Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of ATMPs

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Immediate Past Chair PDA Biopharmaceutical Advisory Board

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 and commercialization of biopharmaceuticals (recombinant proteins, monoclonal antibodies, gene therapies and cellular therapies)*
- *Senior CMC Expert and Vice President Quality in the industry (IDEC Pharmaceuticals, Immunex)*
- *Immediate Past Chair PDA Biopharmaceutical Advisory Board*
- *15+ years as an independent CMC regulatory compliance consultant to the biopharmaceutical industry*

2

Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of ATMPs

Course Goal

The Problem for ATMPs/CGTPs

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 playbook!

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

3

Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of ATMPs

Course Outline

1. ***Overview of ATMPs (CGTPs)***
   Discussion of the increasing diversity of these products and the regulatory authority systems in place to control these evolving processes and products
2. ***ATMP GMPs and Quality Risk Consequences***
   Since a gap in guidance exists, where does it make sense to adapt experience from established regulatory guidance (e.g., monoclonal antibodies, 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 Risk-Based Principles***
   Applying Quality by Design (QbD) and Quality Risk Management (QRM); PDA Technical Report 81

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

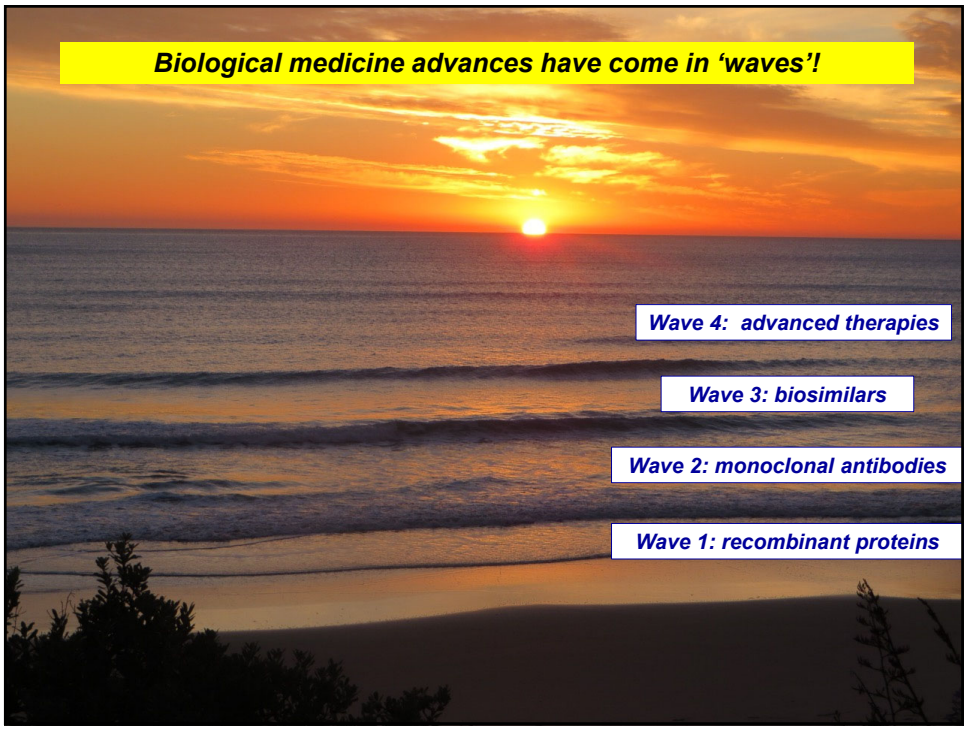
4

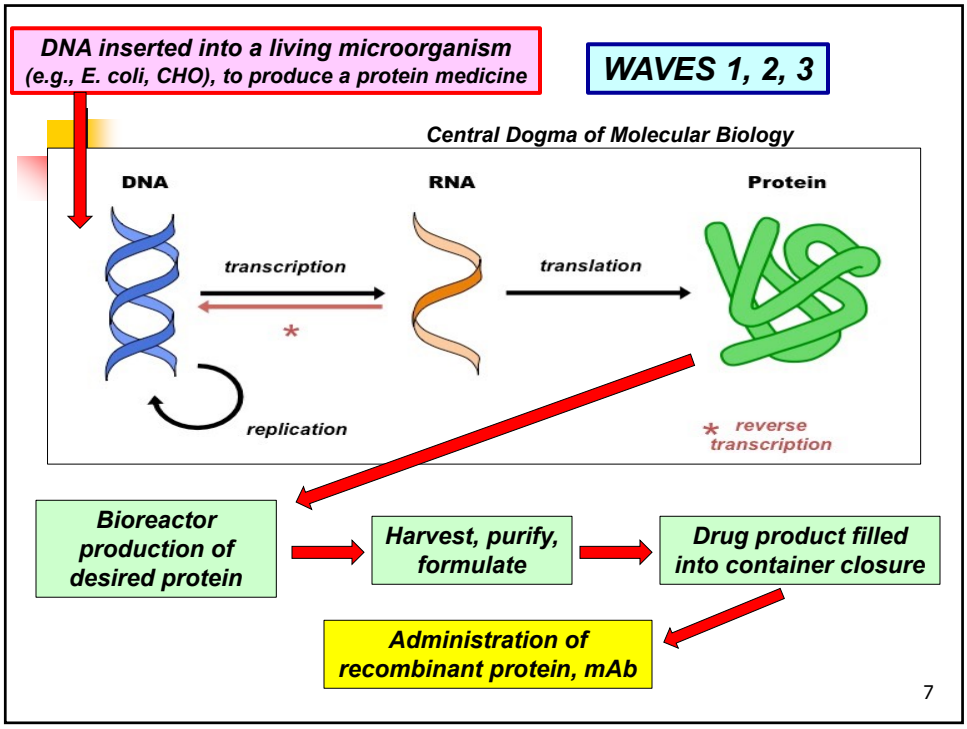
Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of ATMPs

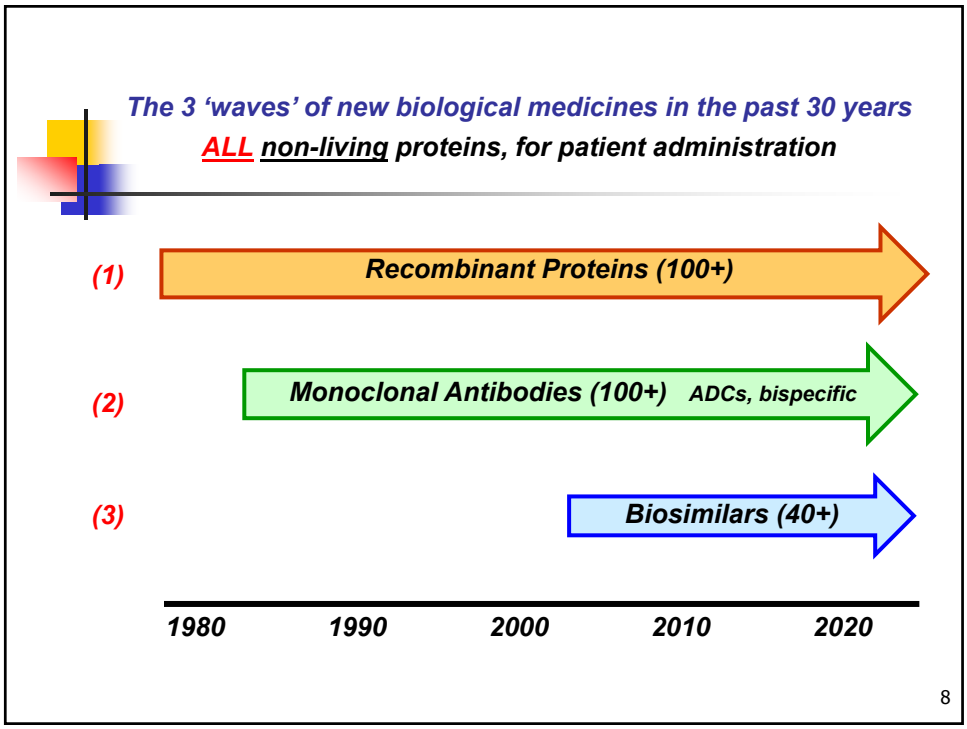
1. Overview of ATMPs (CGTPs)

Discussion of the increasing diversity of these products and the regulatory authority systems in place to control for these evolving processes and products

5



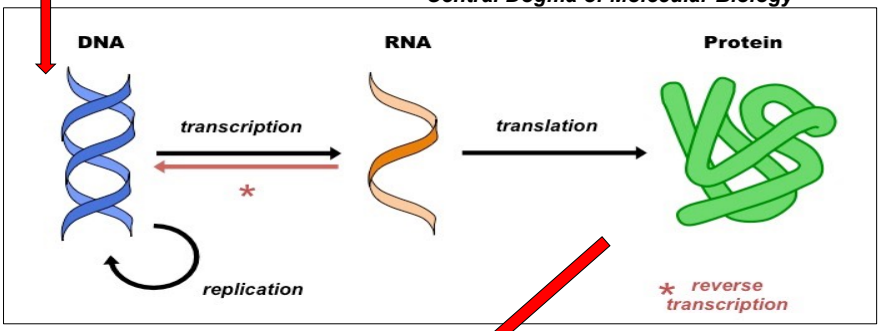

DNA inserted into a living microorganism
(e.g., E. coli, CHO), to produce a protein medicine
WAVES 1, 2, 3
Central Dogma of Molecular Biology
DNA
RNA
Protein
transcription
translation
replication
* reverse transcription
Bioreactor production of desired protein
Harvest, purify, formulate
Drug product filled into container closure
Administration of recombinant protein, mAb
7


The 3 'waves' of new biological medicines in the past 30 years
ALL non-living proteins, for patient administration
(1)
Recombinant Proteins (100+)
(2)
Monoclonal Antibodies (100+) ADCs, bispecific
(3)
Biosimilars (40+)
1980
1990
2000
2010
2020
8

Fixing defective genetic capability or adding new genetic capability to a patient's living human cells

WAVE 4
advanced therapies

Central Dogma of Molecular Biology



The patients, themselves, produce the desired gene product (protein), in situ

9

What a difference the past several years have made for ATMPs coming into the marketplace!

2017/2018	***market approved***
• *Kymriah (CANCER – CAR T-cell gene therapy)*	*FDA/EMA*
• *Yescarta (CANCER – CAR T-cell gene therapy)*	*FDA/EMA*
• *Luxturna (VISION – RPE-65 protein restoration – virus gene therapy)*	*FDA/EMA*
• *Alofisel (FISTULAS – allogeneic somatic adipose stem cell therapy)*	*EMA*
2019/2020	***market approved***
• *Zolgensma (SPINAL MUSCULAR ATROPHY - SMN, survival motor neuron, protein restoration – virus gene therapy)*	*FDA/EMA*
• *Zynteglo (β-THALASSAEMIA – β-globin protein restoration – hematopoietic stem cell gene therapy)*	*[FDA]/EMA*
• *Roctavian (HEMOPHILIA A – clotting factor VIII restoration – virus gene therapy)*	*[FDA]/[EMA]*
• *Liso-Cel (CANCER – CAR T-cell gene therapy)*	*[FDA]*
• *Ide-Cel (CANCER – CAR T-cell gene therapy)*	*[FDA*]*

[under regulatory authority review for market approval]

(Refusal to file due to CMC deficiencies)*

10

The amplitude of wave 4 is predicted 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

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***

11

Large biopharmaceutical companies now jumping in, by acquisition!

GILEAD		*Yescarta*	Kite, A GILEAD Company	*~$12 billion*
NOVARTIS	*Kymriah*	*Zolgensma*	avexis	*~$9 billion*
Bristol-Myers Squibb			JUNO THERAPEUTICS	*~$9 billion*
Roche		*Luxturna*	Spark THERAPEUTICS	*~$5 billion*
Bristol-Myers Squibb	Celgene Committed to improving the lives of patients worldwide®	*Zynteglo*	bluebirdbio recode for life	*~$74 billion*

12

Regulatory Authority Landscape for Advanced Therapies

Europe vs USA

Regulation (EC) No 1394/2007 on ATMPs

ATMP: ADVANCED THERAPY MEDICINAL PRODUCT
(gene therapy, somatic-cell therapy, tissue-engineered medicines)

National Competent Authorities (NCAs) regulate clinical trials

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

Clinical Trials in Europe: Recent Trends in ATMP Development
ALLIANCE FOR REGENERATIVE MEDICINE October 2019

European Medicines Agency (EMA) regulates commercial ATMPs

EUROPEAN MEDICINES AGENCY

COMMITTEE ON ADVANCED THERAPIES (CAT)

(assessment of ATMPs: classification, scientific advice, opinion on market approval)

13

Regulatory Authority Landscape for Advanced Therapies

Europe vs 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"

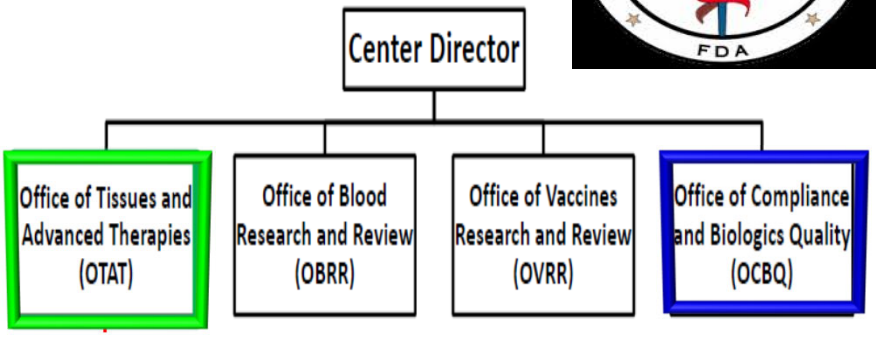
Food and Drug Administration (FDA) regulates both clinical and commercial 'analogous products'

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

14

U.S. FDA

CDER CDRH **CBER**



CMC review *Facility review*

CBER regulates both clinical and commercial CGTPs

15

ATMPs/CGTPs 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

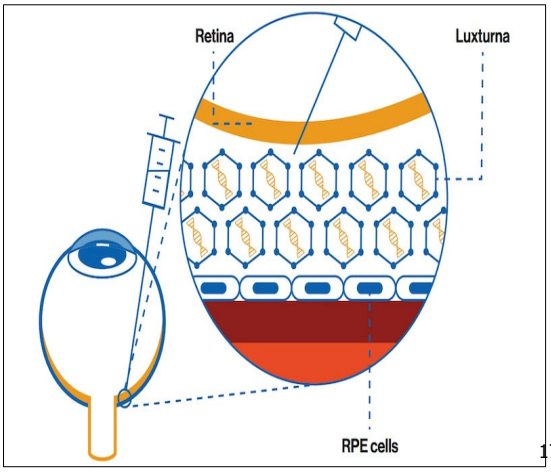
Gene therapies work by inserting 'recombinant' genes into the human body to:

- ***Replace a disease-causing gene with a healthy copy of the gene***
- ***Inactivate a disease-causing gene that is not functioning properly***
- ***Introduce a new or modified gene into the body to help treat a disease***

16

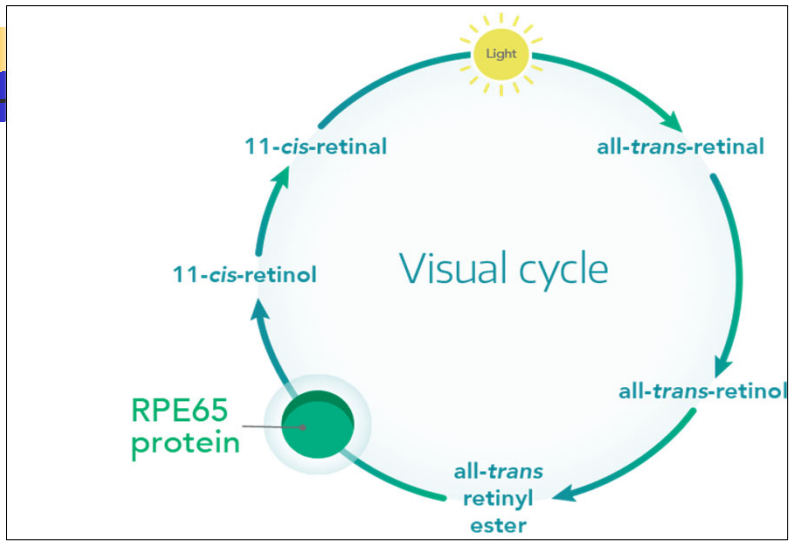
Gene Therapy Medicine: Genetically Engineered Living Virus (gene replacement)

Spark Therapeutics LUXTERNA
adeno-associated virus vector
(with RPE65 gene)
to treat vision loss



17

RPE65 gene produces a protein necessary in the cycle for vision



Direct injection of genetically engineered live virus into the eye to <u>replace defective RPE65-producting gene</u>

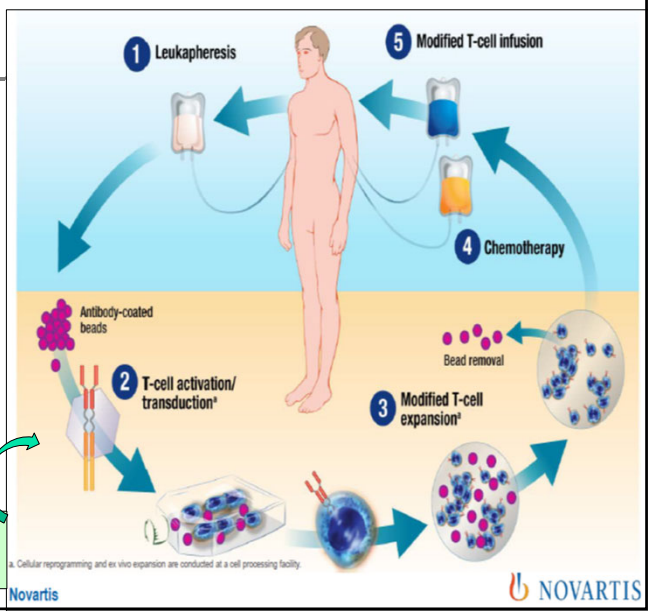
18

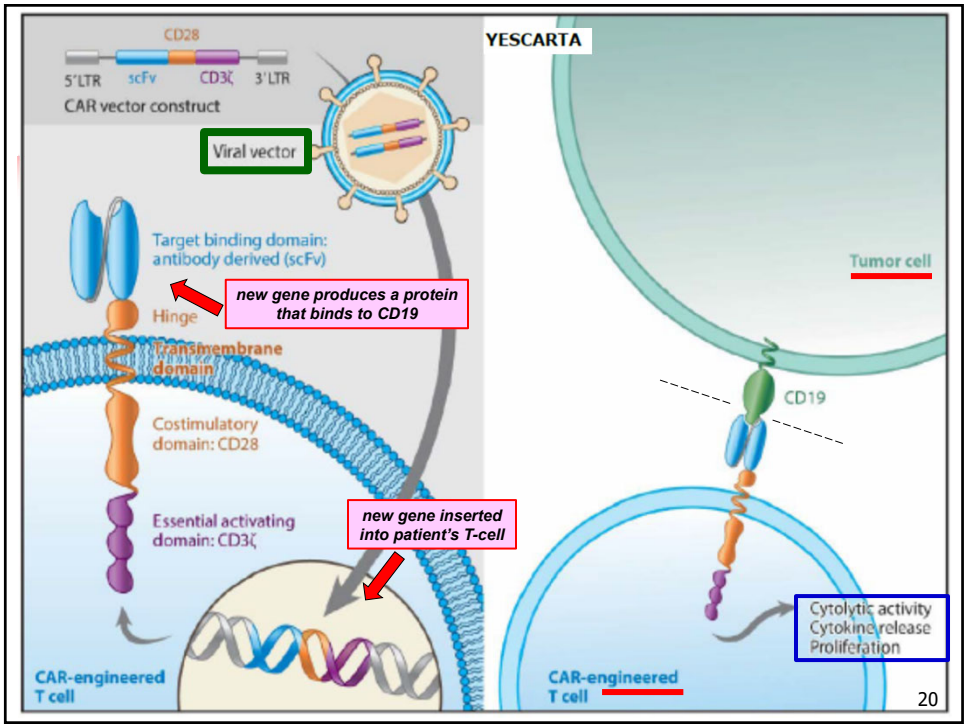
Gene Therapy Medicine: Genetically Engineered Living Cells (gene addition)

Novartis KYMRIAH
Kite YESCARTA

autologous genetically modified T-cells (CAR – chimeric antigen receptor) to bind/kill CD19-containing leukemia cells

Genetically engineered virus to add a gene to the human T-cells





Press Releases

December 07, 2019

Kite Announces Long-term Data From ZUMA-1 Showing Approximately Half of Refractory Large B-cell Lymphoma Patients Were Alive Three Years After Yescarta Treatment

-- 47 Percent of Refractory Large B-cell Lymphoma Patients in ZUMA-1 Pivotal Phase 2 Cohorts Were Alive Three Years after a Single Infusion of Yescarta --

vs Chemotherapy: ***only 20 percent of patients were alive at 2 years***

Blood. 2017 Oct 19; 130(16): 1800–1808.

21

ATMPs/CGTPs 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*
- *shaping*
- *centrifugation*
- *sterilization*
- *irradiation*
- *cell separation*
- *concentration*
- *freezing*
- *cryopreservation*

'Substantial Manipulation' is …

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

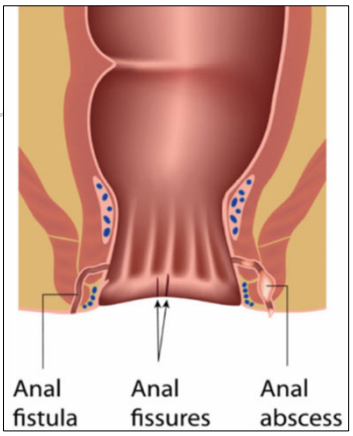
FDA: HCT/P 351 product (CGTP)

FDA: HCT/P 361 product

22

cellular 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.

23

ATMPs/CGTPs are also…

Tissue-Engineered Products

a) tissues that have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved

OR

b) tissues that are not intended to be used for the same essential function or functions in the recipient as in the donor

'tissues that are exclusively non-viable are excluded'

Combined ATMPs

ATMPs with a medical device as an integral part of the medicine

While not covered in this course,
the practical GMP & Quality principles that are discussed are applicable

24

CONFUSED YET!

ATMP

CAT

CGTP

OTAT

substantial manipulation

more than minimal manipulation

not same essential function

not for homologous use

QUESTIONS??

25

Practical Application of Risk-Based GMP & Quality Principles to Clinical Development of ATMPs

2. ATMP GMPs and Quality Risk Consequences

Since a gap in guidance exists, where does it make sense to adapt experience from established regulatory guidance (e.g., monoclonal antibodies, recombinant viral vaccines, etc.), and what minefields might occur if improperly adapted

26

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

Patients cannot check the quality of their medicines

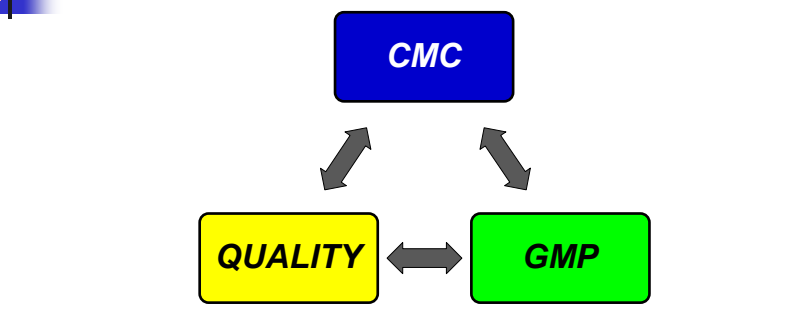
Patients therefore are dependent upon an effective GMP & Quality System!
(facility, process, staff, product – "all doing what is right")

Unsafe or poor quality medicines can harm patients

27

3-Part Control Strategy designed to protect the patient!

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

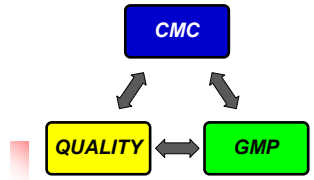


System that ensures regulatory criteria are met by practices carried out by Manufacturing & Quality

Practices carried out by Manufacturing & Quality to meet regulatory criteria

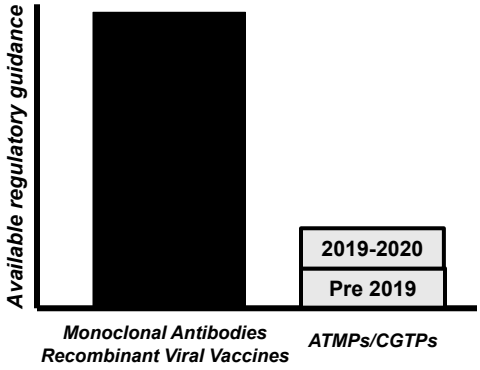
Applicable to all pharmaceuticals, but what about advanced therapy products?

28



Reality today for advanced therapy products

***limited* regulatory guidance and experience compared to other biologics**



***So*, what to do when only limited guidance and experience is available?**

One approach: Adapt from existing biologic guidance and experience

29

Experience adaptable from working with mAbs & viral vaccines

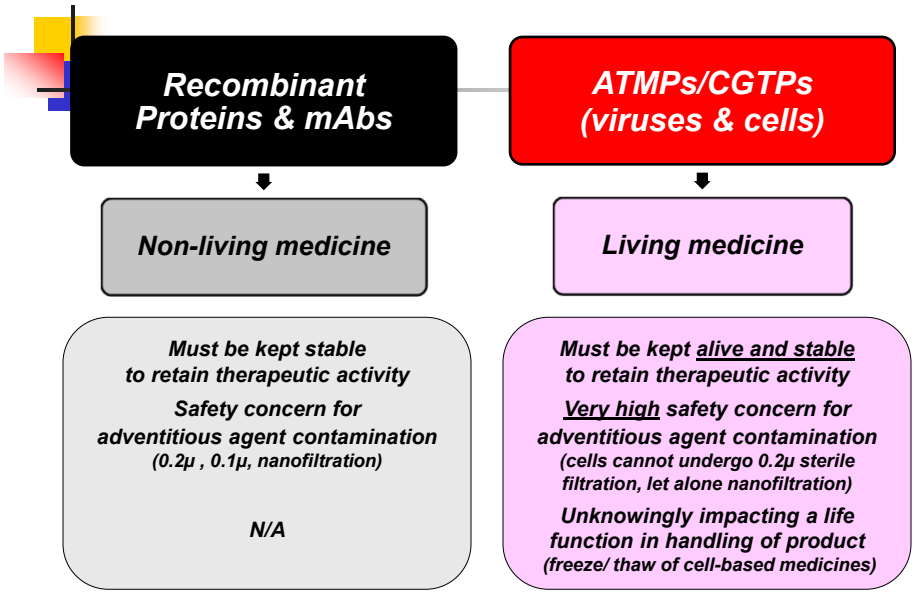
much knowledge about risk-based GMPs and Quality can be brought into the control of advanced therapy manufacturing!

- ***Genetic engineering of transgenes and viral vectors, clone selection***
- ***Cell bank & virus seed manufacture, release, stability, and maintenance***
- ***Handling and expanding cell cultures (adherent and suspension)***
- ***Aseptic processing and handling of open manufacturing process steps***
- ***ICH Quality by Design (QbD) and Quality Risk Management (QRM) principles***
- ***Quality Unit documentation for traceability (SOPs, PBRs, QC test records)***
- ***Quality Unit control strategy (e.g., CofA, batch release, deviation handling, vendor qualification, CAPA, etc.)***

BUT, must factor in significant differences of ATMPs/CGTPs!

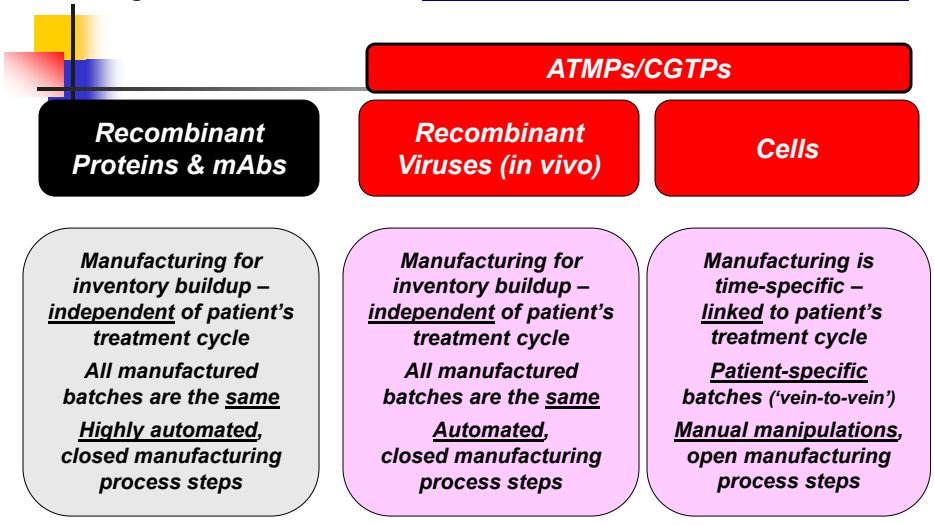
30

Significant Differences – Due to Nature of the Product



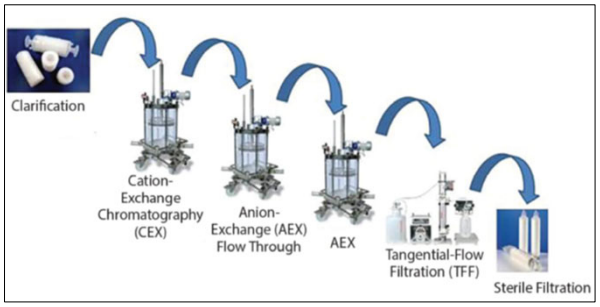
31

Significant Differences – Due to Type of Manufacturing Process



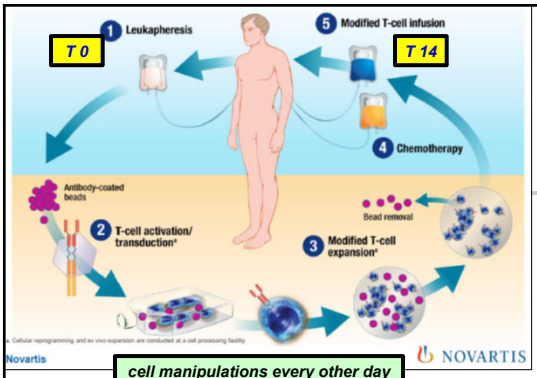
32

mAb manufacturing



virus manufacturing

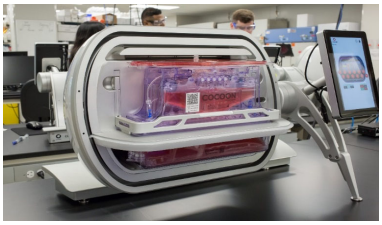
33



cell manipulations every other day

cell-based manufacturing

different manufacturing 'feel'!



the future??

34

Significant Differences – Due to Availability of Testing Tools and Timing to Complete QC Batch Release Tests

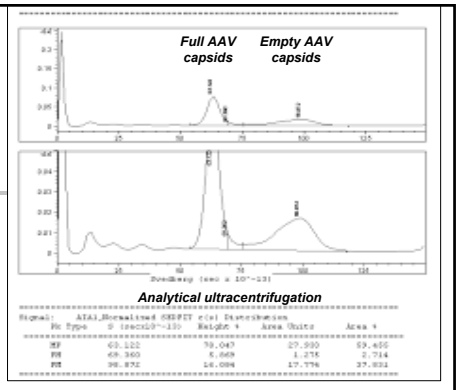
ATMPs/CGTPs

Recombinant Proteins & mAbs	Recombinant Viruses (in vivo)	Cells
Proteins are large and complex, with extensive physicochemical & biological tests available QC samples available for each batch Testing completed prior to batch release	Viruses are larger and more complex, with limited physicochemical & biological tests available QC samples available for each batch Testing completed prior to batch release	Cells are even larger and even more complex, with very limited physicochemical & biological tests available Limited QC samples from each batch 'Just-in-time' or 'after-patient-administration' batch release

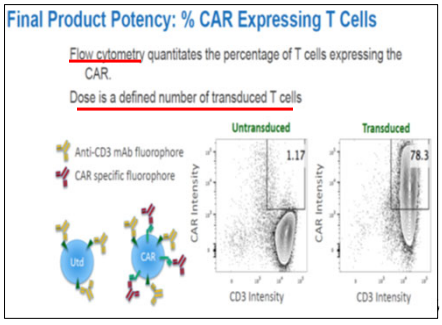
35

ATMPs/CGTPs place intense pressure on the Quality Unit

- *Limitations of test sample availability*
  (small patient-specific batch sizes)
- *Challenging and time-consuming QC tests*
  (flow cytometry, qPCR, AUC)
- *QA batch release days (not months)*
  (deviations, batch record closeout, CofA)



Analytical ultracentrifugation



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

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

'waterproof' – 3' deep, 30 min.

QUESTIONS??

37

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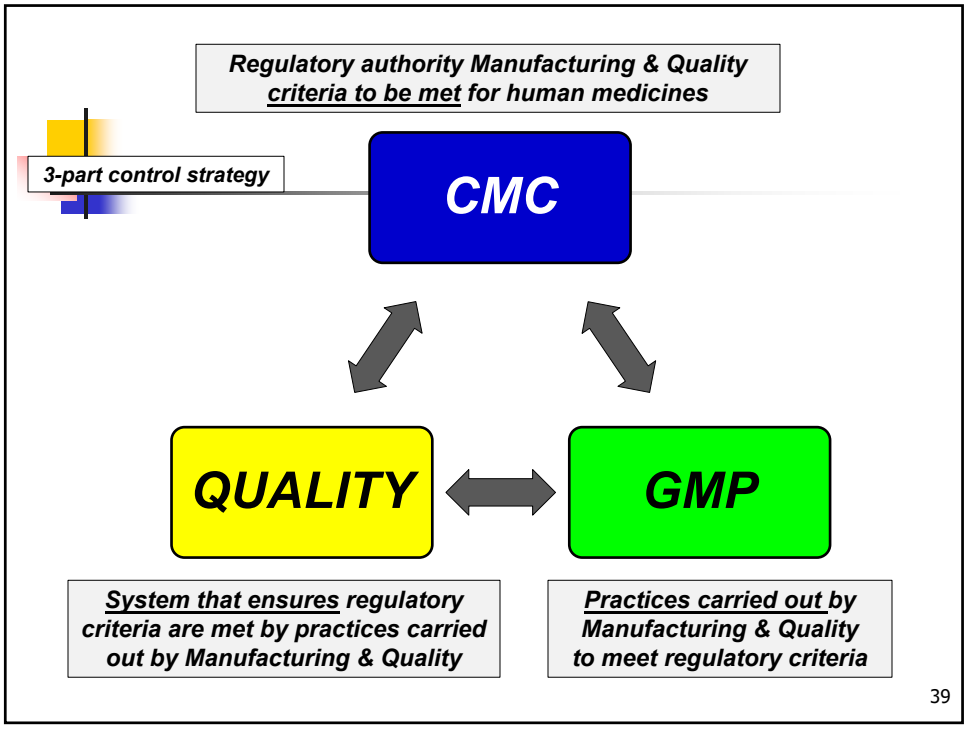
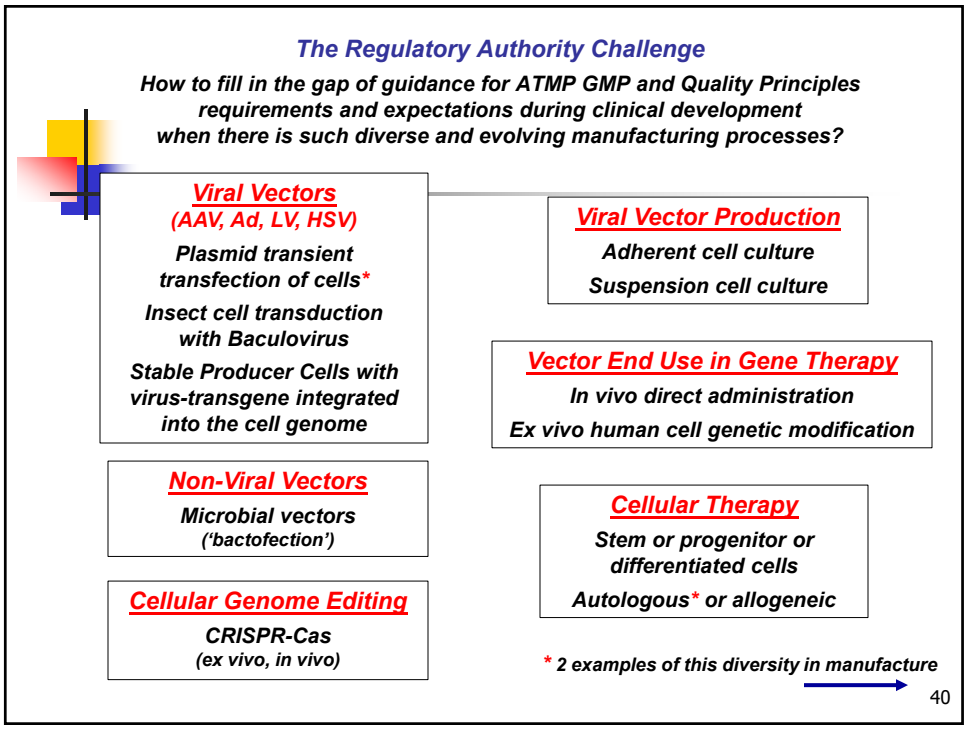
3. Regulatory Authority Expectations During Clinical Development

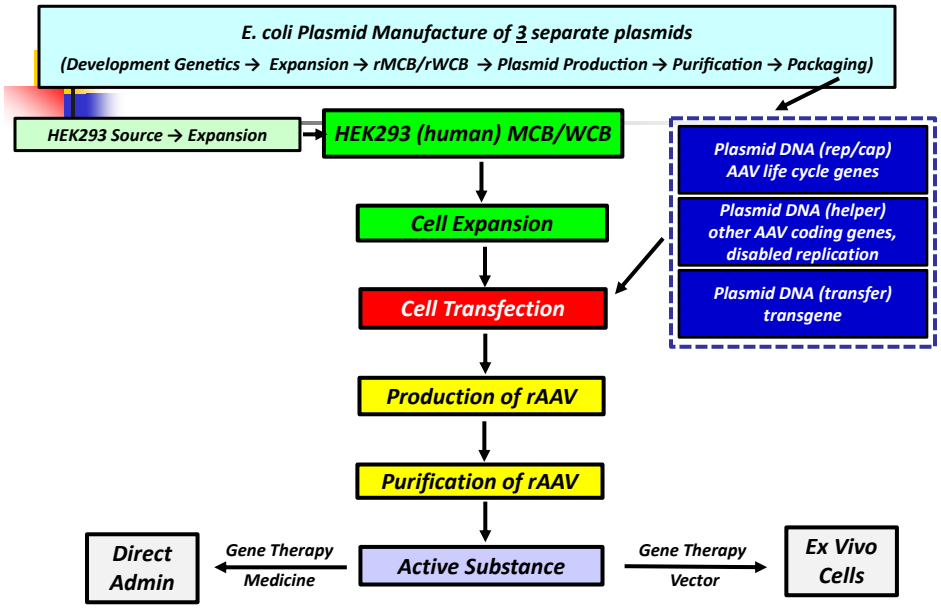
Understanding the regulatory guidance for ATMPs that currently exists, and why those guidances stress the necessity of a risk-based control approach to GMPs and Quality principles during clinical development

38


Regulatory authority Manufacturing & Quality criteria to be met for human medicines
3-part control strategy
CMC
QUALITY
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
39


The Regulatory Authority Challenge
How to fill in the gap of guidance for ATMP GMP and Quality Principles requirements and expectations during clinical development when there is such diverse and evolving manufacturing processes?
Viral Vectors
(AAV, Ad, LV, HSV)
Plasmid transient transfection of cells*
Insect cell transduction with Baculovirus
Stable Producer Cells with virus-transgene integrated into the cell genome
Non-Viral Vectors
Microbial vectors
('bactofection')
Cellular Genome Editing
CRISPR-Cas
(ex vivo, in vivo)
Viral Vector Production
Adherent cell culture
Suspension cell culture
Vector End Use in Gene Therapy
In vivo direct administration
Ex vivo human cell genetic modification
Cellular Therapy
Stem or progenitor or differentiated cells
Autologous* or allogeneic
* 2 examples of this diversity in manufacture
40

rAdeno-Associated Virus (AAV) Manufacturing Using Plasmid DNA Transfection



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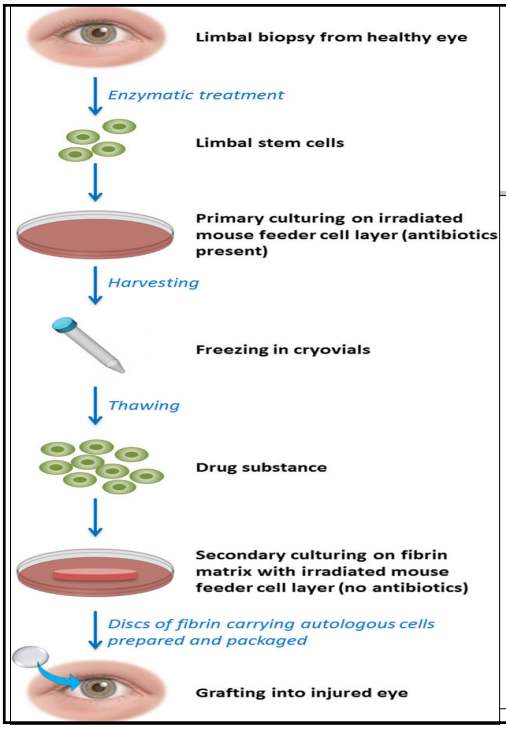
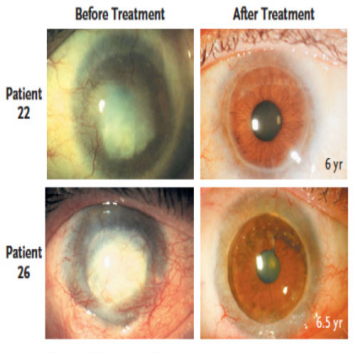


Cellular therapy (autologous)

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



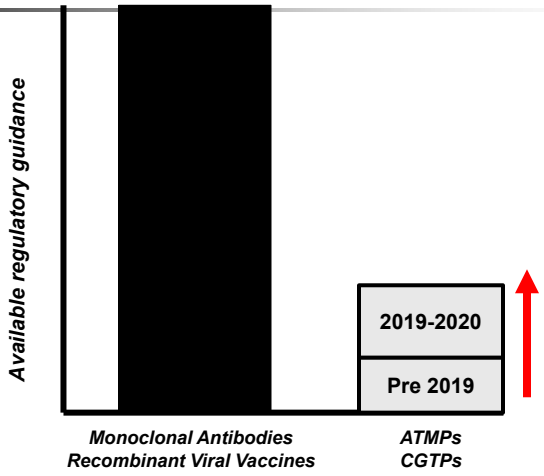
Patient 22, 6 years after transplant
Patient 26, 6.5 years after transplant

EMA approved 2015 FDA (in clinical)

42

Increasing EMA/FDA guidance for GMPs & Quality Principles

gaining year after year



43

EMA/FDA GMPs and Quality Principles for ATMPs/CGTPs

PRE-2019 CMC Regulatory Guidances

EMA

- *Guideline on the Quality, Non-Clinical and Clinical Aspects of Gene Therapy Medicinal Products (2018)*
- *Guideline on the Quality, Non-Clinical and Clinical Aspects of Medicinal Products Containing Genetically Modified Cells (draft, 2018)*
- *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products (2017)*
- *Guideline on Human Cell-Based Medicinal Products (2008)*
- *Guideline on Development and Manufacture of Lentiviral Vectors (2005)*

❖ ***EC Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products (2017)*** *[includes "investigational ATMPs"]*

FDA

- *Guidance for Industry: Recommendations for Microbial Vectors Used for Gene Therapy (2016)*
- *Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (2011)*
- *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)***

❖ *must reads for GMPs and Quality Principles during clinical development*

44

EMA/FDA GMPs and Quality Principles for ATMPs/CGTPs

2019-2020 CMC Regulatory Guidances

EMA

- ***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 (ATM) (2019)*
  - *Q&A – The Use of Out-Of-Specification Batches of Authorised Cell/Tissue-based Advanced Therapy Medicinal Products (2019)*

- *EC Good Practice on the Assessment of GMO-related Aspects in the Context of Clinical Trials with Human Cells Genetically Modified by Means of Retro/Lentiviral Vectors (draft, 2019)*

FDA

- ***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)*
  - *Guidance for Industry: Evaluation of Devices Used with Regenerative Medicine Advanced Therapies (2019)*

PIC/S

- ***Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use (draft, 2019)***
  [includes "investigational ATMPs"]
  (non-binding, informal co-operative arrangement between 53 Regulatory Authorities in the field of GMP)

- ***must reads for GMPs and Quality Principles during clinical development***

45

Risk-Based Approach (RBA) to GMPs & Quality Principles

During Clinical Development of ATMPs/CGTPs

- ***Three (3) key elements in applying a risk-based approach***
  1) ***Absolutely necessary for ATMPs – no one-size-fits-all***
  2) ***-***
  3) ***-***

- ***Eight (8) core GMP & Quality System principles***

46

The diverse and evolving manufacturing processes and products cannot scientifically fit GMPs and Quality Principles into a one-size-fits-all approach!

The quality risks associated with an ATMP are highly dependent on the biological characteristics and origin of the cells/tissues, the biological characteristics of the vectors (*e.g.* replication competence or reverse transcription) and transgenes, the level and characteristics of the expressed protein (for gene therapy products), the properties of other non-cellular components (raw materials, matrixes), and the manufacturing process.

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products
22.11.2017

Due to the wide variety and unique manufacturing aspects of investigational gene and cellular therapy products, manufacturers should consider the appropriateness of additional or specialized controls. Although you should manufacture phase 1 investigational cell and gene therapy products following the recommendations in this guidance, we recognize that it may not be possible to follow each recommendation. For example, with some cellular products, it may be impossible to retain samples of the final cellular product due to the limited amounts of material available. Therefore, we recommend that you include your justification for adopting additional controls or alternative approaches to the recommendations in this guidance in the records on the phase 1 investigational drug.

FDA 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

47

The risk-based approach – good regulatory sense and good business sense!

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.

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.

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products
22.11.2017

48

Risk-Based Approach (RBA) to GMPs & Quality Principles

During Clinical Development of ATMPs/CGTPs

- ***Three (3) key elements in applying a risk-based approach***
  1) ***Absolutely necessary for ATMPs – no one-size-fits-all***
  2) ***Focus must be on patient safety***
  3) ***-***

- ***Eight (8) core GMP & Quality System principles***

49

The risk-based approach is about protecting patients!

- ***A risk-based approach focuses Manufacturing and Quality on 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***

50

EMA: its about patient safety!

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

"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

51

FDA: its about patient safety!

Some vectors, including AAV, can package a large amount of non-vector DNA (e.g., plasmid DNA, helper virus sequences, cellular DNA), and it may not be possible to remove or reduce this DNA from the product to a level to assure safety based on current guidance (Ref. 12). Therefore, we strongly recommend that the cell lines and helper sequences used to make viral vectors that package non-vector DNA, such as AAV, be carefully chosen to reduce the risks of the product. Sponsors should provide necessary quality data, risk assessments, and/or details of their process and product control strategy to address and mitigate potential risks posed by the manufacturing systems used.

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

We recommend the following steps to establish the appropriate manufacturing environment for phase 1 investigational drugs:

- A comprehensive and systematic evaluation of the manufacturing setting (i.e., product environment, equipment, process, personnel, materials) to identify potential hazards
- Appropriate actions prior to and during manufacturing to eliminate or mitigate potential hazards to safeguard the quality of the phase 1 investigational 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

52

Risk-Based Approach (RBA) to GMPs & Quality Principles

During Clinical Development of ATMPs/CGTPs

- ***Three (3) key elements in applying a risk-based approach***
  1) ***Absolutely necessary for ATMPs – no one-size-fits-all***
  2) ***Focus must be on patient safety***
  3) ***Not static, but must evolve/mature***

- ***Eight (8) core GMP & Quality System principles***

53

The risk-base approach must evolve/mature!

- ***Early on in clinical development, there is frequently limited or incomplete understanding of the manufacturing process and the advanced therapy product***
- ***At the early clinical development stage, the risk-based approach provides the needed flexibility to control the manufacturing process and its product based on available knowledge***
- ***However, as clinical development advances, so should the refinement of the risk-based assessments and risk mitigation procedures***

54

EMA: RBA must evolve/mature!

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.

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.

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products
22.11.2017

55

Risk-based approach

In determining the content of the IMPD, a risk-based approach can be applied[2]. The content of the dossier can be adapted having regard to the identified risks. In particular, the applicant can perform at the beginning of product development an initial risk analysis based on existing knowledge on the type of product and its intended use. Aspects to be taken into consideration include the origin of the cells, the type of vector and/or the method used for the genetic modification, the manufacturing process, the non-cellular components and the specific therapeutic use as applicable.

The risk analysis should be updated by the applicant throughout the product life cycle as new data become available. Key points relevant to the understanding of the product development approach chosen, should be summarized in the IMPD.

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

31 January 2019
EMA/CAT/852602/2018

56

FDA: RBA must evolve/mature!

You are not required to complete all CTD sections in your original IND submission. The amount of CMC information to be submitted in your IND depends on the phase of investigation and the scope of the clinical investigation proposed (21 CFR 312.23(a)(7)). The emphasis for CMC review in all phases of development is product safety and manufacturing controls. We expect that sponsors may need to make modifications and additions to previously submitted information as clinical development proceeds and additional product knowledge and manufacturing experience is collected (21 CFR 312.31).

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

This guidance describes an approach manufacturers may use to implement manufacturing controls that are appropriate for the phase 1 clinical trial stage of development. The approach described in this guidance reflects the fact that some manufacturing controls and the extent of manufacturing controls needed to achieve appropriate product quality differ not only between investigational and commercial manufacture, but also among the various phases of clinical trials. Consistent with FDA's CGMP for the 21 Century initiative,[4] where applicable, manufacturers are also expected to implement manufacturing controls that reflect product and manufacturing considerations, evolving process and product knowledge, and manufacturing experience.[5]

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

57

Risk-Based Approach (RBA) to GMPs & Quality Principles

During Clinical Development of ATMPs/CGTPs

- ***Three (3) key elements in applying a risk-based approach***
- ***Eight (8) core GMP & Quality System principles***

QUALITY ⟷ ***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

58

Risk-Based Approach (RBA) to GMPs & Quality Principles

During Clinical Development of ATMPs/CGTPs

- ***Eight (8) core GMP & Quality System principles***
  1) ***Personnel adequately trained; clear allocation of responsibilities***
  2) ***-***
  3) ***-***
  4) ***-***
  5) ***-***
  6) ***-***
  7) ***-***
  8) ***-***

The critical role of trained personnel!

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.

3 'Rights' for manufacturing personnel

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

Recognized limited experience in the small, new companies involved!

Of the medicines admitted into PRIME, 42% are ATMPs, which have the potential to reshape the treatment of a wide range of conditions. A large proportion of these medicines are being developed by small and medium-sized enterprises (SMEs). These often lack experience in the regulatory approval process and can receive valuable guidance through the scheme.

Challenge of finding experienced personnel!

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]

September 2019

PwC Health Research Institute
Beyond the hype:

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

61

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.

62

Aseptic processing simulation training critical to protect patients!

Investigational ATMPs

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

63

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
-

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

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

Risk-Based Approach: Cannot simulate everything, so focus simulations on the most critical process steps – the open processing steps involving human intervention!

64

Lesson learned the hard way: Don't skimp on training!

U.S. NIH clinical manufacturing of cellular therapies

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).

65

1. You failed to establish a quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products. 21 CFR 211.22(a).

2. You failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes. 21 CFR 211.113(b).

3. You failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems for aseptic processing necessary to prevent contamination or mix-ups. 21 CFR 211.42(c)(10).

4. You failed to have facilities used in the manufacture, process, packaging and holding of drug products of appropriate construction to facilitate cleaning, maintenance, and proper operations. 21 CFR 211.42(a).

5. You failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed. 21 CFR 211.192.

6. You failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas. 21 CFR 211.42(c)(10)(iv).

An operator produced drug products intended to be sterile with an exposed wrist and exposed facial hair.

66

FDA Inspection Result: Cell therapy facility shut down for 5 months

Tuesday, April 19, 2016

Statement on Review of NIH Sterile Production Facilities

In light of serious problems identified in the NIH Clinical Center Pharmaceutical Development Section last year, NIH launched a multifaceted effort to ensure that processes for patient safety and quality of care at the hospital are of the highest standards. Accordingly, NIH hired two companies specializing in quality assurance for manufacturing and compounding – Working Buildings and Clinical IQ – to evaluate all of its facilities producing sterile or infused products for administration to research participants.

This evaluation is underway and preliminary findings have identified facilities not in compliance with quality and safety standards, and not suitable for the production of sterile or infused products. As a result, production has been suspended in two facilities: a National Cancer Institute laboratory engaged in cell therapy production and a National Institute of Mental Health facility producing positron emission tomography (PET) materials.

67

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Division of Environmental Protection/ORF

March 27, 2018

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.

CAPA completed

68

Risk-Based Approach (RBA) to GMPs & Quality Principles

During Clinical Development of ATMPs/CGTPs

- ***Eight (8) core GMP & Quality System principles***
  1) *Personnel adequately trained; clear allocation of responsibilities*
  2) ***Premises/equipment suitable for intended use, and maintained***
  3) -
  4) -
  5) -
  6) -
  7) -
  8) -

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***
- ***Appropriate air 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***

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 non-viable particle contamination is verified. Any other aspect of the premises that is critical having regard to the specific risks of the intended manufacturing process should be qualified (*e.g.* containment measures when viral replicating vectors are used). Critical equipment should be qualified also.

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products
22.11.2017

In applying appropriate CGMP, we recommend that manufacturers consider carefully the hazards and associated risks from the manufacturing environment that might adversely affect the quality of a phase 1 investigational drug, especially when the phase 1 investigational drug is manufactured in laboratory facilities that are not expressly or solely designed for their manufacture. For example, of particular importance is the susceptibility of a phase 1 investigational drug to contamination or cross contamination with other substances (e.g. chemicals, biologicals, adventitious agents) that may be present from previous or concurrent research or manufacturing activities.

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

71

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***

72

2.51. • 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.

4.27. It is recommended that the design of the premises permits the production to take place in areas connected in a logical order corresponding to the sequence of the operations and required level of cleanliness. Likewise, the arrangement of the working environment and of the equipment and materials should be adequate to minimise the risk of confusion between different products or their components, to avoid cross-contamination, and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

10.35. 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.

73

Bottom Line: Premises/equipment risk mitigation procedures commensurate with the risk of mix-ups, contamination and cross-contamination

Manufacture of DNA plasmid starting material	***versus***	***Manufacture of infectious virus seed starting material***
Cell culture production of AAV	***versus***	***Cell culture production of LV***
Purification of virus drug substance	***versus***	***Manufacture of virus drug product***

Manufacturing requirements and containment levels

Biosafety level BSL-2 with cells involving lentivirus (LV), BSL-1 after cell transduction under specified conditions

Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified by means of retro/lentiviral vectors[1]

October 2019

74

Risk-Based Approach (RBA) to GMPs & Quality Principles

During Clinical Development of ATMPs/CGTPs

- ***Eight (8) core GMP & Quality System principles***
  1) *Personnel adequately trained; clear allocation of responsibilities*
  2) *Premises/equipment suitable for intended use, and maintained*
  3) ***Adequate documentation system ensuring appropriate specifications are laid down for materials, intermediates, bulk products and the finished product; that the production process is clearly understood, and that appropriate records are kept***
  4) -
  5) -
  6) -
  7) -
  8) -

Adequate documentation system

Documented level of GMP control and Quality!

6.16. The specifications for the materials and the finished product and the manufacturing instructions are intended to ensure compliance with the terms of the marketing authorisation/clinical trial authorisation, product consistency (appropriate to the relevant stage of development), and the required level of quality. Therefore, it is important that specifications and instructions are documented appropriately and that they are clear and detailed enough.

Raw Material ***Critical Raw Material***

Starting Material ***Vector*** ***Cell Bank*** ***Virus Seed*** ***Patient's Cell***

Active Substance (Drug Substance)

Drug Product

Raw Materials are …

Raw materials are the reagents that are used during the manufacturing process but are not part of the final product. Examples include foetal bovine serum, trypsin, digestion enzymes (e.g., collagenase, DNAse), growth factors, cytokines, monoclonal antibodies, antibiotics, resins, cell-separation devices, and media and media components. Reference to quality standards (e.g. compendial monographs or manufacturer's in-house specifications) should be made. Information on the quality and control of non-compendial materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g. media components, monoclonal antibodies, enzymes) are suitable for their intended use should be provided. 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).

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

Risk-Based approach for 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).

Consider: What goes 'into the pot', can end up in the patient (impurity in the product)!

78

Compendial guidance on risk-assessment for raw materials

General Chapter 5.2.12.

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

- ***Sera and serum replacements***
- ***Proteins produced by recombinant DNA technology***
- ***Proteins extracted from biological material***
- ***[Vectors (usually considered starting materials)]***

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

- ***AMs are components, reagents, and materials used during the manufacture of CGTPs but are not intended to be part of the final product***
- ***AMs include cell isolation reagents, culture and cryopreservation media, and disposables such as plasticware and bioprocessing bags***
- ***The term "ancillary material" is not globally recognized by regulators***
- ***Tier 1 (low risk, highly qualified) → → → Tier 4 (high risk, poorly qualified)***

79

"The quality of raw materials is a key factor in the production of ATMPs"

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

31 January 2019
EMA/CAT/852602/2018

Critical Raw Materials

Raw materials that could introduce adventitious agents (e.g., viruses, prions)

Raw materials that leave detectable residuals

Raw materials from single-source vendors

Quality Risk Management (QRM) ***Risk Reduction Activities***
Vendor audits
Receipt of vendor manufacturing controls and certificate of analysis for each batch
Batch functionality/suitability testing prior to use In the process
Confirm vendor's certificate of analysis batch release test results
Develop more stringent or additional internal specifications for QC release

No single measure can guarantee the quality, functionality and safety of a critical raw material of its intended use!

80

Starting Materials are …

Drug Substances (DS) are…

Intermediates are …

Drug Products (DP) are …

The IMPD should be divided into a drug substance (DS)[4] and a drug product (DP)[5] section. For certain ATIMPs, the starting material, the active substance and the finished product can be closely related or nearly identical. The active substance, any intermediate and the final product should be identified, if possible. In those cases where the ATIMPs production is a continuous process, it is not necessary to repeat the information that was already provided in the DS part, into the DP section.

Throughout the guideline, the terminology 'active substance' and 'drug substance' are used interchangeably

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

31 January 2019
EMA/CAT/852602/2018

81

In vivo gene therapy

STARTING MATERIALS ***DRUG SUBSTANCE***

Cell Banks Virus Seed Plasmids → ***Vector (transgene)*** → ***DP*** → ***Patient Administration***

For products consisting of viral vectors, the starting materials are the components from which the viral vector is obtained, i.e. the master virus seed or the plasmids used to transfect the packaging cells and the MCB of the packaging cell line.

The active substance of a gene therapy medicinal product based on gene transfer methods in vivo is composed of the recombinant nucleic acid and the viral or non-viral vector used to deliver it.

In the case of in vivo genome editing approaches, active substances normally comprise the tools used for the intended genome edition.

PIC/S ANNEX 2A

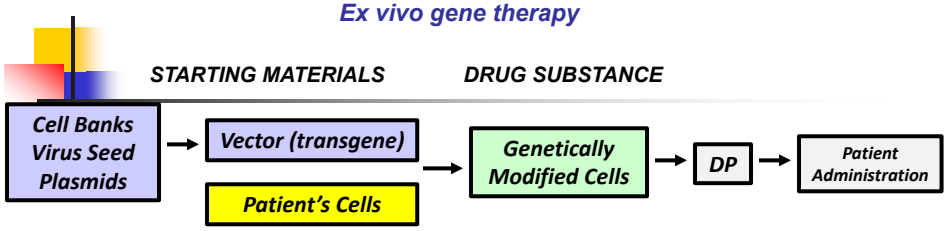
MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE

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

31 January 2019
EMA/CAT/852602/2018

82

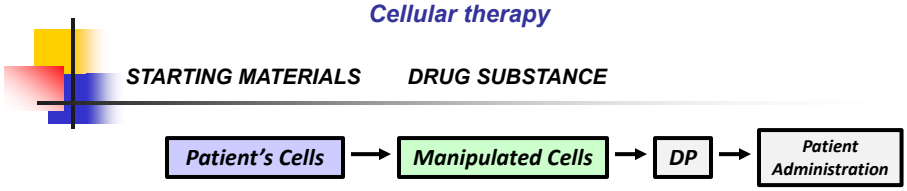
Ex vivo gene therapy



The unmodified cells, the viral or non-viral vectors and any other nucleic acid and/or protein used in the genetic modification of the cells are considered starting material. In this case of ex vivo use, viral vectors, plasmids, recombinant proteins and recombinant mRNA, the components to produce them (e.g. plasmids, cells) are also considered starting materials. In this case, the principles of GMP, as provided in the General Principles in the Guidelines for GMP for ATMP, should be applied from the cells bank systems used to produce the starting materials, when applicable.

In the case of gene therapy ex vivo (i.e. genetically modified cells), the active substance is composed of the modified cells.

Cellular therapy



Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) when combined as an integral part with the manipulated cells are considered part of the active substance and are therefore considered as starting materials, even if not of biological origin.

The active substance of a CBIMP is composed of the manipulated or not same essential function cells

FDA's definition of starting material, intermediate, drug substance

iii. Banking Systems (Starting Materials)

A banking system improves control and consistency in the manufacturing of many biologics. Banking assures an adequate supply of equivalent, well-characterized material for production over the expected lifetime of production. For these reasons, banked materials are a common starting point for many routine production applications. We outline our current thinking for the qualification of different banking systems below, including banks of cell substrates for production of viral vectors, banks of bacterial/microbial cells, allogeneic donor cell banks, and banks of viral vectors. We recommend that you provide a summary of the testing in this section, and COAs in section 3.2.A.2 of the CTD.

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

You should describe whether the vector DS will be formulated into the DP for administration of the genetic material (section V.B.3.b., "Batch Formula (3.2.P.3.2)," of this guidance) or whether it will be formulated as a bulk DS for ex vivo genetic modification of cells (as outlined in section IV.B., "Drug Substance and Drug Product," of this

Vector: A vehicle consisting of, or derived from, biological material that is designed to deliver genetic material. Examples include plasmids, viruses, and bacteria that have been modified to transfer genetic material.

Long Term Follow-Up After Administration of Human Gene Therapy Products
January 2020

Challenge of 'Sole Source' starting materials

***Case Example*: 12+ month clinical start delay**

EDIT-101 – transient AAV manufacture, with CRISPR for in vivo gene editing

1 of 3 plasmid vectors did not meet incoming quality specs

May 15, 2017

> Editas Medicine on May 15 disclosed during a first quarter earnings presentation that its highly anticipated CRISPR gene-editing therapy would be delayed entering the clinic.

"The manufacturing delay related to production of input materials for AAV manufacturing"

November 30, 2018

Editas Medicine Announces FDA Acceptance of IND Application for EDIT-101

***Case Example*: 3 month clincal hold + ___ month partial clinical hold**

November 12, 2019

> Marker previously announced on November 12, 2019, that the FDA placed the trial on clinical hold. The FDA requested additional information and technical specifications for two legacy reagents supplied by third parties used in the MultiTAA-specific T cell manufacturing process. The technical specifications and data requested by the FDA could not be produced by the original suppliers. The Company identified alternative suppliers, satisfying the Agency's request.

February 11, 2020

"Marker currently estimates that the alternative supplier will deliver the final reagent, along with the final data and certificate of analysis required by the FDA, by the end of the second quarter of 2020."

87

GMP for Starting Materials, Drug Substances (DS) and Drug Products (DP)

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

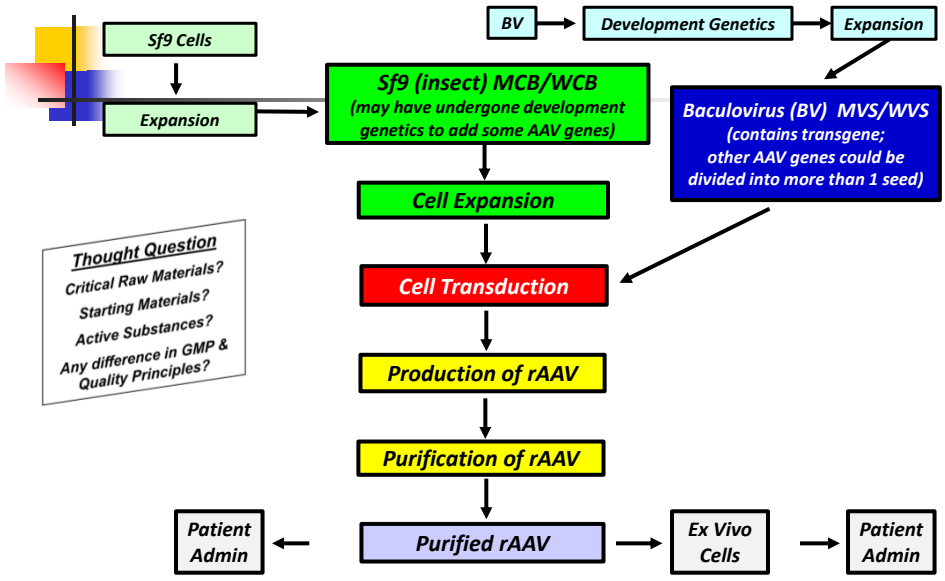
Increasing GMP requirements

PIC/S

MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE ANNEX 2A

88

rAdeno-Associated Virus (AAV) Manufacturing Using Virus Transduction



89

Risk-Based Approach (RBA) to GMPs & Quality Principles

During Clinical Development of ATMPs/CGTPs

- ***Eight (8) core GMP & Quality System principles***
  1) *Personnel adequately trained; clear allocation of responsibilities*
  2) *Premises/equipment suitable for intended use, and maintained*
  3) *Adequate documentation system ensuring appropriate specifications are laid down for materials, intermediates, bulk products and the finished product; that the production process is clearly understood, and that appropriate records are kept*
  4) ***Manufacturing process adequate to ensure consistent production (appropriate to the relevant stage of development), the quality of the product, and the compliance to relevant specifications***
  5) *-*
  6) *-*
  7) *-*
  8) *-*

Manufacturing process must be under adequate control, not necessarily validated!

Investigational ATMPs

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.

10.47. Process validation/evaluation data should be collected throughout the development. It is noted that for the clinical trial to be used in support of a marketing authorisation application it is important to demonstrate that the manufacturing process of the investigational ATMP ensures consistent production.

91

Process validation is the documented evidence that the manufacturing process can consistently produce a result within specific parameters. 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. It is noted that for the confirmatory clinical trial to be used in support of a marketing authorisation process validation is required to demonstrate that the manufacturing process of the ATIMP ensures consistent production.

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

31 January 2019
EMA/CAT/852602/2018

e. Process Validation and/or Evaluation (3.2.S.2.5)

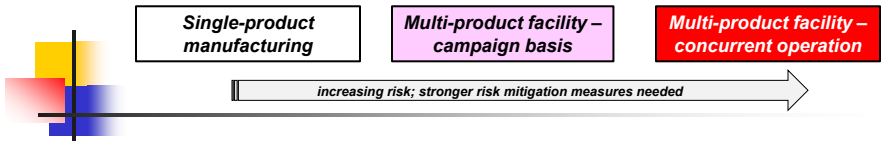
Process validation studies are generally or typically not required for early stage manufacturing, and thus, most original IND submissions will not include process performance qualification. We recommend that you use early stage manufacturing experience to evaluate the need for process improvements and to support process validation studies in the future.

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

92



4.13. Manufacture of ATMPs in a multi-product facility is acceptable when appropriate risk-mitigation measures commensurate with the risks are implemented to prevent mix-ups and cross-contamination. Further explanations can be found in Section 9.4.

9.35. Measures to prevent cross-contamination appropriate to the risks identified should be put in place. Measures that can be considered to prevent cross-contamination include, among others:

(i) Segregated premises.

(ii) Dedicating the whole manufacturing facility or a self-contained production area on a campaign basis (separation in time) followed by a cleaning process of validated effectiveness.

(iii) Use of "closed systems" for processing and material/product transfer between equipment. …

93

Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. QRM principles should be used to assess and control the risks. Depending on the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some ATMPs. Segregated production areas should be used for the manufacturing of ATMPs presenting a risk that cannot be adequately controlled by operational and/or technical measures. (Replaces PICS GMP Guide Part I Section 3.6)

PIC/S MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE ANNEX 2A

We recommend that you manufacture only one phase 1 investigational drug at any given time, in an area or room separate from unrelated activities. However, you could use the same area or room for multiple purposes, including manufacture of other investigational products or laboratory research, provided that appropriate cleaning and procedural controls are in place to ensure that there is no carry-over of materials or products, or mix-ups. In such cases, the design or layout of an area should promote the orderly handling of materials and equipment, the prevention of mix-ups, and the prevention of contamination of equipment or product by substances, previously manufactured products, personnel, or environmental conditions.

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

94

Prospective Emergency Plan for accidental release

9.38. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Qualified decontamination measures should be available taking into consideration the organism used in production, as well as the risks attached to the relevant biological materials.

EUROPEAN COMMISSION
Good Manufacturing Practice for Advanced Therapy Medicinal Products

An emergency plan for dealing with accidental release of viable organisms should be in place. This should address methods and procedures for containment, protection of operators, cleaning, decontamination and safe return to use. An assessment of impact on the immediate products and any others in the affected area should also be made.

PIC/S MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE ANNEX 2A

Lessons learned the hard way (from biopharmaceutical protein processes contaminated with viruses and/or mycoplasma): Accidental release is not the time to call a committee meeting, but needs timely, prospective, well-thought-out action!

PDA TECHNICAL REPORT 83 (2019)

Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness, and Response

- *Virus Contamination Response Plan*
- *Investigation Management Structure & Leadership*
- *Response Plan Elements*

95

Risk-Based Approach (RBA) to GMPs & Quality Principles

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  4) *Manufacturing process adequate to ensure consistent production (appropriate to the relevant stage of development), the quality of the product, and the compliance to relevant specifications*
  5) ***Quality control system which is operationally independent from production***
  6) **-**
  7) **-**
  8) **-**

EUROPEAN COMMISSION
Good Manufacturing Practice for Advanced Therapy Medicinal Products

96

***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.

97

Although quality is the responsibility of all personnel involved in manufacturing, we recommend that you assign an individual(s) to perform QC functions independent of manufacturing responsibilities, especially for the cumulative review and release of phase 1 investigational drug batches.

However, in very limited circumstances and depending on the size and structure of an organization, all QC functions may be performed by the same individual(s) performing manufacturing. For example, in some small operations, it may be necessary to have the same individual perform both manufacturing and QC functions, including release or rejection of each batch. However, in such circumstances, we strongly recommend that another qualified individual not involved in the manufacturing operation conduct an additional *periodic* review of manufacturing records and other QC activities.

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

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

98

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  5) ***Quality control system which is operationally independent from production***
  6) ***Arrangements in place for prospective evaluation of planned changes and approval prior to implementation, and for evaluation of changes implemented***
  7) ***-***
  8) ***-***

Change is an inherent part of the development process!

<u>But</u> change must not negatively impact the process, the product, or the patient!

Investigational ATMPs

2.20. 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, in particular by ensuring consistency of the product, that the results of the clinical trial are not affected by unsatisfactory manufacturing used and that changes of the product throughout the development are adequately documented.

2.21. 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.

Depending on the consequences of the change introduced and the stage of development, a comparability exercise may be necessary to ensure that the change does not have an adverse impact on impact on the quality of the product and therefore on the safety and clinical efficacy of the product. The main purpose of this exercise is to provide assurance that the post-change product is suitable for the forthcoming clinical trials and that it does not raise any concern for the safety of the patients included in the clinical trial. The extent of the comparability exercise needed depends on the nature of the change introduced and the stage of development.

During early phases of non-clinical and clinical studies, comparability testing is generally not as extensive as for an approved product.

When exploratory trials already took place, data filiation program should expand to a full comparability exercise where a higher degree of sameness is expected and a more comprehensive analytical package should be in place. For confirmatory trials, the principles as can be found in ICH Q5E Comparability of Biotechnological/Biological Products should be applied. During the confirmatory clinical studies introducing changes to the manufacturing process and the final product should be avoided, because comparability issues may impact the acceptability of the data.

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

31 January 2019
EMA/CAT/852602/2018

101

The critical role of the Quality Unit Change Management System!

(formal evaluation, documented plan, prospective evaluation criteria, work completed according to signed plan, report, approvals)*

Manufacturing process changes may encompass improvements/change in equipment, raw materials and critical starting materials such as the cells or the vector or their suppliers, manufacturing process scale or product stability. Such changes are frequent, especially in the early stages of development of ATMPs.

Every change in manufacture should be done in accordance with GMP. The criticality of the changes and the estimation of their impact on the characteristics of the product should determine the amount of comparability data needed. Where applicable, the Variation Regulation[1] (for authorised ATMPs) or the clinical trial framework (for investigational ATMPs) should be followed.

Questions and answers
Comparability considerations for Advanced Therapy Medicinal Products (ATMP)

6 December 2019
EMA/CAT/499821/2019

**** ICH Q10 3.2.3 Change Management System***

102

Q3: How does the risk-based approach (RBA) apply to comparability exercises for ATMPs?

A: The potential impact of the proposed change should always be evaluated for its risks to the quality of the final product and the impact on the efficacy and safety profile of the product. The overall extent of the comparability exercise for ATMPs should therefore be driven by a risk-based approach (RBA). Namely, the RBA should be used to determine an appropriate amount of comparability data and to select a suitable set of relevant critical quality attributes (CQAs) to be compared, taking into account the stage of product development and the number of batches available.

Q5: At what timepoint during the product life cycle should comparability be demonstrated?

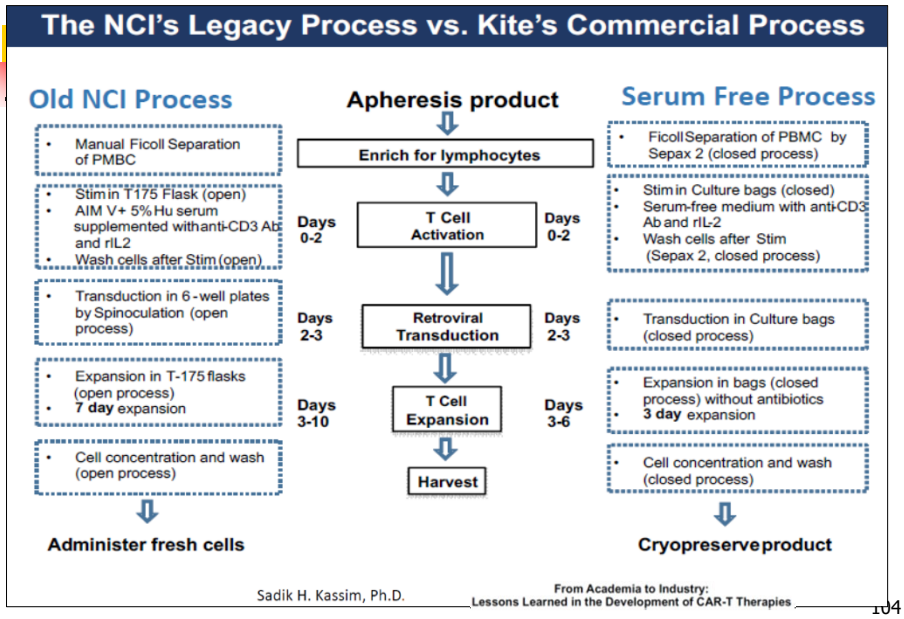
A: It is of importance that the changes implemented in all stages of development are fully evaluated, justified and tracked. Different kinds of changes may be introduced at different phases throughout development. The evaluated risk associated with the change and possible impact on the finished product impact also the focus and level of the expected comparability exercise (see Question 3).

Questions and answers
Comparability considerations for Advanced Therapy Medicinal Products (ATMP)

6 December 2019
EMA/CAT/499821/2019

103

CASE EXAMPLE of how much process change may be necessary to move from academic to industry manufacturing process!



Sadik H. Kassim, Ph.D.

From Academia to Industry: Lessons Learned in the Development of CAR-T Therapies

104

A major challenge is to develop, characterize, and validate the manufacturing process under compressed clinical development timelines, while ensuring comparability between process versions and maintaining the link to clinical data!

FDA: Regenerative Medicine Advance Therapy (RMAT) designation

Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

Food and Drug Administration
Center for Biologics Evaluation and Research
February 2019

EMA: Primary Medicine (PRIME) designation

EMA European Medicines Agency Guidance on Interactions in the Context of PRIME (May 2018)

Exciting clinical speed opportunities … ***… but challenges product comparability!***

105

EMA very concerned about the impact on CMC due to clinical expediting

recognized pressure on product comparability due to PRIME designation

Perspective from EU-EMA *(V. Jekerle (Quality Office, EMA))*

The talk also illustrated the scientific challenges common to PRIME candidates including shortened timelines, which put constraints on the ability to complete commercial manufacturing sites set-up & description, compilation of validation and stability data and determination of the appropriate control strategy including specification setting. Product characterization, in particular, determination of biological activity and demonstration of comparability, is particularly challenging for many PRIME candidate products due to their highly innovative and complex features (i.e. genetically modified cells and viral vector-based products). Finally, global developments require applicants to put extra efforts into demonstrating comparability, where manufacturing processes are being changed or moved across geographic regions and suitable batch-release testing arrangements need to be identified in line with the applicable legal framework. An analysis examining scientific issues most commonly identified by PRIME applicants (as indicated by SA requests) revealed the following areas as the most critical: starting materials, comparability, process validation, analytical control strategy, specifications and stability.

In conclusion EU regulators view PRIME as a support scheme for development, whereby the product quality should not be compromised but considered in the context of the benefit/risk assessment.

Meeting Report:
Workshop with stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies)

25 July 2019
EMA/CHMP/BWP/812924/2018

106

FDA very concerned about the impact on CMC due to clinical expediting

recognized pressure on product comparability due to RMAT designation

Common Challenges for Comparability of CGTPs

FDA

- **Limited lots** (manufacturing history):
  - Comparability studies are not statistically powered
  - Not enough retention/test samples available
- **Limited assay development** (potency, purity); assays not qualified; reference standards not established or adequately characterized.
- **Limited product characterization**; CQAs not known
- **Limited knowledge of product- and process-related impurities**
- **Limited in-process testing**; process variables and critical process parameters (CPP) not known
- **Limited product stability data collected**; limited product attributes tested in stability plan.

Comparability Studies
Unique Challenges and Key Considerations for Cell and Gene Therapy Products (CGTPs)

CASSS: Cell & Gene Therapy Products Symposium 2018
July 10-12, 2018

107

CASE EXAMPLE

CMC struggling to keep pace with expedited Clinical!

Abeona THERAPEUTICS

EB-101 is an investigational, autologous, gene-corrected cell therapy

FDA clinical expedited designations received: RMAT, Breakthrough Therapy, Rare Pediatric

CLEVELAND and NEW YORK, May 31, 2018 (GLOBE NEWSWIRE) -- Abeona Therapeutics Inc. (Nasdaq:ABEO), a leading clinical-stage biopharmaceutical company focused on developing novel gene and cell therapies for life-threatening rare diseases, announced today the opening of The Elisa Linton Center for Rare Disease Therapies, the commercial GMP manufacturing facility for gene and cell therapies in Cleveland, Ohio. The GMP facility will have the capability to manufacture clinical and commercial grade products over Abeona's multiple programs, including recessive dystrophic epidermolysis bullosa (RDEB) and Sanfilippo syndrome. The ribbon-cutting ceremony and first facility walk-through will be held today, May 31, 2018.

Now the new facility has to produce comparable product

NEW YORK and CLEVELAND, Sept. 23, 2019 (GLOBE NEWSWIRE) -- Abeona Therapeutics Inc. (Nasdaq: ABEO), a fully-integrated leader in gene and cell therapy, today announced that it has recently received a clinical hold letter from the U.S. Food and Drug Administration (FDA) clarifying that the FDA will not provide approval for the Company to begin its planned Phase 3 clinical trial for EB-101 until it submits to the FDA additional data points on transport stability of EB-101 to clinical sites. Over the last 12 months, the Company has worked closely with the FDA to address and narrow open Chemical, Manufacturing and Controls (CMC) items and has been working to resolve this one item identified in the FDA Clinical Hold Letter. The Company continues to anticipate receiving CMC clearance for VIITAL™ trial in Q4 2019.

Clinical hold released December 2019

108

CASE EXAMPLE

Struggling to implement all of the required EMA postmarketing CMC changes!

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

EMA clinical expedited designation received: PRIME ***EMA market approved: April 2019***

Postmarketing CMC commitments

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CAT recommends the following points for investigation:

14 recommendations aimed at improving control of raw materials, providing additional stability data for starting materials, installing in process controls and/or limits for LVV and active substance manufacture, completing characterisation of LVV particles, providing further data on LVV and finished product test methods, revising acceptance criteria as warranted, re-evaluation of specifications after manufacture of additional batches of LVV and finished product, implementing additional test methods and acceptance criteria, respectively.

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 22, 2019-- bluebird bio, Inc. (Nasdaq: BLUE) announced today that the European Medicines Agency (EMA) approved the refined commercial drug product manufacturing specifications for ZYNTEGLO™ (autologous CD34+ cells

109

Risk-Based Approach (RBA) to GMPs & Quality Principles

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  5) ***Quality control system which is operationally independent from production***
  6) ***Arrangements in place for prospective evaluation of planned changes and approval prior to implementation, and for evaluation of changes implemented***
  7) ***Quality defects/process deviations are identified as soon as possible; causes identified, appropriate corrective and preventative measures taken*** ***(ICH Q10 3.2.2 CAPA System)***
  8) ***Adequate systems of traceability of the ATMPs, starting and critical raw materials***

no time to discuss

'Bottom Line' RBA Thoughts

- ***Always protect the patient!***
  - ***Do the comprehensive and thorough risk analysis***
- ***Good business practice: reduce uncertainty, if possible!***
  - ***Implement appropriate and adequate risk minimization steps***
- ***Focus on the end target (→ getting to the market)***
  - ***Unfortunately this means investing in Manufacturing & Quality early in clinical development before medical success is known!***

QUESTIONS??

111

4. Industry Practice in Applying Risk-Based Principles

Applying Quality by Design (QbD) and Quality Risk Management (QRM); PDA Technical Report 81

112

Two core approaches used widely by biologic manufacturers!

not mandatory, but highly recommended ('expected')

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.

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.

ICH harmonisation for better health

113

QbD/QRM – not mandatory, but expected

CASE EXAMPLE: applied to market approved allogeneic cell therapy manufacturing

Assessment report

14 December 2017
EMA/CHMP/64055/2018

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.

The control of critical steps and intermediates has been established on a risk based assessment as per ICHQ11. The limits and ranges for in-process controls (IPC) for MCS and AS were established during development and include biological and microbiological parameters established based upon the quality target product profile (QTPP).

Validation of the AS manufacturing process was performed based on aspects that could impact the critical quality attributes (CQAs) of the only intermediate of the process, the MCS, and of the final AS.

The steps taken during development of the manufacturing process were described. This was initially based on published data and the development of an autologous version of the product for which scientific advice was received from EMA. Relevant aspects for the process performance or the quality of the product were monitored through the development process and the critical steps were identified CPPs

In general the information provided is acceptable. Data provided confirmed process consistency. The control strategy implemented for MCS and AS manufacturing processes was based on ICH Q11v.

114

QbD/QRM – not mandatory, but expected

CASE EXAMPLE: applied to market approved ex vivo gene therapy cells

Assessment report

26 April 2019
EMA/CHMP/226273/2019

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)

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.

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

Transduced Cells (Active Substance)

Tabular overviews of CPPs and IPCs have been adequately described.

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

115

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

QbD/QRM recommended for ATMPs during clinical development

CQAs and CPPs, even with limited process/product understanding

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.

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

31 January 2019
EMA/CAT/852602/2018

116

U.S. FOOD & DRUG ADMINISTRATION

QbD/QRM recommended for ATMPs during clinical development

CQAs and CPPs, even with limited process/product understanding

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.

guidance (Ref. 12). Therefore, we strongly recommend that the cell lines and helper sequences used to make viral vectors that package non-vector DNA, such as AAV, be carefully chosen to reduce the risks of the product. Sponsors should provide necessary quality data, risk assessments, and/or details of their process and product control strategy to address and mitigate potential risks posed by the manufacturing systems used.

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

117

QbD, QRM – not mandatory, but expected!

proven invaluable for biopharmaceutical manufacturing

Quality by Design (QbD) elements

118

QTPP • Quality Target Product Profile

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.

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 common vision

119

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

Illustration of a QTTP template for Cellular Therapy

	Category of Attributes	Criteria (Example)
Drug Product Attributes	Therapeutic Indication	Orthopedics, immune, cardiovascular
	Dosage Form	Liquid suspension, tissue equivalent, cryopreserved, fresh
	Dose Regimen	Daily, monthly, single infusion
	Volume per Dose	mL
	Container Closure System	Bag, vial, sterile-sealed
	Stability and Storage Conditions	2-8 °C, 18-25 °C, cryopreserved in vapor phase LN_2, <-130 °C
Drug Product Quality Attributes	Safety	Microbial testing which, depending on the nature of the product, is likely to be based on a multidimensional approach encompassing in-process and final-product testing
	Identity	Tests to distinguish the specified cells through physical or chemical characteristics of the cell line (i.e., phenotype, genotype, or other markers; qPCR of transgene; tissue-specific gene expression)
	Content	#cells/dose, #cells/cm^2, cells/kg, active (transduced) cells/kg
	Viability	
	Purity	Tests to assess product purity, considering the product (e.g., live cells, dead cells)
	Impurities	Process-related impurities (e.g., contaminating cells, cellular fragments), viral residuals, paramagnetic beads, residual detergent, enzyme, or other potent compounds that are used in process, but are not desirable in a drug substance
	Potency	Measure of the relevant product biological functions Method to assess product biological activity based on the different elements involved with the MoA, often multiple tests evolving from specific markers in early stage to more functional assays at later stage
	General	Appearance, visible particulates, packaging

120

CQA • Critical Quality Attributes

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

Primary structure
Higher order structure (HOS)
Product-related impurities
Process-related impurities
Compendial (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.

ICH Q11

- ***For biologics, most of the CQAs of the drug product are associated with the manufacture of the drug substance***
- ***The identification of CQAs for complex products (biologics) is challenging, and it might not be possible to fully evaluate the impact of each one (clinically meaningful)***

121

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

1) identify all quality attributes (QAs)

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

Rating	Impact
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

Uncertainty	Prior Knowledge
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

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

122

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

Illustration of CQA determination for Cellular Therapy

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	An autologous chondrocyte product must contain chondrocytes, which are characterized by their expression of specific chondrogenic markers
Impurities				
Fibroblastic Cells	High	Medium	CQA	Available data suggests fibroblasts may interfere with stable hyaline cartilage regeneration
Residual Trypsin	Low	Low	Non-CQA	In products manufactured to date, 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
Residual Fetal Bovine Serum	High	Medium	CQA	Levels in final product known to potentially impact safety
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 is measured as surrogate assay for function
Strength/Dose				
Total Cell Number/ Dose Unit	Medium	Low	CQA	Link between dose and efficacy needs to be established during development
Safety				
Endotoxin	High	Low	CQA	Endotoxins (mainly lipopolysaccharides from gram negative bacteria) 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
Mycoplasma	High	Low	CQA	Mycoplasma can cause serious contamination in cell cultures, which may affect phenotypical characteristics and normal growth of the cells; a few species can be pathogenic
Adventitious virus	High	Low	CQA	Manufacture requires use of cell substrates and raw materials of human and animal origin that could be contaminated with a virus, which potentially can be carried over into the product

23

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 with many PPs***
- ***KPP (Key Process Parameter) – a process parameter that has no impact of a CQA, but does impact process performance (e.g., product yield)***

124

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 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 parameter has no impact on CQAs

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

Impact Severity	
Low	non-CPP
Medium	pCPP or CPP
High	CPP

125

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

CPP

pCPP

Non-CPP

Unit Operation Step	Process Parameter	CQA A	CQA B	CQA C	CQA …
Expansion	Number of trays or flasks				
	Seeding density for each expansion				
	Media volume for each expansion				
	Incubation time for each expansion				
	Incubation temperature for each expansion				
	% 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				

126

• Control Strategy

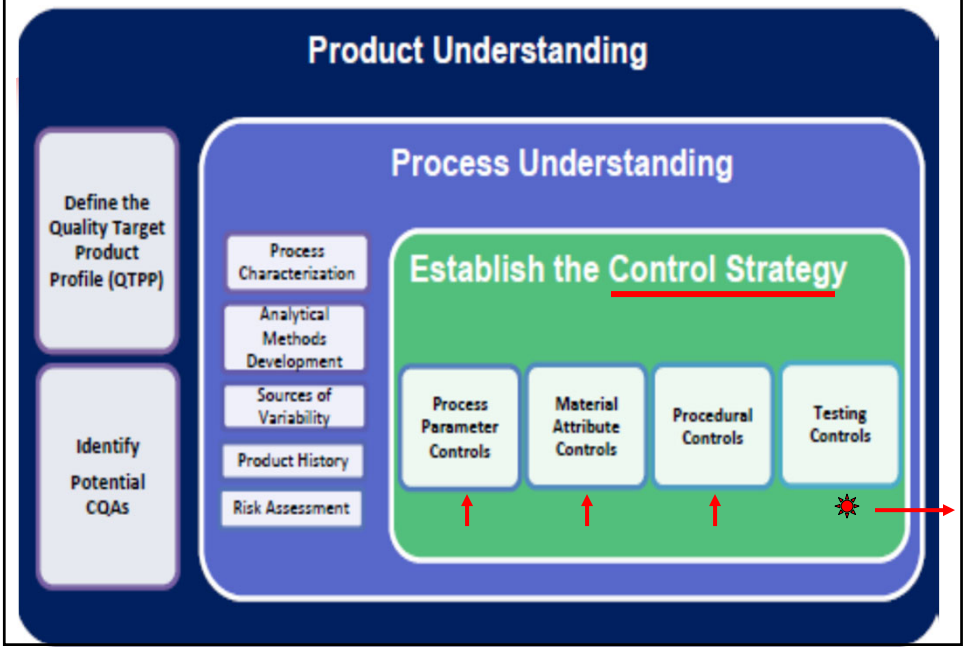
ICH Q8(R2)

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!***

127

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



Recognize the limitation of '<u>Testing Controls</u>' in the Control Strategy during clinical development of ATMPs/CGTPs

availability of test methods (suitable not required to be validated), meaningfulness of test results (preliminary wide specs)

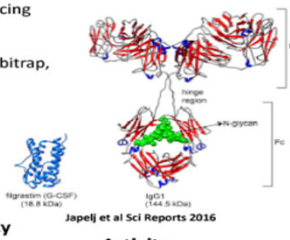
<u>Mature</u> testing tool box for recombinant protein & mAb products

1° Sequence/PTMs
AA analysis
N- and C-term Sequence
Peptide Mapping and Sequencing
LC-MS/MS
Free sulfhydryls
MALDI-TOF, ESI-QTOF-MS, orbitrap, etc....

HOS
Near- and Far-UV CD
FTIR
DSC
HDX-MS
X-ray
NMR

Glycan Analysis
ESI- MS
MALDI-TOF MS
Labeled, PNGaseF released
HPAEC-PAD
HPLC-FD
HILIC (HPLC, UHPLC)
CE-LIF (MS)

Charge
cIEF
icIEF
ICE
IEX- HPLC
CZE



Japelj et al Sci Reports 2016

Process Related Impurities
DNA, HCP, Protein A, etc.

Size/ Purity
SEC-HPLC
HIC-HPLC
RP-HPLC
CE-SDS
CGE
AUC
A4F

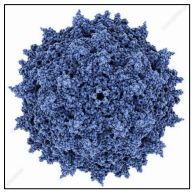
Activity
In vitro Bioassays
Reporter gene assays
Ag/Receptor Binding assays
(mAbs – FcR, C1q)
SPR
Strength (UV A280)

Safety
Bioburden
Sterility
Endotoxin
LAL
KT

129

<u>Under development</u> testing tool box for living virus products

Virus



- ***<u>Composition</u>***
  (genome integrity and size, molecular mass, stoichiometry of capsid proteins)
- ***<u>Primary Structure</u>***
  (nucleic acid sequence)
- ***<u>Physical Properties</u>***
  (aggregation, glycoproteins)
- ***<u>Product-Related Impurity</u>***
  (nature of encapsulated DNA/RNA, empty capsids)
- ***<u>Safety – Replication Competency</u>***
  (AAV vector – low risk LV vector – higher risk)
- ***<u>POTENCY</u>***
  (infectious potency, ratio of full:infectious virus particles)

Special note about potency

130

Potency assay: early development is critical!

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

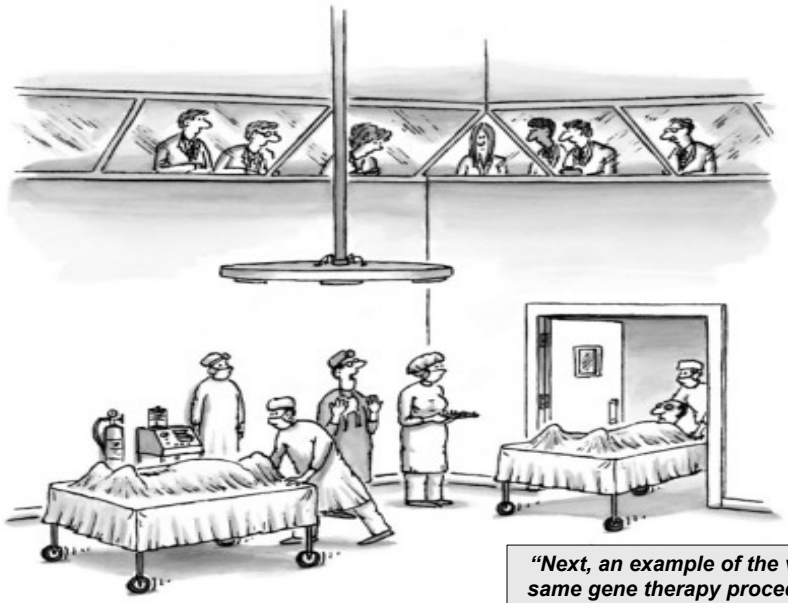
31 January 2019
EMA/CAT/852602/2018

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)).

U.S. FOOD & DRUG ADMINISTRATION

Potency Tests for Cellular and Gene Therapy Products Center for Biologics Evaluation and Research January 2011

131



"Next, an example of the very same gene therapy procedure when done correctly."

QUESTIONS??

132

Resources for Industry

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Committee for Advanced Therapies (CAT)

https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

Advanced therapy classification

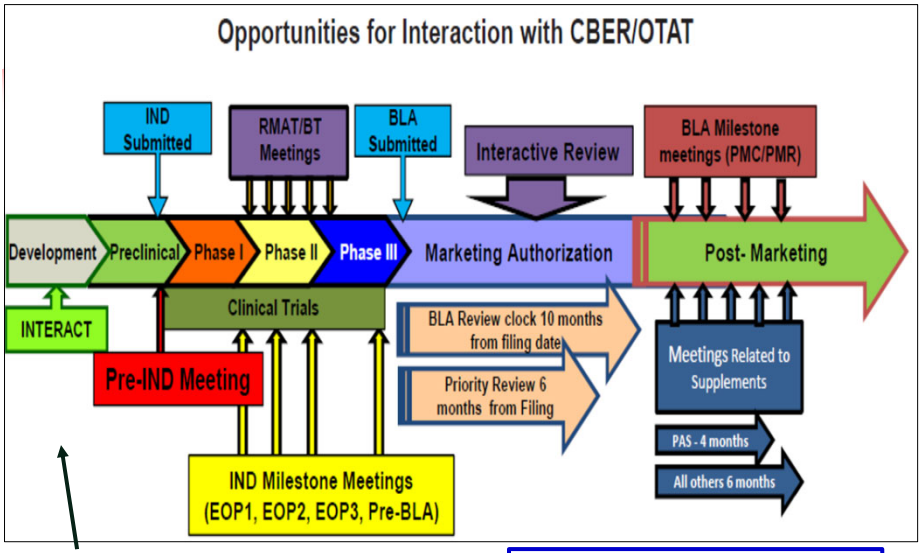
Companies can consult the European Medicines Agency (EMA) to determine whether a medicine they are developing is an advanced therapy medicinal product (ATMP). The procedure allows them to receive confirmation that a medicine, which is based on genes, cells or tissues, meets the scientific criteria for defining an ATMP.

Certification procedures for micro-, small- and medium-sized enterprises (SMEs)

The European Medicines Agency's Committee for Advanced Therapies (CAT) provides a certification procedure for advanced therapy medicinal products (ATMPs) under development by micro-, small- and medium-sized enterprises (SMEs). This is an opportunity for SMEs to get an assessment of the data they have generated and check that they are on the right track for successful development.

133

FDA CBER Office of Tissues and Advanced Therapies (OTAT)



INTERACT – INitial Targeted Engagement for Regulatory Advice on CBER's ProducTs

https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/default.htm

134

FDA OTAT Learn

(video courses on how FDA regulates CGTPs)

https://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*

135

CELL & GENE THERAPY: SPEAKER PRESENTATIONS

free downloadable presentations from CASSS.org

2018: https://www.casss.org/page/CGTP1817

2019: https://www.casss.org/page/CGTP1917

FDA Perspective on Aseptic Process Simulation for Cell Therapy Product Manufacturing

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

Manufacturing of Gene Therapy Products: Advances in Process Development and Scale-Up Methods to Meet Future Demand

Early Stage Manufacturing Considerations for Cell Therapy Products

Comparability Is Not a Nightmare, Just Think Ahead!

136

PDA

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/interest-groups

137

Practical Application of Risk-Based GMP & Quality Principles To Clinical Development of ATMPs

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 for GMPs and Quality of ATMPs*
- → *Above all else: Patient safety must never be compromised!*

Thank you

138