification of Specification	We recognize that acceptance criteria may be adjusted throughout the product development stages, based on both manufacturing and clinical experience. For early stage clinical studies, assays used to characterize production lots may be more variable than those used in later phase investigations. For later stage investigational studies in which the primary objective is to gather meaningful data about product efficacy, we recommend that acceptance criteria be tightened to ensure batches are well-defined and consistently manufactured.	It is acknowledged that during early clinical development when there is only limited experience, the acceptance criteria may be wide. However, for those quality attributes that may impact patient safety, the limits should be carefully considered taking into account available knowledge (e.g. impurities). Further refinement is expected as knowledge increases and data become available.

U.S. FOOD & DRUG ADMINISTRATION

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

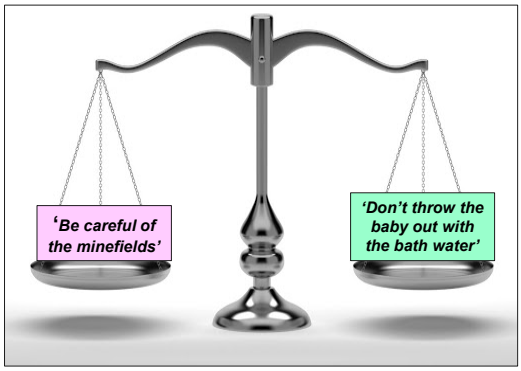
Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

31 January 2019
EMA/CAT/852602/2018

51

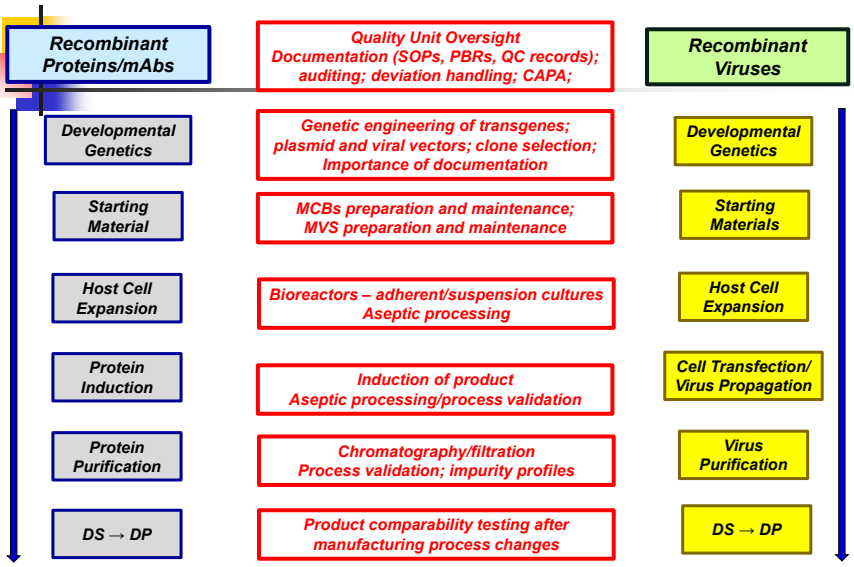
Lessons Learned from Across the Biological Industry

But: ***There are also similarities between the design and control of the manufacturing processes, and the testing of the products***



52

Many Similarities Across the Biologic Industry



(will discuss some of these in next section)

53

QTPP CQA CPP Control Strategy

Need to communicate with the CMC language of the regulatory authorities

*not mandatory, but highly recommended ('expected') – **including ATMPs!***

ICH Q8(R2) Quality by Design (QbD)

> **Quality by Design (QbD):**
> A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

QTPP
CQA
CPP
CS

ICH Q9 Quality Risk Management (QRM)

> **Quality Risk Management:**
> A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

RRF
FMEA
DOE

54

QbD/QRM - the language of communicating with regulatory authorities

during ATMP clinical development

Process characterisation/evaluation data should be collected throughout the development. It is acknowledged that some degree of variability of the active substance due to the characteristics of the starting materials is intrinsic to ATMPs. In this regard, it is recommended that critical process parameters, critical quality attributes and the associated acceptance criteria should be set based on the development data and current knowledge. This is achieved through implementation of appropriate monitoring and control measures. Summaries of the process characterisation and verification studies need to be provided, but the reports themselves are not required to be submitted as part of the IMPD.

CQA
CPP

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

31 January 2019
EMA/CAT/852602/2018

Your summary should also include a description of potential CQAs that are relevant to the safety and biological activity of the product as they are understood at the time of submission. A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (Ref. 6). We acknowledge that limits may be broader during early development when you are still gaining information about your product. In addition, as your product progresses through development the list of potential CQAs may be revised as your knowledge of the product increases.

CQA

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

55

QbD/QRM - the language of communicating with regulatory authorities

for ATMP market approval

The active substance of Zynteglo is an autologous CD34+ cell-enriched population that contains hematopoietic stem cells transduced with lentiviral vector encoding the β^{A-T87Q}-globin gene.

Lentiviral Vector (LVV Starting Material)

Process characterisation studies were deployed to identify the impact of the process parameters on critical quality attributes (CQAs) and establish proven acceptable range (PAR) for the process parameters.

CQA

For each process step, critical process parameters (CPPs), non-CPPs, and in-process controls (IPCs) are provided. The parameters are controlled within specified ranges.

CPP

Transduced Cells (Active Substance)

Tabular overviews of CPPs and IPCs have been adequately described.

CPP

Transduced Cells (Drug Product)

Control strategy

A summary of the FP manufacturing process design and development, including classification of quality attributes and justification for IPCs is provided. Assessment of criticality of process parameters and definition of their operational range was based on a risk estimate and process characterisation studies (DOE). Further detail was provided on the risk assessment and the characterisation studies during the

CPP
RRF
DOE

Assessment report

26 April 2019
EMA/CHMP/226273/2019

56

QbD, QRM – not mandatory, but expected!

proven invaluable across the entire biological manufacturing field

Quality by Design (QbD) elements

Quality Risk Management (QRM) tools for prioritization

57

Target Product Profile (TPP) – ***the company's strategic vision of the desired characteristics of the future commercial drug product***

(changeable, not static)

ICH Q8(R2)

Quality Target Product Profile (QTPP):

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

QTPP: an effective project management tool

Presents a common view of the target, across all disciplines

(R&D, Clinical, Manufacturing, Quality, Regulatory Affairs, Marketing)

Goal: to keep the different disciplines from drifting away from the target

The QTPP is a living document, subject to change as the science of the product evolves and the target shifts

58

Case Example QTPP
recombinant virus

CBER CMC BLA Review Memorandum 2019

onasemnogene abeparvovec-xioi
ZOLGENSMA

The process control strategy involved determining the quality target product profile, which informed the CQA selection. The AVXS-101 Quality Target Product Profile served as a basis for development of the manufacturing process and describes the high-level quality, safety and efficacy requirements for AVXS-101. Among other key attributes, the route of administration, dosage form, strength, and stability targets for AVXS-101 are defined in Table 11 AVXS-101 Drug Product Quality Target Product Profile.

Product QTPP Element	Product QTPP Element Target	Justification
Concentration	AVXS-101 drug product for intravenous administration should be formulated at a target concentration of 2.0 x 10^{13} vg/mL.	Target concentration based on pharmaceutical development and intended doses.
Excipients	Each (b) (4) of AVXS-101 (IV) DP solution in (b) (4) contains 20 mM Tromethamine, 1 mM Magnesium Chloride, 200 mM Sodium Chloride, and 0.005% m/V Poloxamer 188 (b) (4)	(b) (4)
Dosage Form and Volume	intravenous infusion in pediatric patients. The recommended dose of AVXS-101 for intravenous infusion in pediatric patients with a body weight of (b) (4) to 8.5kg is 1.1×10^{14} vector genomes/kg.	Ease of administration, stability of product during administration and transport, compatibility with desired product efficacy, and volumes necessary to meet recommended dosage.
Dosage Strength	The intravenous dosage strength studied in clinical trials was (b) (4). The planned commercial intravenous dosage strength is 2.0 × 10^{13} vg/mL.	Recommended dosage based on clinical trial data.
Container Closure System	AVXS-101 is supplied in (b) (4), cyclic olefin polymer 10mL vials. The vials are stoppered with a 20 mm Chlorobutyl rubber serum stopper with silicone coating, the vials are finally sealed with an aluminum seal and plastic flip cap.	Recommended storage using commonly available container closure components. Non-glass is preferred to avoid breakage and assure seal integrity at cryo temperatures.

59

CQA • ***Critical* Quality Attributes**

***Quality Attribute* (QA) – a physical, chemical, biological or microbiological *property or characteristic* of the product**

Primary structure (genetic sequence)
Higher order structure (viral capsids)
Product-related impurities
Process-related impurities
Compendial tests (safety, content)

(changeable, not static)

ICH Q8(R2)

Critical Quality Attribute (CQA):
A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

A CQA forces the focus onto those properties or characteristics of the product that are most important – especially those that are related to patient safety!

Non-CQA ⟷ CQA, a two-way continuum (as scientific understanding changes)

Most of the time CQAs result in specifications, but not always (see control strategy)

60

Case Example CQA
cellular therapy

PDA Technical Report 81 Cell-Based Therapy Control Strategy (2018)

1) identify all quality attributes (QAs)

2) rank each quality attribute for criticality (severity, uncertainty)

Rating	Severity
Negligible to Low	Marginal patient impact; no potential for decreased safety; attribute is not expected to impact safety or efficacy
Medium	Small potential for patient impact that does not change the overall risk/benefit profile for the product; attribute may have a manageable adverse effect, but significant patient impact is improbable
High	Significant to catastrophic patient impact, changing the risk/benefit profile of the product

Rating	Uncertainty
Low	Extensive literature available on this attribute; in-house data (in vitro, nonclinical, or clinical) available
Medium	Attribute well understood based on scientific rationale; in-house data (in vitro, nonclinical, or clinical) available
High	Limited scientific understanding of this attribute; no clinical experience; limited in-house data

3) set threshold for CQA vs non-CQA

Severity	Uncertainty		
	Low	Medium	High
Low	non-CQA	non-CQA	CQA
Medium	CQA	CQA	CQA
High	CQA	CQA	CQA

61

Illustration cellular therapy *PDA Technical Report 81 Cell-Based Therapy Control Strategy (2018)*

Attribute	*Severity*	*Uncertainty*	*Result*	*Rationale*
Visual appearance				
Visible Foreign Particles	High	Medium	CQA	Absence of visible foreign particles is expected for all parenterals
Identity				
Expression of Chondrogenic Markers	High	Low	CQA	Autologous chondrocyte product must contain chondrocytes, characterized by their expression of specific chondrogenic markers
Impurities				
Residual Trypsin	Low	Low	Non-CQA	Measured trypsin levels are 10x less than levels known to have a biological effect; as human recombinant trypsin was used, there is no risk for an immune reaction
Residual Collagenase	Low	Medium	Non-CQA	Collagenase is added to the process at levels 100x below the level known to have a biological effect
Dead Cells	Medium	Low	CQA	Presence of dead cells monitored through cell viability
Potency				
Functional Activity	High	Low	CQA	Lack of function will inevitably result in a lack of clinical efficacy; expression of specific genes measured as surrogate assay for function
Safety				
Endotoxin	High	Low	CQA	Endotoxins (mainly lipopolysaccharides) are highly pyrogenic substances that cause dose-dependent fever and shock
Sterility	High	Low	CQA	Sterility is a general safety requirement for all parenteral dosage forms to assure that cell products are free of microbial contamination

Risk Ranking & Filtering (RRF): severity x uncertainty
Failure Mode and Effects Analysis (FMEA): severity x occurrence x detection

Note, can use rankings of
1 to 3
1 to 5
1 to 10

The weakest link in all of these criticality determinations is the staff involved –
Are they competent/experienced?
Are they knowledgeable about your manufacturing process/product?

CQAs will be discussed in next section

62

CPP • Critical Process Parameters

Process Parameter (PP) – an element of manufacturing process control

Individual actions within each process step ↕ *(changeable, not static)*

ICH Q8(R2)

Critical Process Parameter (CPP):
A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Biologic manufacturing processes have many steps, each step has many PPs

Anion Exchange Chromatography (virus)

- *Loading*
  - *Solution treatment*
  - *Virus load*
  - *Load volume*
  - *Load rate*
- *Elution*
  - *Buffer conductivity*
  - *Buffer pH*
  - *Elution rate*
  - *Residence time*
- *…*

KPP (Key Process Parameter) – a process parameter that has no impact on a CQA but does impact process performance (e.g., product yield)

63

Illustration CPP approach
cellular therapy

PDA Technical Report 81 Cell-Based Therapy Control Strategy (2018)

1) *identify all process parameters (PPs)*
   detailed process diagram of each unit operation

2) *rank each process parameters for criticality (impact on CQA)*

Impact	Criteria
High	Small to moderate change of this process parameter has a significant impact on a CQA
Medium	Large change of this parameter or a small change in parameter, in combination with other factors, has a significant impact on a CQA
Low/Negligible	The process parameter has no impact on CQAs

3) *set threshold for CPP vs non-CPP*

Impact on CQA	
Low	Non-CPP
Medium	Non-CPP or CPP
High	CPP

→

64

PDA Technical Report 81 Cell-Based Therapy Control Strategy (2018)

Illustration cellular therapy

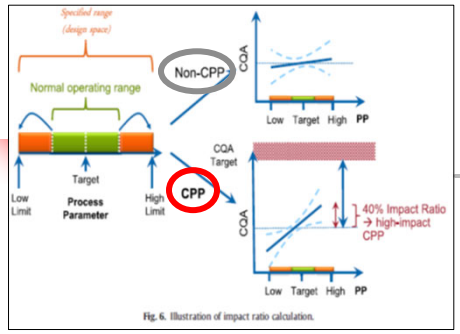


Fig. 6. Illustration of impact ratio calculation.

CPP
Non-CPP

Unit Operation Step	Process Parameter	CQA A	CQA B	CQA C	CQA …
Expansion	Number of trays or flasks				
	Seeding density for expansion				
	Media volume for each expansion				
→	Incubation time for each expansion				
→	Incubation temperature				
→	% CO_2 during expansion				
Wash	Wash volume following expansion				
	Wash time				
	Wash agitation				
Detachment	Volume of trypsin				
→	Detachment time				
→	Detachment temperature				
	Handling of trays to dislodge cells				

65

CS • Control Strategy

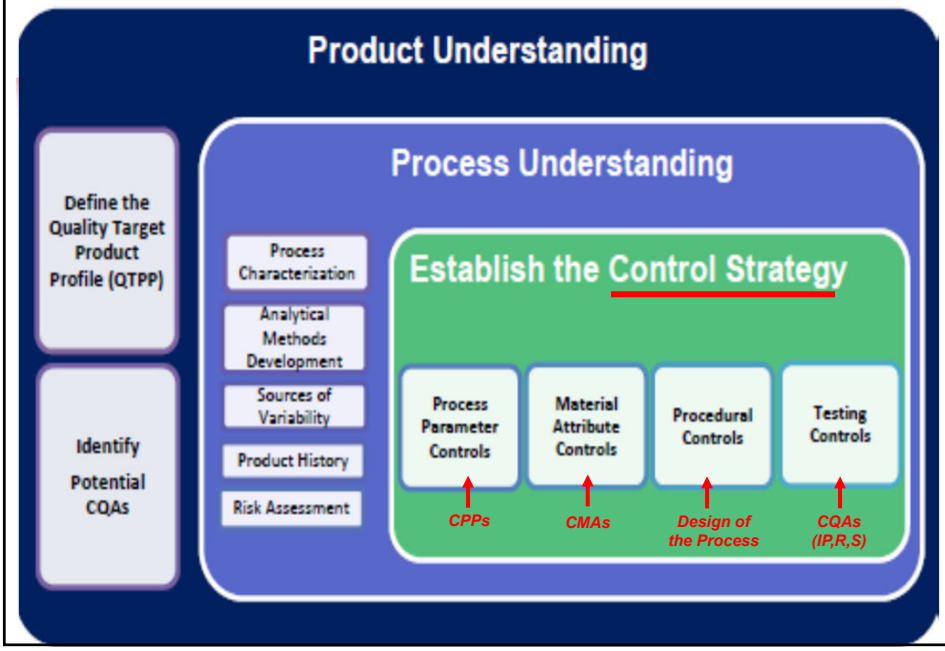
ICH Q8(R2)

Control Strategy:
A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

The Control strategy is <u>much more</u> than just product release specifications!

66

PDA Technical Report 81 Cell-Based Therapy Control Strategy (2018)



Tread carefully if you have not operated in the ATMP/CGTP arena before!

Danger of 'Unknown Unknowns' – "Surprises" – Murphy's Law

water resistant vs waterproof

QUESTIONS??

68

Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of Advanced Therapy Products

Course Outline

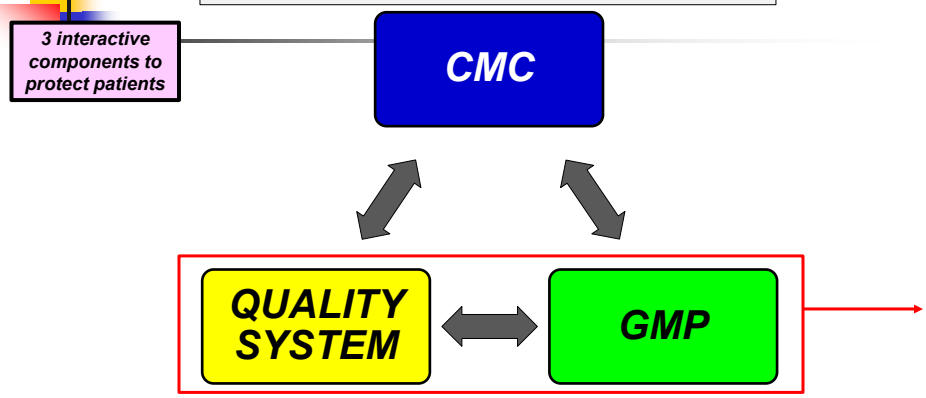
3. Regulatory Authority Expectations During Clinical Development

- ***Understanding the regulatory guidance for ATMPs that currently exist***
- ***Why those guidances stress the necessity of a risk-based control approach to GMPs and Quality Principles during clinical development***

69

Regulatory authority Manufacturing & Quality criteria to be met for human medicines

3 interactive components to protect patients



System that ensures regulatory criteria are met by practices carried out by Manufacturing & Quality

Practices carried out by Manufacturing & Quality to meet regulatory criteria

70

QUALITY SYSTEM ⟷ **GMP**

System that ensures *regulatory criteria are met by practices carried out by Manufacturing & Quality*

Practices carried out by *Manufacturing & Quality to meet regulatory criteria*

1.10. Compliance with good manufacturing practice ("GMP") is mandatory for all medicinal products that have been granted a marketing authorisation. Likewise, the manufacture of investigational medicinal products must be in accordance with GMP.

EUROPEAN COMMISSION — Good Manufacturing Practice for Advanced Therapy Medicinal Products

GMP applies to the lifecycle stages from the manufacture of investigational medicinal products, technology transfer, and commercial manufacturing through to product discontinuation.

PIC/S — Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use

71

Classroom Work Problem

Starting Material → Upstream Process → Downstream Process → Formulation → Drug Product

◄ ***risk-based control of the manufacturing process*** ►

across clinical development stages

REFERENCE 3

Read the EC document where the term 'investigational ATMP' is used over 50 times

What guidance does this document provide on the LEVEL OF GMP CONTROL over the manufacturing process across the clinical development stages?

breakout rooms
read, discuss
fill in table

72

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products

~15 minutes

REFERENCE 3

Guidance		GMP Manufacturing Process Control for Investigational ATMPs
2.20	*Why GMPs are Necessary*	
2.51	*Facilities & Equipment Control*	
9.11	*Controls for Manufacturing Process*	
10.14	*Air Quality System*	
10.35	*Cleaning Validation*	
10.46	*Process Validation*	

73

4. Premises

4.1. General principles

4.10. Premises must be suitable for the operations to be carried out. In particular, they should be designed to minimise the opportunity for extraneous contamination, cross-contamination, the risk of errors and, in general, any adverse effect on the quality of products.

Basic GMPs for 'Fit-for-Use' Manufacturing Facility

- ***Designed to permit production in a logical order corresponding to the sequence of the operations and required level of cleanliness***
- ***Cleaning, maintenance and repair***
- ***Lighting, temperature, humidity, ventilation***
- ***Room cleanliness classification***
- ***Environmental monitoring (air pressure differentials; non-viable/viable air; viable surface/personnel, etc.)***
- ***Pest control***
- ***Prevention of entry of unauthorized personnel***
- ***Restrictions on what operations are allowed in facility***

74

5. Equipment

5.1. General principles

5.10. Equipment used in production or control operations should be suitable for its intended purpose and it should not present any hazard to the product. Parts of production equipment that come into contact with the product should not have unwanted reactive, additive, adsorptive or absorptive properties that may affect the quality of the product. In addition, parts of the equipment that come into contact with cells/tissues should be sterile.

Basic GMPs for 'Fit-for-Use' Manufacturing Process Equipment

- ***Arranged to permit production in a logical order corresponding to the sequence of the operations***
- ***Identified to prevent mix-ups***
- ***Integrity of equipment components (during the defined operating process)***
- ***Qualification of relevant equipment (DQ, IQ, OQ, PQ)***
- ***Adequate maintenance (e.g., calibrated, cleaned, inspected, repaired, storage, movement in facility, etc.)***
- ***Defective equipment labelled as such or removed***

Process equipment of the future →

75

***Mandatory* training on aseptic processing simulation**

10.46. The manufacturing process for investigational ATMPs is not expected to be validated but appropriate monitoring and control measures should be implemented to ensure compliance with the requirements in the clinical trial authorisation. Additionally, it is expected that the aseptic processes (and, where applicable, sterilising processes) have been validated.

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products
22.11.2017

In addition the process characterisation/ evaluation summaries, validation of the aseptic process and the viral removal/inactivation steps are expected to be validated prior to the FIH clinical trials. Details on manufacturing steps intended to remove or inactivate viral contaminants should be provided in the section A2, Adventitious agents safety evaluation.

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

31 January 2019
EMA/CAT/852602/2018

77

Because product sterility is a critical element of human subject safety, you should take special precautions for phase 1 investigational drugs that are intended to be sterile. You should give thorough consideration to implementing appropriate controls for aseptic processing to ensure a sterile phase 1 investigational drug. The guidance issued by FDA on aseptic processing is a good reference when using aseptic processing (Ref. 7). Particular manufacturing controls include:

- Conducting aseptic manipulation in an aseptic workstation (e.g., laminar air flow workbench, biosafety cabinets, or barrier isolator system) under laminar airflow conditions that meet Class A, ISO 5. You should perform all manipulations of sterile products and materials under aseptic conditions.
- Conducting a process simulation using bacterial growth media to demonstrate that the aseptic processing/controls and production environment are capable of producing a sterile
- drug

U.S. FOOD & DRUG ADMINISTRATION

Guidance for Industry
CGMP for Phase 1 Investigational Drugs

Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2008

7 FDA "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices." September 2004

PDA on Aseptic Process Simulations: TR 22 (2011); TR 62 (2013); PTC (2016)

78

Classroom Work Problem

REFERENCE 3

Guidance		GMP Manufacturing Process Control for Investigational ATMPs
2.20	Why GMPs are Necessary	The application of GMP to investigational ATMPs is intended to protect the clinical trial subjects and it is also important for the reliability of the results of the clinical trial …
2.51	Facilities & Equipment Control	In early phases of clinical research (clinical trial phases I and I/II) when the manufacturing activity is very low, calibration, maintenance activities, inspection or checking of facilities and equipment should be performed at appropriate intervals, which may be based on a risk-analysis. The suitability for use of all equipment should be verified before it is used.
9.11	Controls for Manufacturing Process	In case of investigational ATMPs, the knowledge and understanding of the product may be limited, particularly for early phases of clinical trials (phase I and I/II). It is therefore acknowledged that the manufacturing process (including quality controls) may need to be adapted as the knowledge of the process increases. In the early phases of development, it is critical to carefully control and document the manufacturing process. It is expected that the manufacturing process and quality controls become more refined as development progresses.
10.14	Air Quality System	For investigational ATMPs, it is expected that at least the suitability of the air quality system (in accordance with ISO 14644-1 and ISO 14664-2) and the suitability of the premises to adequately control the risk of microbial and nonviable particle contamination is verified.
10.35	Cleaning Validation	For investigational ATMPs, cleaning verification is acceptable. In such cases, there should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.
10.46	Process Validation	The manufacturing process for investigational ATMPs is not expected to be validated but appropriate monitoring and control measures should be implemented to ensure compliance with the requirements in the clinical trial authorisation.

Classroom Work Problem

Starting Material → Upstream Process → Downstream Process → Formulation → Drug Product

◄ *risk-based control of the manufacturing process* ►

across clinical development stages

REFERENCE 3

Read the EC document where the term 'investigational ATMP' is used over 50 times

What guidance does this document provide on the
MATURITY OF THE QUALITY SYSTEM
over the manufacturing process across the clinical development stages?

breakout rooms
read, discuss
fill in table

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products

~15 minutes

REFERENCE 3

Guidance		Quality System for Investigational ATMPs
2.21 2.22	Quality System	
2.52	Documentation	
6.21	Specifications	
10.50	Validation of Test Methods	

81

Independence of Quality Unit from Manufacturing

GMP 'checks and balances'

3.35. The roles and responsibilities of key personnel should be clearly defined and communicated within the organisation.

3.40. The same person can perform the role of person responsible for quality control and QP. It is also possible for the QP to be responsible for production. However, responsibility for production and for quality control cannot be assumed by the same person. In small organisations, where teams are multi-skilled and trained in both quality control and production activities, it is acceptable that the same person is responsible for both roles (production and quality control) with respect to different batches. For any given batch, the responsibility for production and quality control of the batch must be vested on two different persons. Accordingly, it becomes particularly important that the independency of the quality control activities from the production activities for the same batch is clearly established through appropriate written procedures.

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products

82

You should summarize the QC plan that is in place to prevent, detect, and correct deficiencies that may compromise product integrity or function, or that may lead to the possible transmission of adventitious infectious agents. We recommend that QC responsibilities be performed independently from production responsibilities by dedicated QC personnel who are familiar with QC principles. You should conduct internal audits at planned intervals to evaluate effective implementation of the quality plan and to determine if processes and products meet established parameters. You should develop and document audit procedures to ensure that the planned audit schedule takes into account the relative risk of the various QC activities, the results of previous audits and corrective actions, and the need to audit the entire operation at least annually.

U.S. FOOD & DRUG ADMINISTRATION

Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)

Food and Drug Administration
Center for Biologics Evaluation and Research
April 2008

We recommend that you include a description of your Quality Unit whose duties should include establishing procedures to qualify reagents and critical materials, prevent microbial contamination, cross-contamination, and product mix-ups. In addition, your Quality Unit should have procedures in place to investigate lot failures, out-of-specification results, and ways to implement corrective actions as product development progresses. We recommend that your IND include a summary of your Quality Unit, including the manner in which quality control testing and oversight are separated from the manufacturing unit.

U.S. FOOD & DRUG ADMINISTRATION

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

83

Trained personnel a necessity!

3.1. General principles

3.10. The ATMP manufacturer should have an adequate number of personnel with appropriate qualifications and adequate practical experience relevant to the intended operations.

3.11. All personnel involved in the manufacturing or testing of an ATMP should have a clear understanding of their tasks and responsibilities, including knowledge of the product appropriate to the assigned tasks.

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products

3 'Rights' for GMP personnel

doing the right thing, in the right way, at the right time

84

3.2. Training

3.12. All personnel should receive training on the principles of GMP that affect them and receive initial and periodic training relevant to their tasks.

3.13. There should be appropriate (and periodic) training in the requirements specific to the manufacturing, testing, and traceability of the product.

3.14. Personnel working in clean areas should be given specific training on aseptic manufacturing, including the basic aspects of microbiology.

3.15. Prior to participating in routine aseptic manufacturing operations, personnel should participate in a successful process simulation test (*see* Section 9.5.2). Training in the

3.17. In addition, there should be appropriate training to prevent the transfer of communicable diseases from biological raw and starting materials to the operators and vice versa. Personnel handling genetically modified organisms ("GMOs") require additional training to prevent cross-contamination risks and potential environmental impacts.

Challenge of finding experienced personnel!

So on-the-job training becomes critical!

Train talent to avoid production bottlenecks: Staffing will be another key challenge for producers of gene therapies. Due to the novel techniques and technologies used in manufacturing gene therapy products – and the small number of approved gene therapy products – few prospective employees have ready-to-hire experience in gene therapy.[9]

PwC Health Research Institute
Beyond the hype:
September 2019

https://www.pwc.com/us/en/industries/health-industries/assets/pwc-health-research-institute-beyond-the-hype-gene-therapy-report.pdf

Lonza 200+ positions advertised (Feb 2021)

Classroom Work Problem

REFERENCE 3

Guidance		Quality System for Investigational ATMPs
2.21 2.22	Quality System	It is important to ensure that data obtained from the early phases of a clinical trial can be used in subsequent phases of development. Therefore, a functional quality system should be in place for the manufacturing of investigational ATMPs. The quality and safety of the product needs to be ensured from the first stages of development. Nevertheless, it is acknowledged that there is a gradual increase in the knowledge of the product and that the level of effort in the design and implementation of the strategy to ensure quality will step up gradually.
2.52	Documentation	The level of formality and detail for the documentation can be adapted to the stag of development. The traceability requirements should however be implemented in full.
6.21	Specifications	In the case of investigational ATMPs, the level of detail of the specifications and instructions should be adapted to the type of product and to the stage of development. Given the evolution/refinement of the manufacturing process and quality controls that is typical of investigational products, it is important that the level of documentation is sufficient to enable the identification of the specific characteristics of each batch. It is also noted that a deficient characterisation of the product may hinder the acceptability of the results of the clinical trial for the purposes of obtaining a marketing authorisation.
10.50	Validation of Test Methods	First-in-man and exploratory clinical trials: Sterility and microbial assays should be validated. In addition, other assays that are intended to ensure patient's safety should also be validated (e.g. when retroviral vectors are used, the analytical methods for testing for replication competent retrovirus should be validated). Throughout the clinical development, the suitability of analytical methods used to measure critical quality attributes (e.g. inactivation/removal of virus and/or other impurities of biological origin) should be established but full validation is not required. Potency assays are expected to be validated prior to pivotal clinical trials.

GMP and Quality System Deficiencies Impacting Advanced Therapy Products

3 Case Examples

U.S. National Institutes of Health (NIH)

manufacturer for clinical cell therapy

sterile operations suspended after FDA cGMP for-cause inspection

ERA The Netherlands B.V.

Manufacturer for cellular therapy – MAA filed

GMP non-compliance – suspension of manufacturing

Emergent Biosolutions

Genetically engineered live virus (COVID-19 vaccines) cross-contamination

FDA 483 report

Case Example 1

U.S. National Institutes of Health (NIH)

The FDA inspection occurred after the report of fungal contamination of two vials of albumin in the PDS in April.

From May 19, 2015 to May 29, 2015, U.S. Food and Drug Administration (FDA) investigators inspected the NIH Clinical Center Pharmacy Department, Building 10, 10 Center Drive, Bethesda, MD 20892. We inspected the following areas:

- the Pharmaceutical Development Section (PDS), where you produced drugs for Phase 1 and Phase 2 clinical trials
- the Intravenous Admixture Unit (IVAU), where you produce sterile drugs for administration to patients at the NIH Clinical Center.

In the PDS, our investigators observed significant violations of current good manufacturing practice (CGMP) requirements for finished pharmaceuticals, causing your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

89

1) Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, an operator was observed processing sterile drug products with an exposed wrist from a gap between their gloves and their gown. The same operator had exposed facial hair.

2) Systems for maintaining equipment used to control aseptic conditions in the aseptic processing areas are deficient.

Specifically, there are no air flow pattern studies performed in the ISO 5 horizontal airflow hood used to prepare total parenteral nutritional drug products and no dynamic airflow pattern studies were performed to determine whether products are protected from non-sterility risks in any of the five ISO 5 hoods used to make other drug products intended to be sterile.

4) Drug product operations and procedures are not performed in specifically defined areas of adequate size to prevent contamination or mixups.

Specifically, facilities were not designed and controlled to prevent contamination risks to sterile drugs in that:
a) There is inadequate separation of the aseptic processing area from the common pharmacy and uncontrolled flow of personnel between the two areas.
b) There is a lack of a differential pressure cascade between adjacent areas. The Deputy Chief Pharmacy Department explained "that no air pressure differential measurements" can be obtained "in the pharmacy because there are no doors" i.e., between the compounding area and the adjacent pharmacy preparation area. There is no specific minimal airflow velocity from the buffer area to the adjacent pharmacy as the feet per second air velocity is unknown.

17 observations total

https://clinicalcenter.nih.gov/phar/pdfs/483-2015.pdf

90

Impact from FDA Inspection

NIH Task Force on the Clinical Center Pharmacy Department

PDS – Pharmaceutical Development Service
IVAQ – Intravenous Admixture Unit

Background: The PDS formulates and packages batches of investigational drugs and other research products for use in research protocols at the NIH Clinical Center. The IVAU formulates and packages sterile products on a case-by-case basis to fulfill medical prescriptions for individual participants and patients while they are at the Clinical Center. FDA conducted an inspection of the NIH Clinical Center Pharmacy Department between May 19 and May 29, and reported a number of deficiencies in the PDS and IVAU. The FDA observations included problems with facilities, personnel training, and standard operating procedures in both units. NIH suspended sterile operations of the PDS on May 22 and posted the FDA observations on June 4.[1] Because the FDA observations in the IVAU were less serious, NIH has been able to maintain IVAU operations during the course of ongoing remediation efforts.

About half of the affected protocols were cell therapy studies that used a cryopreservative dispensed by the PDS. These studies are managed by the NIH Department of Transfusion Medicine. The cryopreservative is available commercially, so there was no interruption in the supply of cryopreservative for these protocols. However, some cell therapy research participants did require immediate treatment. Based on evaluation of risks and benefits, the FDA allowed use of the quarantined PDS product (i.e. with cells already mixed with the PDS-dispensed cryopreservative) on a case-by-case basis for individual research participants.

91

Final CAPA from 2015 FDA Inspection of NIH: new, properly designed facility

DEPARTMENT OF HEALTH & HUMAN SERVICES

March 27, 2018

National Institutes of Health
Bethesda, Maryland 20892
www.nih.gov

Division of Environmental Protection/ORF

Modern facilities are critical for NIH to perform their mission. The construction of the new Current Good Manufacturing Practice (cGMP) laboratory unit will allow NIH to create a new modern facility and help perform its mission.

SCOPE OF THE PROJECT:

The National Cancer Institute (NCI) is in urgent need of a new Tumor Infiltrating Lymphocytes (TILs) production facility to serve NCI Surgery Branch at the National Institutes of Health (NIH) Bethesda Campus. The new program under this project involves design and construction of a Current Good Manufacturing Process (cGMP) modular facility. This proposed project will relocate the existing NCI Cell Processing Facility from Building 10 into a new modular cGMP cell processing facility, external to Building 10, but on the NIH campus premises.

The new proposed facility is to provide more ISO controlled space for the NCI Surgery Branch, enabling a greater throughput of product. The new manufacturing program operated in this facility is required to comply more closely with the latest cGMP, CGTP, and Food and Drug Administration (FDA) requirements and regulations. This facility is required to produce reliable TIL doses for safe injection into human subjects in compliance with FDA Regulations and requirements.

92

Case Example 2

June 2020 filed MAA for cellular therapy triggering inspection Feb 2021

Issued following an inspection in accordance with :
Art. 15 of Directive 2001/20/EC

The competent authority of Netherlands confirms the following:

The manufacturer :*ERC The Netherlands B.V.*

Site address : *Nistelrooise Baan 3, SCHAIJK, 5374RE, Netherlands*

STATEMENT OF NON-COMPLIANCE WITH GMP

Nature of non-compliance :During the inspection performed on February 25th, 2021 at ERC The Netherlands B.V. Nistelrooise Baan 3, Schaijk thirteen (n=13) deficiencies were identified in total, one deficiency (n=1) was classified as critical and one deficiency (n=1) as major. ERC The Netherlands B.V. showed a lack of ability to adhere to the principles of Good Manufacturing Practice for ATMPs. The five main parts of the critical deficiency are summarized here: ERC has not sufficiently ensured the safety and effectiveness of their product according to the following observations: 1. Quality and safety of starting materials is not guaranteed. Inspection of chemicals and consumables is insufficient. 2. The quality and safety of the final product is not guaranteed. The product is not sufficiently defined and characterized. 3. The effectiveness of a gama irradiation step, and therefore the safety of the product, is not guaranteed. The change for the transition from Contractor 1 to Contractor 2 for gamma irradiation of cells has not been carried out as referred to in the GMP for ATMPs. 4. Prevention of (cross) contamination is not sufficiently guaranteed. 5. The environmental monitoring program and personnel monitoring are inadequate. As a result of this, the quality and safety of the product ERC1671 Gliovac manufactured at the site is not ensured.

Prohibition of supply
Suspension of the distribution of the ATMP ERC1617/Gliovac.

Others
Suspension of licensed activities until a sufficient GMP level has been confirmed by the NCA.

eudragmdp.ema.europa.eu/inspections /gmpc/searchGMPNonCompliance.do

93

Case Example 3

REFERENCE 4

for later reading

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Baltimore District (BLT-DO) 6000 Metro Drive, Suite 101 Baltimore, MD 21215 (410) 779-5455 orabioinspectionalcorrespondence@fda.hhs.gov	4/12/2021 – 4/20/2021
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	FEI NUMBER
TO: Dino S. Muzzin, Senior Vice President Manufacturing Operations	3015448605
FIRM NAME	STREET ADDRESS
Emergent Manufacturing Operations Baltimore, LLC.	5901 East Lombard Street
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Baltimore, MD 21224	Vaccine Drug Substance Manufacturer

Observation 1

Failure to conduct thorough investigations into unexplained discrepancies.

Specifically,

a. The cross-contamination of client (b) (4) viral vaccine drug substance batch (b) (4), which was manufactured between (b) (4) and (b) (4), with the virus from client (b) (4) as described in deviation 3100012112 initiated on 3/17/2021 has not been thoroughly investigated. Specifically,

62 Million Doses in the Balance

Shortly before 6:20 p.m. on March 25, an urgent email landed in the inboxes of top officials at the Department of Health and Human Services. "Developing Situation _ Emergent Bayview," the subject line read.

What followed was even more alarming: "Viral cross-contamination confirmed in the control cells for JANSSEN GMP Lot #8."

The message, referring to the Johnson & Johnson vaccine production at Emergent's Baltimore factory, set off a series of hurried nighttime telephone calls, according to officials familiar with the situation.

The Johnson & Johnson and AstraZeneca vaccines use the same technology: A harmless version of a virus — known as a viral vector — is transmitted into cells to make a protein that stimulates the immune system to produce antibodies.

Sometime in February, Emergent workers had unknowingly contaminated Johnson & Johnson's viral vector with AstraZeneca's. The error was not discovered for weeks, until, in one of the final checks before release, Johnson & Johnson sampled a batch of 13 million to 15 million doses' worth of vaccine for purity.

94

Take GMP and Quality Systems seriously with advanced therapy products!

Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2A

Type and source of material	Example product	Application of this guide to manufacturing steps shown in grey			
Human and/or animal sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells[1]	Vector manufacturing; cell isolation, culture and purification	Ex-vivo genetic modification of cells, Establishment of MCB, WCB or primary cell lot	Formulation, filling
	Somatic cell therapy	Donation, procurement and testing of starting tissue / cells[1]	Establishment of MCB, WCB or primary cell lot or cell pool	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, fill
	Tissue engineered products	Donation, procurement and testing of starting tissue / cells[1]	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, fill
Non-Human and/or animal sources	Gene Therapy: in Vivo Viral Vectors by stable producer cell lines	Plasmid manufacturing[1]	Producer cell lines manufacturing	Vector Manufacturing	Formulation, filling
	Gene Therapy: in Vivo Viral Vectors by transient production system	Virus manufacturing[1]	Cell system manufacturing	Vector Manufacturing	Formulation, filling

Increasing GMP requirements

[1] Separate GMP requirements may apply where required under national law.

Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of Advanced Therapy Products

Course Outline

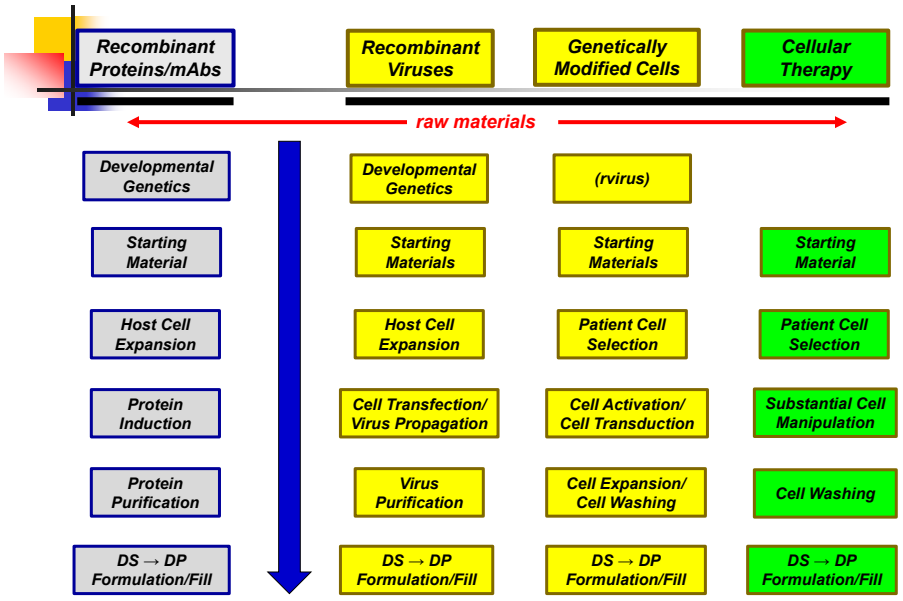
4. Industry Practice in Applying the Risk-Based Principles to ATMPs

- ***Applying Quality by Design (QbD) and Quality Risk Management (QRM) to ATMPs***
- ***PDA Technical Report 81 on Cell-Based Therapy Control Strategy***

Case examples and references are from public sources
(CGT manufacturers do not voluntarily reveal their manufacturing details)

Comparison of Manufacturing Process Flow Diagrams

Similarities and Differences

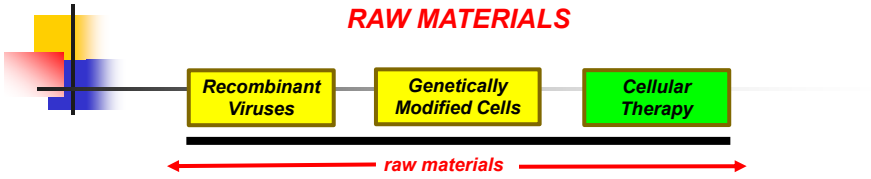


97

Regulatory CMC Requirements & Expectations

Across the CGTP Manufacturing Process

RAW MATERIALS



Raw materials are the reagents used in the manufacturing process (e.g., cell growth, differentiation, selection, purification, etc.), but are <u>not</u> part of the final drug product

<u>Examples:</u>

- *complex cell culture media (many times proprietary)*
- *human plasma, human serum albumin*
- *fetal bovine serum (FBS)*
- *digestive enzymes (e.g., trypsin, collagenase, DNAse/RNAse)*
- *growth factors (TGF-ß1, EGF, BMP-2, PDGF-BB)*
- *cytokines (e.g., IL-2, IL-3, IL-6, IFN-γ , GM-CSF)*
- *antibiotics (e.g., gentamicin)*
- *transfection reagents (e.g., calcium phosphate, PEI, FuGENE lipids)*
- *surfactants (e.g., Triton X-100)*
- *monoclonal antibodies*
- *antibody-coated beads*
- *chromatography resins (e.g., affinity, AEX)*
- *filters (e.g., 0.2 µm, nanofilters)*
- *…..*

includes processing aids that come in contact with the product

United States Pharmacopeia (USP) uses the term 'ancillary materials'

98

Core IND/IMPD Submission Requirement

List of Raw Materials – Along with Safety Assessment

Control of Materials (3.2.S.2.3)

You must provide a list of all materials used in manufacturing and a description of the quality or grade of these materials (21 CFR 312.23(a)(7)(iv)(b)).
This information which may be provided in tabular format, includes the identity of the material, the supplier, the quality (e.g., clinical-grade, FDA-licensed), the source of material (e.g., animal, human, insect), and the stage at which each material is used in the manufacturing process (e.g., culture media, vector purification).

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

S.2.3. Controls of Materials

Materials used in the manufacture of the active substance (starting materials and raw materials) should be listed and their acceptance criteria for production should be provided, identifying where each material is used in the process.
The manufacturing materials and reagents need to be qualified from the perspective of safety prior to human clinical trials.

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

31 January 2019
EMA/CAT/852602/2018

99

Application of Risk-Based Approach to Raw Materials

2.29. The application of the risk-based approach requires that the manufacturer has a good understanding of the role of the raw material in the manufacturing process and, in particular, of the properties of the raw materials that are key to the manufacturing process and final quality of the product.

2.30. Additionally, it is important to take into account the level of risk of the raw material due to the intrinsic properties thereof (e.g. growth factors v. basic media, culture media containing cytokines v. basal media without cytokines, raw material from animal origin v. autologous plasma, etc.), or the use thereof in the manufacturing process (higher risk if the raw material comes into contact with the starting materials).

2.31. Finally, it needs to be assessed if the control strategy (e.g. qualification of suppliers, performance of suitable functional testing, etc.) is sufficient to eliminate the risks or to mitigate them to an acceptable level.

7.14. In the case of critical raw materials, the specifications should include quality requirements to ensure suitability for the intended use, as well as the acceptance criteria. … For investigational ATMPs, the technical specifications for the critical raw materials should be agreed with the suppliers whenever possible. The assessment whether a specific raw materials is critical should be done by the manufacturer having regard to the specific risks. The decisions taken should be documented.

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products

22.11.2017

100

General Compendial Guidance on Assessing Raw Material Risk

European Pharmacopeia

General Chapter 5.2.12

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

***Risk assessment:** serum, recombinant proteins, proteins extracted from biological materials, vectors*

(definition, production, identification, tests, assay)

2. Risk Assessment

Evaluation of the impact of the raw material on the quality, safety and efficacy of cell-based/gene therapy medicinal products must be performed by the user of the raw material. No single measure or combination of measures can guarantee the quality, functionality and safety of a raw material for its intended use. Therefore, a risk assessment must consider the biological origin and traceability of the raw material, the production steps applied to it and the ability of the drug product manufacturing process to control or remove the raw material from the final medicinal product.

101

General Compendial Guidance on Assessing Raw Material Risk

United States Pharmacopeia

<1043> Ancillary Materials (AMs) for Cell-, Gene-, and Tissue-Engineered Products

***Risk classification:** 4 tier levels, with corresponding risk reduction activities*

Regardless of the stated grade of the AM, the CGT product manufacturer is responsible for developing comprehensive and scientifically sound qualification plans to ensure the traceability, consistency, suitability, purity, and safety of the AM.

The evaluation of AM risk to CGT product quality should be based on scientific knowledge, with the ultimate goal of patient protection. ICH Q9 (step 4) "Quality Risk Management" provides a useful approach to risk management principles, process, methods, and definitions. Risk management processes include identifying, analyzing, and evaluating risks, followed by controlling potential risks. Tools or methods, such as a risk evaluation matrix (REM), can quantify risk and facilitate appropriate decision-making and risk acceptance.

ISO Technical Committee 276 Biotechnology, Working Group 4 Bioprocessing

Technical Standard 20399 on Ancillary Materials

under development

102

Raw Material Classifications/Grades

Higher Risk		Lower Risk
'For Research Use Only'	⟷	GMP grade
Non-Compendial	⟷	Compendial
Animal Derived (AD)	⟷	Animal-Derived Component Free (ADCF)

Raw Materials ⟷ **Critical Raw Materials**

What can make a raw material 'critical'?

- sole source
- poorly defined
- adventitious agent risk
- patient safety due to impurity
- lacking documentation on traceability
- connected to a critical process parameter
- .....

103

Regulatory Authority Critical Concerns for Raw Materials

Patient Safety + Manufacturing Consistency

PATIENT SAFETY

Where possible, the use of animal reagents should be avoided and replaced by non-animal derived reagents of defined composition. This is due to their potential to introduce adventitious agents and resulting additional testing requirements.

Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

3 November 2020
EMA/CAT/GTWP/671639/2008 Rev. 1
Committee for Advanced Therapies (CAT)

IMPACT ON MANUFACTURING PROCESS CONSISTENCY

Certain animal-derived materials, such as sera, are complex mixtures that are difficult to standardize and such materials may have significant batch-to-batch variations that may affect the reproducibility of your manufacturing process or the quality of your final product

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

104

EMA on Regulatory CMC Requirements & Expectations

For Raw Materials During Clinical Development

The quality of starting and raw materials is a key factor in the production of ATMPs. Therefore avoiding contamination, minimising variability of starting and raw materials is vital for the manufacturing process.

Considerations for suitability of a given material should focus on its identity, safety and functionality in respect of the intended use in the manufacturing process.

While raw materials should be of pharmaceutical grade, it is acknowledged that, in some cases, only materials of research grade are available. The risks of using research grade materials should be understood (including the risks to the continuity of supply when larger amounts of product are manufactured).

For all raw materials of biological origin, the information on the supplier and the respective stage of the manufacturing process where the material is used should be indicated and a risk assessment conducted. Specific guidance is provided in Ph.Eur. (5.2.12) Raw Materials for the Production of Cell based and Gene Therapy Medicinal Products. Summaries of adventitious agents safety information for biologically-sourced materials should be provided in Appendix A.2.

The same safety principles should apply to those critical raw materials generated in biological systems that were used for the manufacture of starting materials such as viral vectors, gene editing products or induced pluripotent stem cells (iPSC).

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

31 January 2019
EMA/CAT/852602/2018

105

FDA on Regulatory CMC Requirements & Expectations

For Raw Materials During Clinical Development

You should establish a qualification program and provide documentation that the materials used for manufacturing meet standards appropriate for their intended use (e.g., test results, certificates of analysis (COAs), package inserts). … the extent of recommended testing will depend on the specific material and the manner in which it is used in the manufacturing process.

Certain animal-derived materials, such as sera, are complex mixtures that are difficult to standardize, and such materials may have significant batch-to-batch variations that may affect the reproducibility of your manufacturing process or the quality of your final product. We recommend that you consider using non-animal-derived reagents if possible (e.g., serum-free tissue culture media and recombinant proteases).

We recommend that you use FDA-licensed, approved, or cleared materials, or other clinical-grade materials, when they are available. If the material is not FDA-licensed, approved, or cleared (or in the absence of recognized standards), additional information on the manufacturing and/or testing may be needed to evaluate the safety and quality of the material.

You should also consider that many monoclonal antibodies and recombinant proteins (such as cytokines) used during the manufacture of gene therapy products may be purified by affinity chromatography using antibodies generated from mouse hybridomas. This may introduce the risk of contamination with adventitious agents from rodents, which should be controlled for by the supplier.

If human albumin is used, you should use FDA-licensed products and have procedures in place to ensure that no recalled lots were used during manufacture or preparation of the product.

For all other reagents that are human-derived, you should identify whether the reagent is a licensed product (e.g., HSA, IL-2) or is clinical or research grade and provide a COA or information regarding testing of the donor or reagent.

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

106

Regulatory CMC Requirements & Expectations

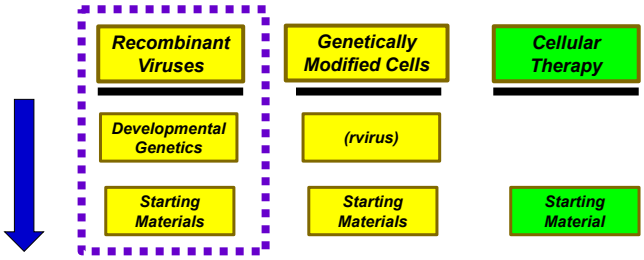
Across the CGTP Manufacturing Process

STARTING MATERIALS

Defined Starting Materials (ICH Q11)

Chemical Drug – significant structural component present

rprotein/mAb – Master Cell Bank (MCB)



Starting Materials are specific to each of these 3 ATMP types

Due to time limitations

107

Control of Starting Materials for CGTPs

A GMP certificate is not required for manufacturing and testing sites of starting materials for ATMPs. For certain starting materials of biological origin[1], (such as e.g. linear DNA used as template for ex vivo transcription into mRNA, plasmids to generate viral vectors and/or mRNA, and vectors[2]) used to transfer genetic material for the manufacturing of ATMPs it is, however, mandatory that the principles of GMP are complied with.

The assessment of the minimal requirements is performed by the ATMP manufacturer (or, as appropriate, the sponsor or marketing authorisation holder or importer to the European market). The ATMP manufacturer should have access to information about the starting materials that is relevant to ascertain the impact thereof on the quality, safety and efficacy profile of the finished product. To this end, the contract/technical agreement between the supplier of the starting material(s) and the ATMP manufacturer should provide for the transfer of information about the starting material that is relevant to the quality, safety and/or efficacy of the finished product.

In cases where the manufacturer, importer, sponsor and marketing authorisation holder are different legal entities, there should be a written agreement between the parties which lays down the respective duties in this process.

108

In laying down the principles of GMP applicable to starting materials, it is necessary to recognise a certain level of flexibility for investigational ATMPs based on a risk based approach (RBA), especially in early phases of clinical trials (phase I and phase I/II), due to the often incomplete knowledge about the product as well as the evolving nature of the routines.

How principles of GMP are defined?

Risk factors for consideration should include, but are not limited to:

Example Products	Application of GMP to manufacturing steps is shown in dark grey GMP Principles should be applied where shown in light grey starting material - active substance - finished product →

Questions and answers on the principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs

24 February 2021
EMA/246400/2021

109

Starting Materials for …

Transient Manufacture of Recombinant Virus for Gene Therapy

MCB/WCB for Plasmid Production

Bacterial MCBs are frequently used as the starting material to generate plasmid DNA, which can be used as a gene therapy DS or used as a manufacturing intermediate to generate a DS for other gene therapy products, such as AAV or lentiviral vectors.

We generally recommend the establishment of a bacterial MCB, as it can provide a consistent starting material for the manufacture of plasmids or microbial vectors.

We recognize the diversity of uses for bacterial MCBs, and recommend that you appropriately qualify the bank, and submit sufficient detailed information for the qualification of the banked material regardless of use.

MCB/WCB for Virus Propagation

Master Cell Banks Used as Substrates for Production of Viral Vectors

Prior to selecting a cell line for viral vector manufacturing, you should carefully consider characteristics of the cells that may impact the safety of the final product (such as presence of tumorigenic sequences).

We also recommend that you consider cell attributes that can affect production capacity (e.g., growth characteristics, vector production capacity), prior to generation of a cell bank

→

110

DNA Plasmids as 'Intermediates'

Intermediates in gene therapy manufacturing may also include DNA plasmids that are used in the manufacture of other gene therapy products, such as AAV or lentiviral vectors. We recommend that DNA plasmid intermediates be derived from qualified banks, as described in more detail above and in section V.A.2.c., "Control of Materials (3.2.S.2.3)," of this guidance. In addition, we recommend that you provide information on the plasmid manufacturing procedures, reagents, and plasmid specifications for use, regardless of whether they were made by the IND sponsor or a contract manufacturer. In general, we recommend that this testing include assays to ensure the identity, purity, potency, and safety of the final product. For a DNA plasmid, this may include sterility, endotoxin, purity (including percent of supercoiled form and residual cell DNA, RNA, and protein levels), and identity testing (restriction digest and sequencing if sequencing was not performed on the bacterial bank). A COA documenting plasmid quality testing should be included in the IND (section 3.2.A.2 of the CTD).

EUROPEAN MEDICINES AGENCY

The establishment of bacterial/cell/virus seed or bank(s) is expected for starting materials which are bankable. Where possible, a Master Cell/Seed Bank (MCB/MSB) should be established prior to the initiation of exploratory trials. It is acknowledged that a Working Cell/Seed Bank (WCB/WSB) may not always be established.

The MCB/MSB and/or WCB/WSB should be characterised and results of tests performed should be provided. Banks should be characterised for relevant phenotypic and genotypic markers so that the identity, viability, and purity of cells used for the production are ensured.

Application of GMP to manufacturing steps is shown in dark grey
GMP Principles should be applied where shown in light grey

Example Products	starting material - active substance - finished product			
In vivo gene therapy: mRNA	Plasmid, manufacturing and linearization	In vitro transcription	**mRNA** manufacturing and purification	Formulation, filling
In vivo gene therapy: non-viral vector (e.g. naked DNA)	Plasmid manufacturing	Establishment of bacterial bank (MCB, WCB)	**DNA** Manufacturing fermentation and purification	Formulation, filling
In vivo gene therapy: viral vectors	Plasmid manufacturing	Establishment of a cell bank (MCB, WCB) and virus seeds when applicable	**Vector** Manufacturing and purification	Formulation, filling

In the table above, the AMTP starting materials are underlined and the ATMP active substances appear in bold.
The construction of the plasmid by in silico and molecular biological methods occurs before the plasmid manufacturing and is considered research and development. Therefore it is not under the scope of the current Q&A.

Questions and answers on the principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs

24 February 2021
EMA/246400/2021

113

Starting Materials for Transient Manufacture of Recombinant Viruses

***E. coli* Plasmid Manufacture of 3 separate plasmids**
(*Developmental Genetics* → *Expansion* → *rMCB/rWCB* → *Plasmid Production* → *Purification*)

HEK293 Source → Expansion → ***MCB/WCB*** *HEK293 (human)*

PLASMID DNA *AAV life cycle genes*
PLASMID DNA (helper) *other AAV coding genes, disabled replication*
PLASMID DNA (transfer) *TRANSGENE*

transfection

RECOMBINANT VIRUS

could be treated either as starting materials or critical raw materials

In Vivo – Direct Injection

AAV2 – Luxturna (Spark)
AAV9 – Zolgensma (AveXis)

Adeno-Associated Virus (AAV)
Does not integrate into cell genome
single stranded DNA
~20 nm

114

Case Example

The Starting Materials for onasemnogene abeparvovec consist of a mammalian cell bank and three recombinant plasmids. An overview of raw materials used in the manufacturing of the active substance has been provided including information on their intended use, whether they are compendial or non-compendial, and specifications for non-compendial material. Information on the vendors of critical raw materials is provided. Specifications and representative certificates of analysis are provided.

For the starting materials, information on the source, history, and generation of the plasmids and the cell banks has been provided. The applicant used a vial of HEK 293 cells to create a pre-MCB (master cell bank). Subsequently a MCB and three WCBs (working cell banks) were manufactured under GMP. All three generated WCBs will be used for manufacture of clinical and commercial material.

Zolgensma AS is produced by co-transfection of HEK293 cells withthree plasmids:

- Vector Plasmid (pSMN)
- AAV Plasmid (pAAV2/9) containing the AAV rep2 and cap9 wild-type genes
- Adenovirus Helper Plasmid (pHELP).

Plasmid DNA maps are provided. The plasmid manufacturing and testing sites are provided.

Zolgensma
onasemnogene abeparvovec

Assessment report

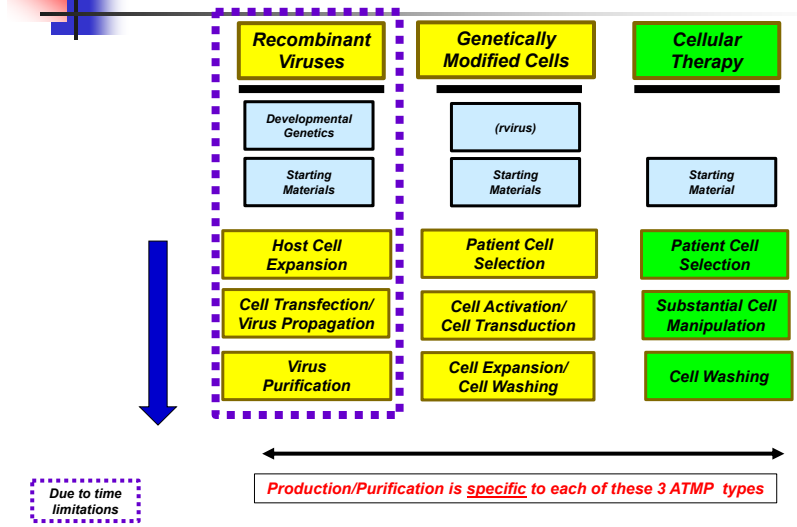
26 March 2020
EMA/200482/2020

115

Regulatory CMC Requirements & Expectations

Across the CGTP Manufacturing Process

PRODUCTION & PURIFICATION

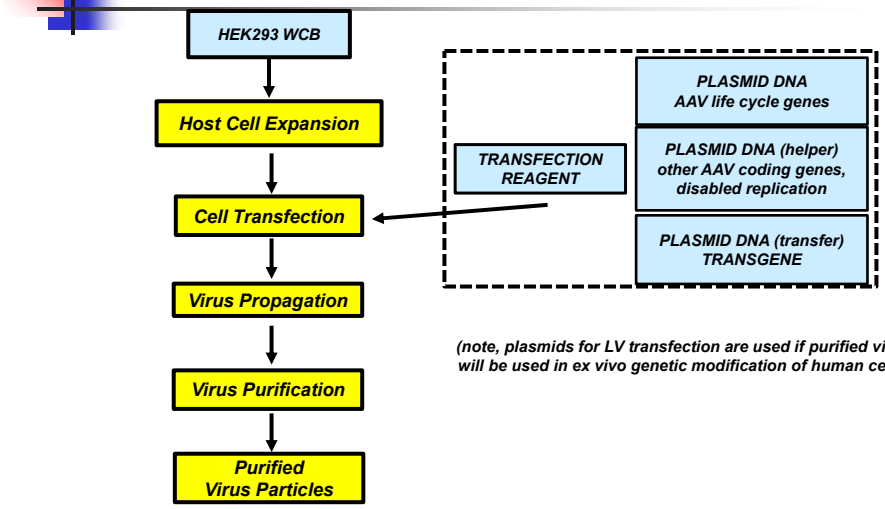


116

Production & Purification for CGTPs

Manufacturing Process Dependent

manufacture of recombinant virus gene therapy



(note, plasmids for LV transfection are used if purified virus will be used in ex vivo genetic modification of human cells)

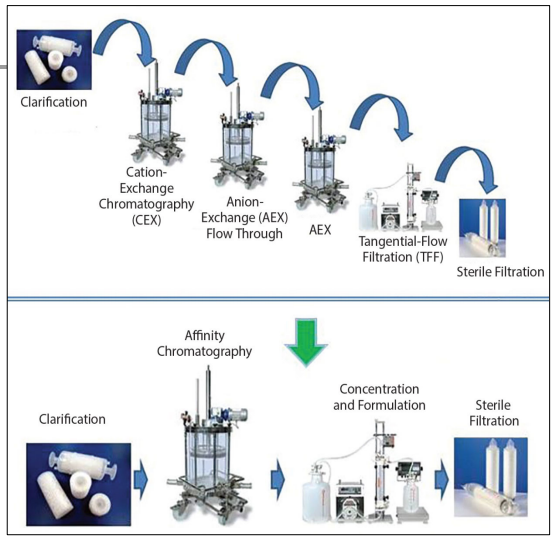
117

Manufacturing of recombinant viruses

(process looks similar to that of mAbs)

suspension cells

adherent cells



USP ***DSP***

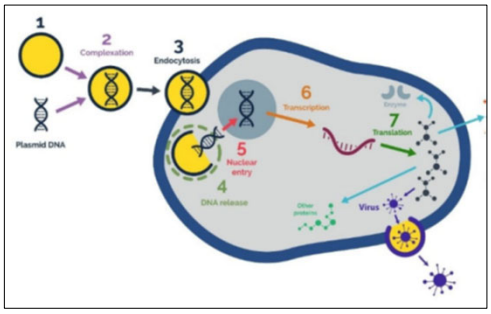
118

Transfection

***Free* technical manuals providing extremely useful information (e.g., CPPs)**

Guide for DNA Transfection in iCELLis® Bioreactor Systems for Gene Therapy Vector Manufacturing

PALL Biotech



The following parameters are key for best transfection conditions:

- Transfection media
- DNA/cell ratio
- DNA/PEIpro ratio
- Plasmid ratios (when using several plasmids)

CPPs

cationic lipid-based transfection reagents

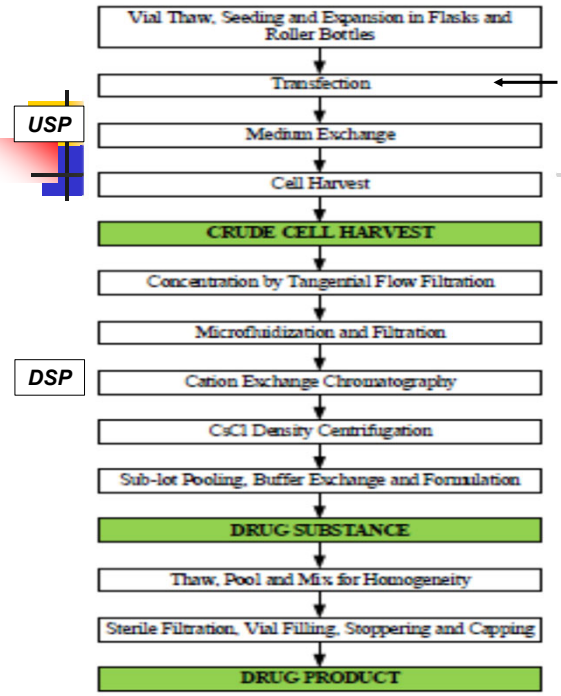
FuGENE® HD Transfection Reagent

Instructions for Use of Products

Promega

119

Case Example



transient transfection with 3 separate plasmids

USP

DSP

Spark Luxturna

FDA Advisory Committee Meeting

October 12, 2017

120

Case Example

The AS Upstream manufacturing process consists of five steps, or unit operations: 1) Cell Expansion, 2) Bioreactor Operations, 3) Bioreactor Harvest, 4) Harvest Clarification, and 5) Intermediate.
During Upstream manufacturing, one vial of the human embryonic kidney cells (HEK293) working cell bank (WCB) is thawed, and cells are expanded. The expanded cells are harvested and used to inoculate the bioreactor. The cells expanded are transfected with a triple DNA plasmid solution. After cell culture, the cells are harvested and clarified. The clarified harvest is processed to Intermediate and frozen. All open cell/product manipulations in the Upstream manufacturing process occur inside a biosafety cabinet (BSC) within an ISO 7 area. Media, solutions, and buffers that are prepared by AveXis are prepared in an ISO 8 area.

The AS Downstream manufacturing process includes thawing and pooling of the intermediate, clarification process, chromatographic purification step, filtration and centrifugation steps and filling of the AS. No reprocessing is allowed.

Zolgensma
onasemnogene abeparvovec

Assessment report

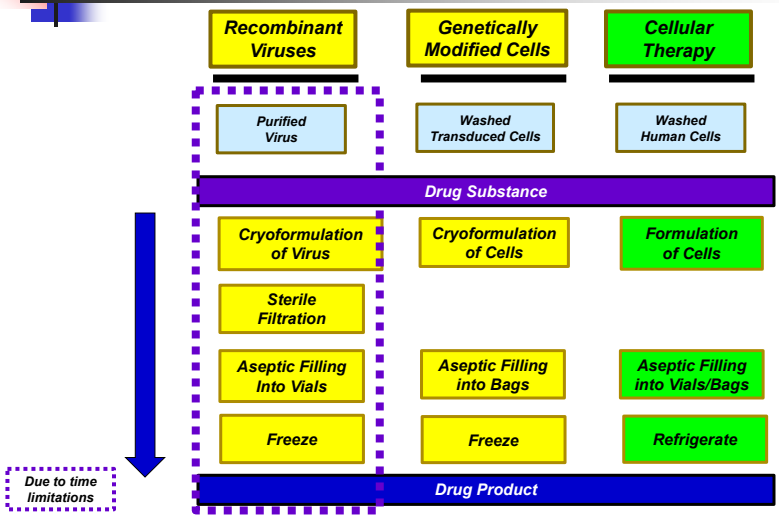
26 March 2020
EMA/200482/2020

121

Regulatory CMC Requirements & Expectations

Across the CGTP Manufacturing Process

DRUG SUBSTANCE → DRUG PRODUCT

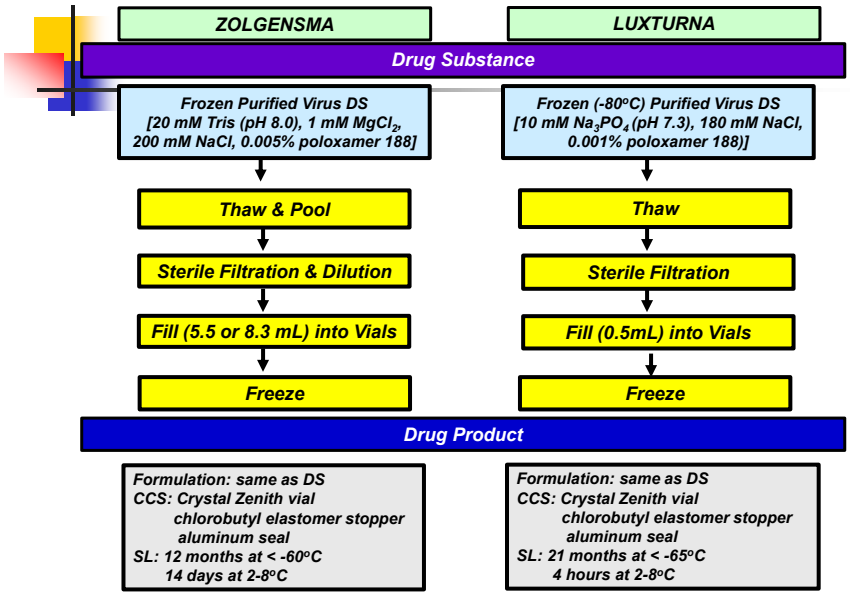


122

DRUG SUBSTANCE → DRUG PRODUCT

manufacture of recombinant virus gene therapy

Case Examples
European Public Assessment Report
FDA Package Insert



123

More than the drug product – Ensuring the drug product is accurately and consistently administered to the patient

– *(especially if dilution and/or a delivery device in necessary)*

Using MRI navigation, direct delivery of a gene therapy into a patient's brain tumor

Intravenous administering of CAR T-cells

124

Important to understand the risks involved in how the drug product is administered to the patient

special reconstitution concerns (high dilutions, selected diluent); delivery devices (e.g., into the brain)

For products requiring additional preparation of the medicinal product (e.g. reconstitution), the compatibility with the used materials (e.g. solvents, diluents, matrix) should be demonstrated and the method of preparation including the equipment used should be summarised (reference may be made to a full description in the clinical protocol or in a separate document). Through appropriate studies it should be demonstrated that the specified reconstitution process is sufficiently robust and consistent to ensure that the product fulfils the specifications and can be administrated without negative impact on quality/safety/clinical properties of the ATMP.

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

31 January 2019
EMA/CAT/852602/2018

125

f. Compatibility (3.2.P.2.6)

You should discuss the compatibility of the DP with the diluent used for reconstitution or the delivery device, as appropriate.

We recommend that compatibility studies include measures of both product quantity and product activity (e.g., for viral vectors, a measure of physical particles and infectivity (or potency) to assess both adsorption and inactivation). These in-use and in-device stability data should support recommended hold times and conditions outlined in the clinical protocol for patient administration. The absence of an understanding of in-use and in-device stability, and the potential impacts on product performance, may not justify risks associated with clinical study treatment(s). Therefore, we recommend that you carefully control and assess DP compatibility and the final steps of product preparation and administration.

Details regarding product stability after preparation for delivery and delivery device compatibility data should be included in Module 3 (sections 3.2.P.8 and 3.2.P.2.6, respectively) of the CTD (Ref. 1). Instructions for drug handing and preparation for administration at the clinical site (e.g., Pharmacy Manual, Instructions for Use, Investigator's Brochure) should be provided in the appropriate section of your IND (Module 5 of the CTD) and hyperlinked to the QOS in Module 2. Detailed information about the delivery device may be included in the "Regional Information (3.2.R)" section of the CTD (Ref. 1).

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

126

Case Example

Phase 1 Clinical Hold

VY-HTT01 for Huntington's Disease

- Voyager is developing VY-HTT01 as a one-time AAV-based gene therapy treatment designed to knock down expression of the HTT gene. Voyager's approach is focused on delivering VY-HTT01 directly into the brain and targeting a reduction of the levels of HTT protein in the striatum and cortex to potentially slow the progression of both motor and cognitive symptoms.
- In September 2020, Voyager submitted an IND application for VY-HTT01 in Huntington's disease, and in October, Voyager was notified that the IND had been placed on clinical hold pending the resolution of certain CMC information requests. Voyager recently received written feedback from the FDA requesting additional information on specific CMC topics, including drug-device compatibility and drug substance and product characterization. Voyager plans to work closely with the agency to resolve the additional information request in a timely manner.
- Following clearance of the IND by the FDA, Voyager expects to begin a Phase 1b clinical trial of VY-HTT01 in Huntington's disease patients.

AAV gene therapy

IND Clinical Hold lifted April 2021

(6 month delay)

127

Challenging Issues Across the Manufacturing Process
(STARTING MATERIAL → DRUG SUBSTANCE → DRUG PRODUCT)
for Advanced Therapy Processes and Products

"The Process is the Product"

For chemical drugs – the quality of the product can be independent of the process (e.g. generics)

For mAbs – the quality of the product may strongly/weakly be defined by the process (e.g., biosimilars)

For CGTPs – the quality of the product is defined by the process

CRITICAL QUALITY ATTRIBUTES (CQAs)

Importance of identifying sooner than later in clinical development

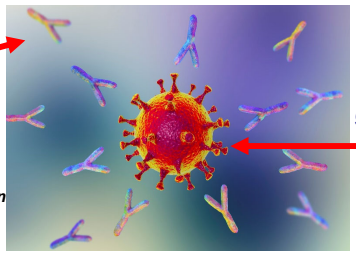
128

Importance of identifying product CQAs, and then linking them to the manufacturing process CPPs – sooner than later in clinical development

mAb (~10 nm)

77 Quality Attributes

- *6 – physiochemical*
- *7 – primary structure*
- *4 – higher order structure*
- *36 – post-translational modification*
- *15 – biological activity*
- *9 – immunochemical activity*



How many more QAs for a genetically engineered virus?

AAV (~25 nm)

And how many even more QAs for a cell?
(~10,000 nm)

Comparison of consistency and complementarity of reporting biosimilar quality attributes between regulatory and scientific communities: An adalimumab case study

Biologicals 69 (2021) 30–37

129

CQA • ***Critical Quality Attributes***

ICH Q8(R2)

Critical Quality Attribute (CQA):
A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Property or Characteristic	
Appearance	*General*
Safety	
Quantity	
Identity	*Process- and/or Product-specific*
Purity	
Product-related Impurities	
Process-related Impurities	
Potency	
Product-Specific Safety	

Note: not all CQAs require a specification, but all CQAs must be controlled (e.g., control of some residual impurities through process validation, choice of raw material grade, etc.)

130

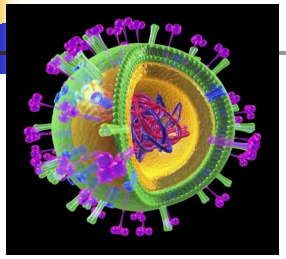
Challenge of Determining CQAs for Advanced Therapy Products

The general chemistry, manufacturing and controls (CMC) considerations for product manufacturing, testing and release of GT products for rare diseases are the same as those described for other GT products (Ref. 1). However, some aspects of the development programs for rare diseases, such as limited population size and fewer lots manufactured, may make it challenging to follow traditional product development strategies. In traditional product development, critical quality attributes (CQAs) of the product are evaluated during each phase of clinical development, and characterization data from many drug product lots are correlated to clinical outcomes. Smaller study populations may result in the need for fewer manufacturing runs, which can make it difficult to establish the critical process parameters (CPP) necessary for ensuring CQAs. In addition, GT products may have CQAs with higher variability than drugs or well-characterized biologics, which can add to CQA uncertainty. However, demonstrating process control to ensure a consistent product with defined CQAs for potency, identity and purity is required to demonstrate compliance with licensure and regulatory requirements[3] (Refs. 2 and

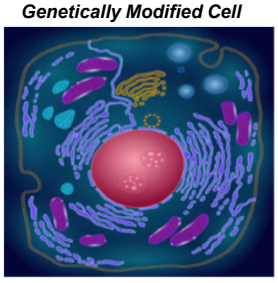
CQA Considerations: General Compendial Requirements

Obligatory (as dosage form appropriate)

Recombinant Virus



Genetically Modified Cell



Appearance
- ***Physical State***
- ***Color/ Degree of Coloration***
- ***Clarity/ Degree of Opalescence***
- ***Visible Particles***

Safety
- ***Sterility***
- ***Endotoxin***
- ***Absence of Mycoplasma***
- ***Absence of Adventitious Virus***
- ***Particulate Matter in Injections/ Particulate Contamination: Sub-Visible Particles***

Quantity
- ***Product amount (# virus particles, # cells*)***
- ***pH***
- ***Osmolality***
- ***Excipient Content (Functional)***
- ***Volume in Container/ Extractable Volume***

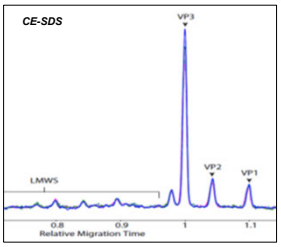
** Genetically Modified Cells: ≥ 70% Viability (FDA)*

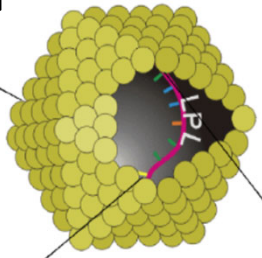
CQA Considerations: Product- and Process-Specific

***Illustration* of Plasmid Transient Produced Gene Therapy AAV**

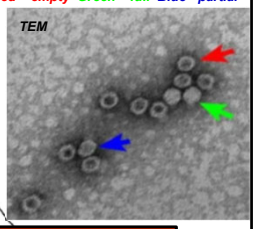
Changes in the capsid proteins (amino acid sequence, glycosylation) can impact transport of virus into a cell

Protein Capsid





Red – empty Green – full Blue - partial



What's Inside your Capsid?

Capsid Content
Transgene Present (Full) or Empty

Product-Related Impurities
Transgene Sequence Variants

Process-Related Impurities
DNA from Host Cell*
DNA from Transient Plasmids

** < 10 ng DNA/dose, DNA size < 200 base pairs*

Transgene + AAV Life Genes

Intact transgene sequence necessary for functionality

AAV capsids comprise ~1% of the protein and nucleic acid generated; most is process-related impurities (HCPs, HCDNA, media components)

133

Quality	Attribute	Example Assays	Next Generation Assays
Identity	Genetic identity	Genome sequencing (NGS) PCR	
	Protein identity	SDS-PAGE Mass spectrometry (MS) Western blot (immunoblot)	CE-SDS Automated Western blot
Strength/ Potency	Physical viral titer	ELISA qPCR Optical density ($A_{260/280}$) NanoSight HPLC (AAV packaging ratio)	MADLS ddPCR CE-SDS or CE-LIF (AAV packaging ratio)
	Functional viral titer	Plaque-forming assay Fluorescence foci assay $TCID_{50}$ (end point dilution assay)	ECIS - impedance
Purity	Process impurities (detergents, resin)	MS Chromatography TEM	LC-MS
	Host cell-related impurities	**Host cell DNA/RNA:** Picogreen, DNA Threshold assay, qPCR **Host cell proteins:** SDS-PAGE, ELISA, HPLC, TEM	LC-MS, LC-MS/MS
	Capsid content (empty: full capsids)	ELISA/qPCR HPLC MS TEM AUC	CE-LIF, cIEF (isoelectric focus) LC-MS
Safety	Sterility	Standard sterility tests (EP 2.6.1, USP71)	Rapid microbial methods (RMM)
	Endotoxin	LAL method (EP 2.6.14, USP85) Rabbit pyrogen assay	Recombinant Factor C (rFC)
	Mycoplasma	Cell-based assays	qPCR
	Replication competent virus (rep/cap sequences)	Southern blotting qPCR	
	Adventitious agents	*In vivo* and *in vitro* cellular assays	
Stability	pH	Potentiometry	
	Osmolality	Osmometry	
	Aggregate formation	Light microscopy DLS SEC-MALLS TEM AUC FFF-MALS	MADLS TRPS

Table 1. Examples of current and next generation analytical assays used to assess viral vector CQAs.

CQA Illustration

Gene Therapy Viral Vector

Insights on Successful Gene Therapy Manufacturing and Commercialization

134

Table 1. KYMRIAH Lot Release Specifications

	Test	Requirements for commercial use	Sample used for testing
A	Appearance	Colorless to slightly yellow	Formulated product (b) (4)
ID	Identity by CAR q-PCR	Positive for PCR signal	(b) (4)
PU	Percentage of viable T cells	(b) (4)	Final product (b) (4)
PU	Determination of transduction efficiency by CAR-q-PCR	(b) (4)	(b) (4)
Q	Cell viability	(b) (4)	Final product (b) (4)
PSI	Determination of residual beads by microscopy	(b) (4)	(b) (4)
PSI	Percentage of viable CD19+ B cells	(b) (4)	Final product (b) (4)
Q	Total cell count[4]	Report cells/mL	Final product (b) (4)
Q	Number of viable cells (calculated)	(b) (4) total viable cells	Final product (b) (4)
Q	Dose (calculated)	• 0.2 to 5.0 × 10^6 CAR positive viable T cells/kg body weight (≤50 kg) • 0.1 to 2.5 ×10^8 CAR positive viable T cells (> 50 kg)	Final product (after thaw)[2] Calculation formula: *(%CAR expression x Viable cell concentration x Volume per dose)/100 (per patients (≤ 50 kg this number is divided per Kg body weight)*
PO	Determination of CAR expression by flow cytometry	(b) (4)	Final product (b) (4)
PO	Release of IFNγ in response to CD19-expressing target cells	• (b) (4) • (b) (4)	Final product (b) (4)
S	Bacterial Endotoxins	(b) (4)	Final product (b) (4)
S	Sterility	Negative	Formulated product (b) (4)
S	Mycoplasma	Negative	(b) (4)
PSS	Determination of VSV-G DNA by quantitative PCR (qPCR)	(b) (4)	(b) (4)

CQA Case Example

CAR T-Cell

Summary Basis for Regulatory Action
CBER/OTAT August 30, 2017

FDA Advisory Committee Briefing Document
Novartis 12-Jul-2017

Testing for residual beads is performed using a sample prior to formulation

No spec is set for Total Cell Count since it is not a CQA, just used in Dose calculation

(ID) Identity
(PU) Purity
(PTI) Product-related Impurities
(PSI) Process-related Impurities
(PO) Potency
(PSS) Product-Specific Safety

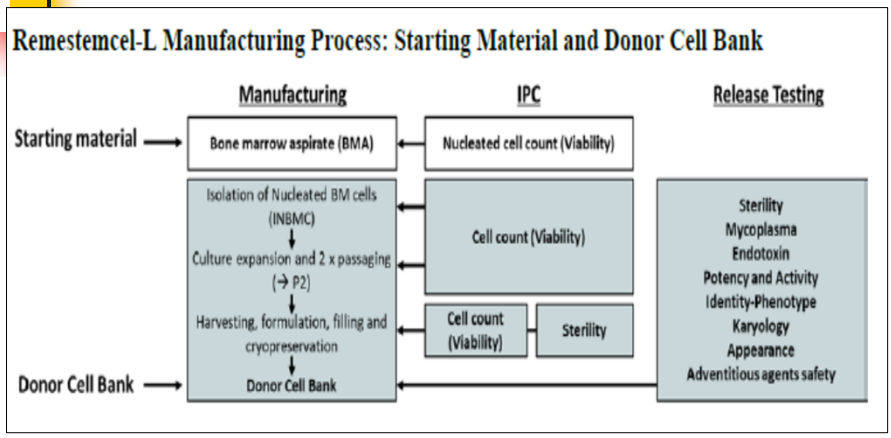
(A) Appearance
(S) Safety
(Q) Quantity

Mycoplasma tested at end of cell culture and final formulation

135

CQA Case Example

Cellular Therapy



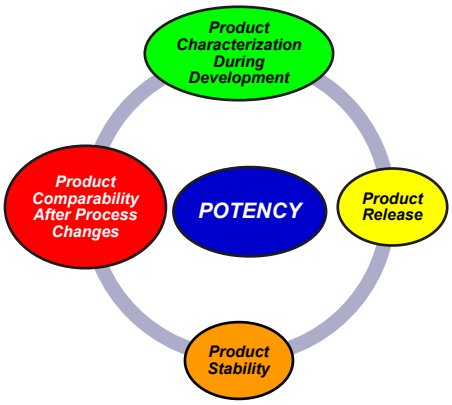
remestemcel-L
MESOBLAST

FDA Advisory Committee
13 August 2020

136

*Critically High Risk CQA: **POTENCY***

The cornerstone of a strong control strategy!



137

Potency Assay: Early Development is Critical!

Preferably, a suitable potency assay should be in place already when material for the first clinical trial is produced and it should be validated prior to phase III clinical trials unless otherwise justified. Lot release and shelf life specifications for potency should be determined and amended during product development, as appropriate. It is strongly recommended that the development of a suitable potency assay be started as soon as possible.

Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer — 21 July 2016 EMA/CHMP/BWP/271475/2006 rev.1

It is strongly recommended that the development of a suitable potency assay be started as soon as possible. Preferably, a suitable potency assay should already be in place when material for the FIH clinical trial is produced and it should be validated prior to confirmatory clinical trials unless otherwise justified. Surrogate potency markers can be considered for release tests, but appropriate justification on their relevance in the context of the intended action of the ATIMP is needed.

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials — 31 January 2019 EMA/CAT/852602/2018

138

Potency Assay: Early Development is Critical!

product. Because the ability to measure potency is fundamentally related to product characterization, you should initiate potency assay development by way of product characterization during preclinical and early clinical investigations to obtain as much product information as possible.

Potency Assay: Can Also Become a Clinical Development Show Stopper!

As clinical study progresses and product knowledge increases, you should develop and implement improved potency measurement(s) that quantitatively assesses relevant biological product attribute(s) (see 21 CFR 312.23(a)(7)).

2. Later phase product development:

The primary objective of later phase investigational studies (i.e., Phase 3, pivotal[17]) is to gather meaningful data about product efficacy, which is determined by adequate and well-controlled clinical trial(s). One aspect of an adequate and well controlled trial is administering product lots with similar potency, in that conformance to established limits for potency is necessary to provide reasonable confidence that product lots will perform as expected at a given dose in patients. Therefore, your potency assay or assay matrix design and acceptance criteria should establish appropriate limits for potency to assure that product lots are well-defined, biologically active, and consistently manufactured. If you do not provide sufficient assurance of potency of product lots to be used in your pivotal trial(s), your trial may be considered "deficient in design to meet its stated objectives" and may be placed on clinical hold (21 CFR 312.42(b)(2)(ii)).

Potency Tests for Cellular and Gene Therapy Products

Food and Drug Administration
Center for Biologics Evaluation and Research
January 2011

139

Case Example

Potency concern delayed BLA filing

IOVANCE BIOTHERAPEUTICS

Iovance Biotherapeutics Provides Regulatory Update for Lifileucel Potency Assays

May 18, 2021

SAN CARLOS, Calif., May 18, 2021 (GLOBE NEWSWIRE) -- Iovance Biotherapeutics, Inc. (NASDAQ: IOVA), a late-stage biotechnology company developing novel T cell-based cancer immunotherapies, today announced receipt of regulatory feedback from the U.S. Food and Drug Administration (FDA) regarding its potency assays for lifileucel. Previously, the company reported the submission of assay data to the FDA and recently the FDA provided comments regarding the data package.

Following FDA feedback, Iovance will continue its ongoing work developing and validating its potency assays and plans to submit additional assay data and to meet with the FDA in the second half of 2021. The company's biologics license application (BLA) submission for lifileucel is now expected to occur during the first half of 2022.

"TIL is a first-in-class, one-time administration cell therapy and the first potential BLA for a cell therapy in solid tumors," stated Maria Fardis, Ph.D., MBA, Iovance President and Chief Executive Officer. "As such, TIL product is complex by nature and alignment with FDA on a potency assay is an important step toward BLA submission. With a regenerative medicines advanced therapy (RMAT) designation for lifileucel, FDA recognizes the unmet need for patients with metastatic melanoma who progress after anti-PD1 therapy."

minimum of 1 year delay in filing BLA

140

Case Example

Potency concern delayed BLA approval
(relevance of chosen potency assay)

U.S. FOOD & DRUG ADMINISTRATION

ODAC Briefing Document

BLA 125706
Remestemcel-L
Applicant: Mesoblast

August 13, 2020

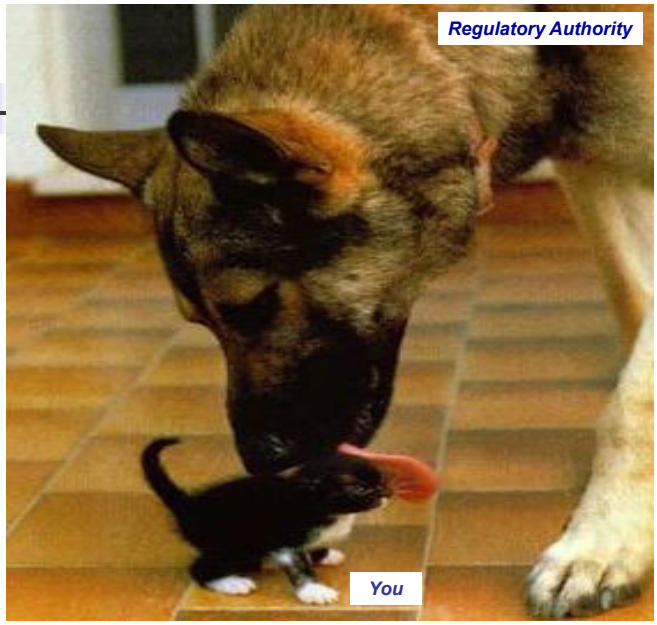
The purpose of the morning session of this Advisory Committee meeting is to discuss the product attributes of remestemcel-L and their relation to product quality and effectiveness. The Applicant has defined critical quality attributes (CQAs) for remestemcel-L that are proposed to be related to the potency and activity of the product (see Section 5.1 *Critical Quality Attributes* in the Applicant's briefing document). FDA's position is that the product attributes the Applicant has identified as related to potency and activity, however, do not have a demonstrated relationship to the clinical performance of specific DP lots, and that the product's proposed immunomodulatory mechanism of action has not been demonstrated *in vivo* in study subjects receiving remestemcel-L. Without a demonstrated relationship with clinical effectiveness and/or *in vivo* potency/activity, controlling these CQAs may not be sufficient to ensure the manufacturing process consistently produces remestemcel-L lots of acceptable quality.

MESOBLAST RECEIVES COMPLETE RESPONSE LETTER FROM THE FDA **October 2, 2020**

The FDA also identified a need for further scientific rationale to demonstrate the relationship of potency measurements to the product's biologic activity. Assays measuring the potency of remestemcel-L will continue to be refined to provide further scientific rationale for its use in severe inflammatory diseases with high mortality risk, such as SR-aGVHD and COVID-19 ARDS.

141

Regulatory authorities are your 'friend'!



QUESTIONS??

142

Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of Advanced Therapy Products

Course Outline

- ✓ ***Overview of the CGTP Landscape***

  Due to the increasing diversity of these advance therapy medicines, the regulatory authorities have control systems in place to regulate these evolving manufacturing processes and products

- ✓ ***Advanced Therapy Product GMP and Quality Risk Consequences***

  Knowledge from established regulatory guidances and experiences (e.g., mAbs, recombinant viral vaccines, etc.) can be adapted, but pay attention to the minefields

- ✓ ***Regulatory Authority Expectations During Clinical Development***

  Regulatory guidance clearly stresses the necessity of a risk-based control approach to GMPs and Quality Principles during clinical development

- ✓ ***Industry Practice in Applying the Risk-Based Principles to ATMPs***

  A risk-based strategy needs to be applied across the manufacturing process from starting materials to production to purification to administered drug product

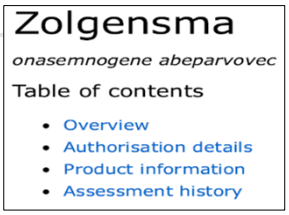
143

Where is all of this CMC information located on the regulatory authorities websites?

ATMPs approved by EMA

www.ema.europa.eu/en/search/search/field_ema_web_topics%3Aname_field/Advanced%20therapies

www.ema.europa.eu/en/medicines/human/EPAR/zolgensma


Zolgensma

onasemnogene abeparvovec

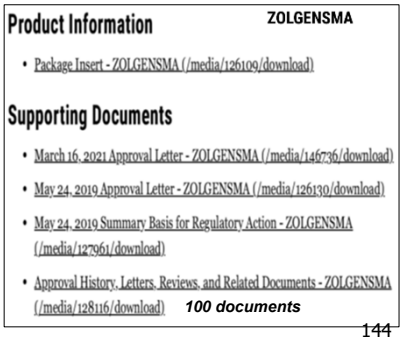
Table of contents

- Overview
- Authorisation details
- Product information
- Assessment history

CGTPs approved by FDA CBER

www.fda.gov/vaccines-blood-biologics/biologics-products-establishments

www.fda.gov/vaccines-blood-biologics/zolgensma


Product Information ZOLGENSMA

- Package Insert - ZOLGENSMA (/media/126109/download)

Supporting Documents

- March 16, 2021 Approval Letter - ZOLGENSMA (/media/146736/download)
- May 24, 2019 Approval Letter - ZOLGENSMA (/media/126130/download)
- May 24, 2019 Summary Basis for Regulatory Action - ZOLGENSMA (/media/127961/download)
- Approval History, Letters, Reviews, and Related Documents - ZOLGENSMA (/media/128116/download) ***100 documents***

144

FDA OTAT LEARN

(video courses on how FDA regulates CGTPs)

www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- ***The Chemistry, Manufacturing and Controls (CMC) Section of a Gene Therapy IND***
- ***Formal Meetings PDUFA Products Between the FDA and Sponsors or Applicants of Industry***
- ***Cellular Therapy Products***
- ***Early-Phase Trials of Cellular and Gene Therapies***
- ***Fast Track (FT) for Products Regulated in OCTGT (now OTAT)***
- ***Breakthrough Therapy Designation***
- ***Biologic License Applications to OCTGT (now OTAT)***
- ***Advanced Topics: Successful Development of Quality Cell and Gene Therapy Products***
- ***Advanced Topics: Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines and Related Products***

(videos don't activate all of the time)

145

CELL & GENE THERAPY: SPEAKER PRESENTATIONS

free, downloadable presentations from CASSS.org

2018: ***www.CASSS.org/page/CGTP1817***
2019: ***www.CASSS.org/page/CGTP1917***
2020: ***www.CASSS.org/page/CGTP2015***

FDA Perspective on Aseptic Process Simulation for Cell Therapy Product Manufacturing

FDA's Approach to the Development of Cell and Gene Therapy Products

Manufacturing Challenges of AAV Gene Therapy Products

Early Stage Manufacturing Considerations for Cell Therapy Products

Manufacturing Logistical and Capacity Considerations For Cell and Gene Therapy Products

Comparability Is Not a Nightmare, Just Think Ahead!

146

CELL & GENE THERAPY: NEWS JOURNAL

free downloadable

www.insights.bio/cell-and-gene-therapy-insights/home

147

CfPIE® The Center for Professional Innovation and Education, Inc.

CMC REGULATORY COMPLIANCE STRATEGY FOR CELL & GENE THERAPY MEDICINES

INSTRUCTOR: JOHN GEIGERT, PH.D.

Focus on advance therapy medicines

(2 days)

CfPIE® The Center for Professional Innovation and Education, Inc.

CMC REGULATORY COMPLIANCE FOR BIOPHARMACEUTICALS, BIOSIMILARS AND OTHER BIOLOGICS

INSTRUCTOR: JOHN GEIGERT, PH.D.

Focus on rproteins, and mAbs

(3 days)

148

PDA Parenteral Drug Association — Connecting People, Science and Regulation

https://www.pda.org/publications/pda-technical-reports

82+ Technical Reports – freely assessable to PDA members (but also can be purchased)

Technical Report No. 81
Cell-Based Therapy Control Strategy

Cell & Gene Therapy Interest Group

https://www.pda.org/scientific-and-regulatory-affairs/pda-interest-groups

149

Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of Advanced Therapy Products

In Conclusion

- → ***ATMPs manufacturing processes are challenging, but risk-manageable***
- → ***Not a formula of "do's and don'ts", but an applied risk-based approach***
- → ***Flexibility and adaption are essential tools for CGTPs***
- → ***Above all else: Patient safety must never be compromised!***

Thank you

150