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

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Course Goal

The Challenge for Advanced Therapy Medicines

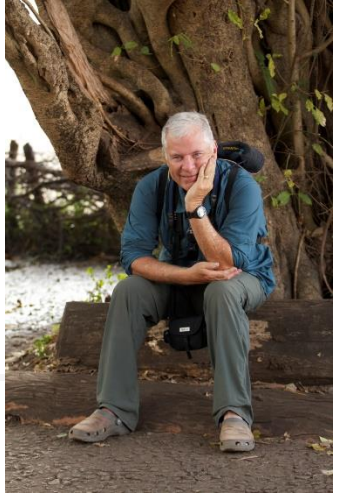
Because of the diverse and evolving manufacturing processes for these living medicinal products (gene and cellular therapies), no single set of GMP & Quality Principles will fit all!

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

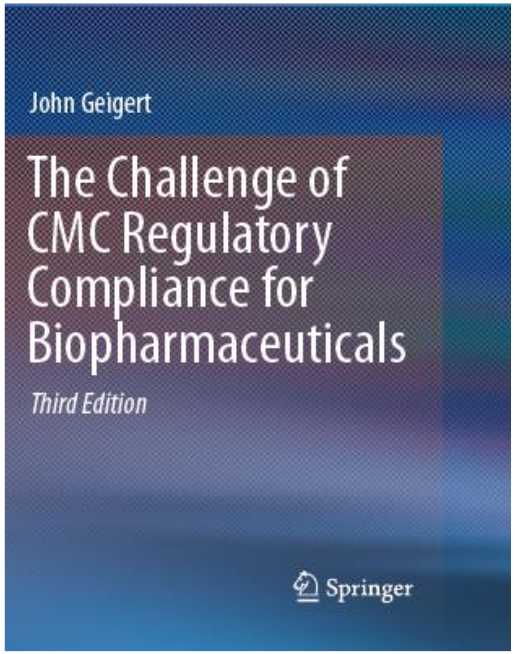
A Solution

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

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



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



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

Who are you? Who do you work for? Interest/experience in CMC?

Manufacturing	***Process Development***	***Project Management***
Quality Control	***Analytical Development***	***Senior Management***
Quality Assurance	***Regulatory Affairs***	***…***

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

Course Outline

1. **Overview of the ATMP Landscape**

   Discussion of the increasing diversity of these advance therapy medicines; introduction to the regulatory authority systems in place to regulate these evolving manufacturing processes and products

2. **Advanced Therapy Product GMP and Quality Risk Consequences**

   Adapting knowledge from established regulatory guidances and experiences (e.g., mAbs, recombinant viral vaccines); avoiding what minefields might occur if improperly adapted

3. **Regulatory Authority Expectations During Clinical Development**

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

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

   Applied risk-based strategy across the entire manufacturing process from starting materials → production → purification → bulk drug substance → formulation → drug product → administered drug

(Continuous presentation over the 6 hours of instruction)

(Please ask your questions)

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

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1. Overview of the ATMP Landscape

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

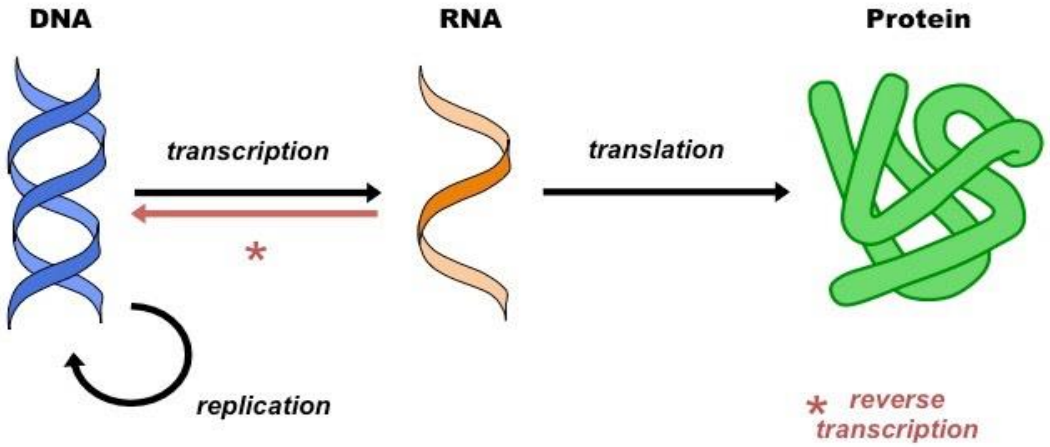
The Majority of Biologic Medicinal Medicines TODAY

Recombinant DNA-Derived Proteins and Monoclonal Antibodies (300+)

Gene inserted into a living microorganism (e.g., E. coli, CHO, Sf9, HEK293)

Recombinant cell line having genetic capability for producing protein

Production in a BIOREACTOR → recombinant protein/mAb



Central Dogma of Molecular Biology

Harvest, purify, formulate, fill

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

The Majority of Biologic Medicinal Medicines IN THE FUTURE

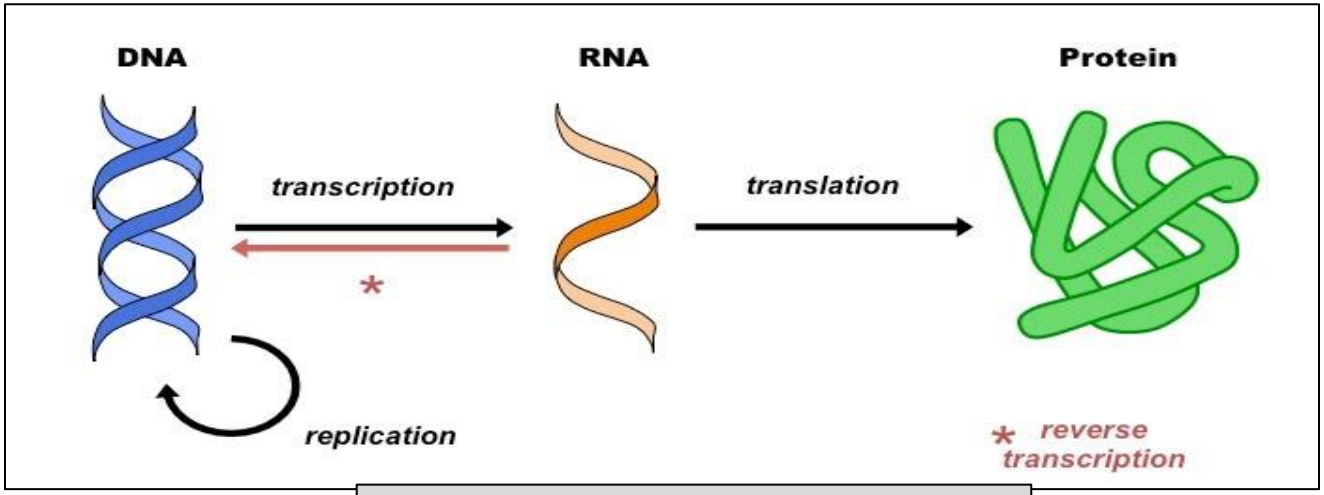
Gene Therapy + …

DNA inserted into a living virus (e.g. AAV)

RNA encapsulated into lipid nanoparticles (LNPs)

Injection of nucleic acid directly into the patient

Production in the PATIENT → gene product (protein)



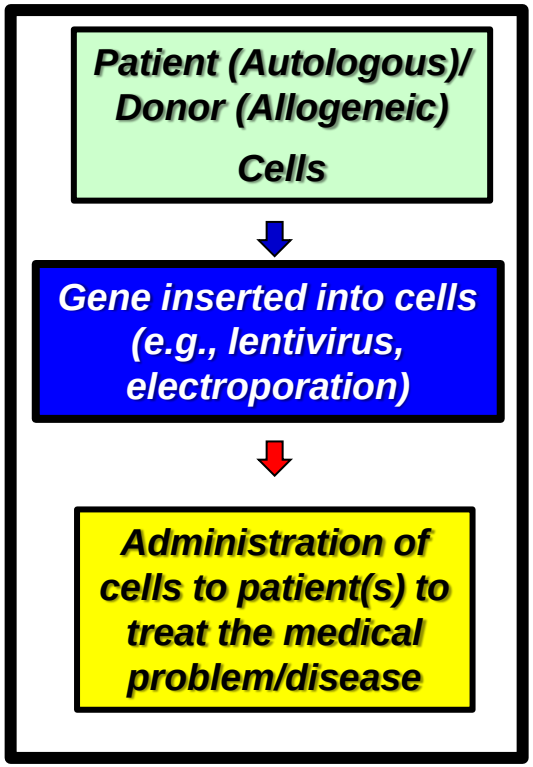
Central Dogma of Molecular Biology

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

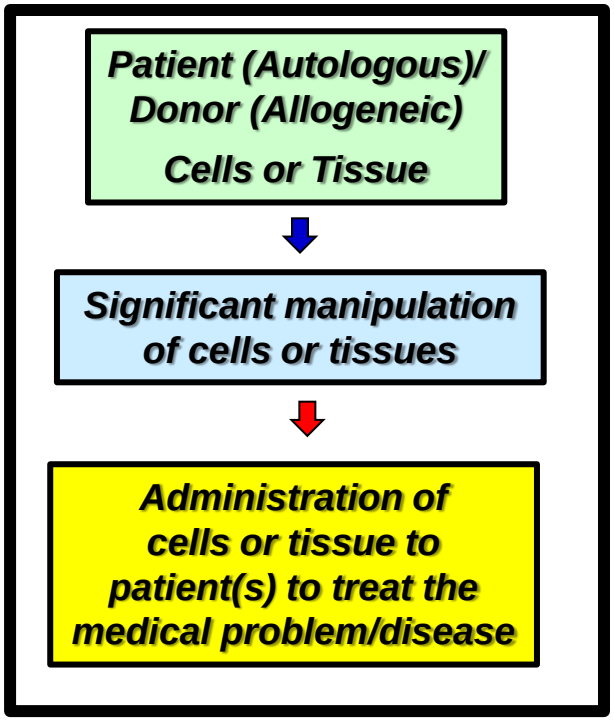
In Vivo Gene Therapy

The Majority of Biologic Medicinal Medicines IN THE FUTURE

… + Cellular Therapy (manipulated cells) & Tissue-Engineered Products



Ex Vivo
Gene Therapy



Cellular Therapy
Tissue-Engineered Product

GILEAD — Kite, A GILEAD Company — *Yescarta Tecartus*

NOVARTIS — avexis — *Kymriah Zolgensma*

Roche — Spark THERAPEUTICS — *Luxturna*

Bristol-Myers Squibb — JUNO THERAPEUTICS — *Abecma Breyanzi*

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson — *Carvykti*

BIOMARIN

bluebirdbio — *Zynteglo Skysona*

AMGEN — *Imlygic*

Orchard therapeutics — *Strimvelis Libmeldy*

Lonza

FUJIFILM Diosynth biotechnologies

ThermoFisher SCIENTIFIC

Catalent BIOLOGICS

Miltenyi Biotec

Advanced Therapies are …

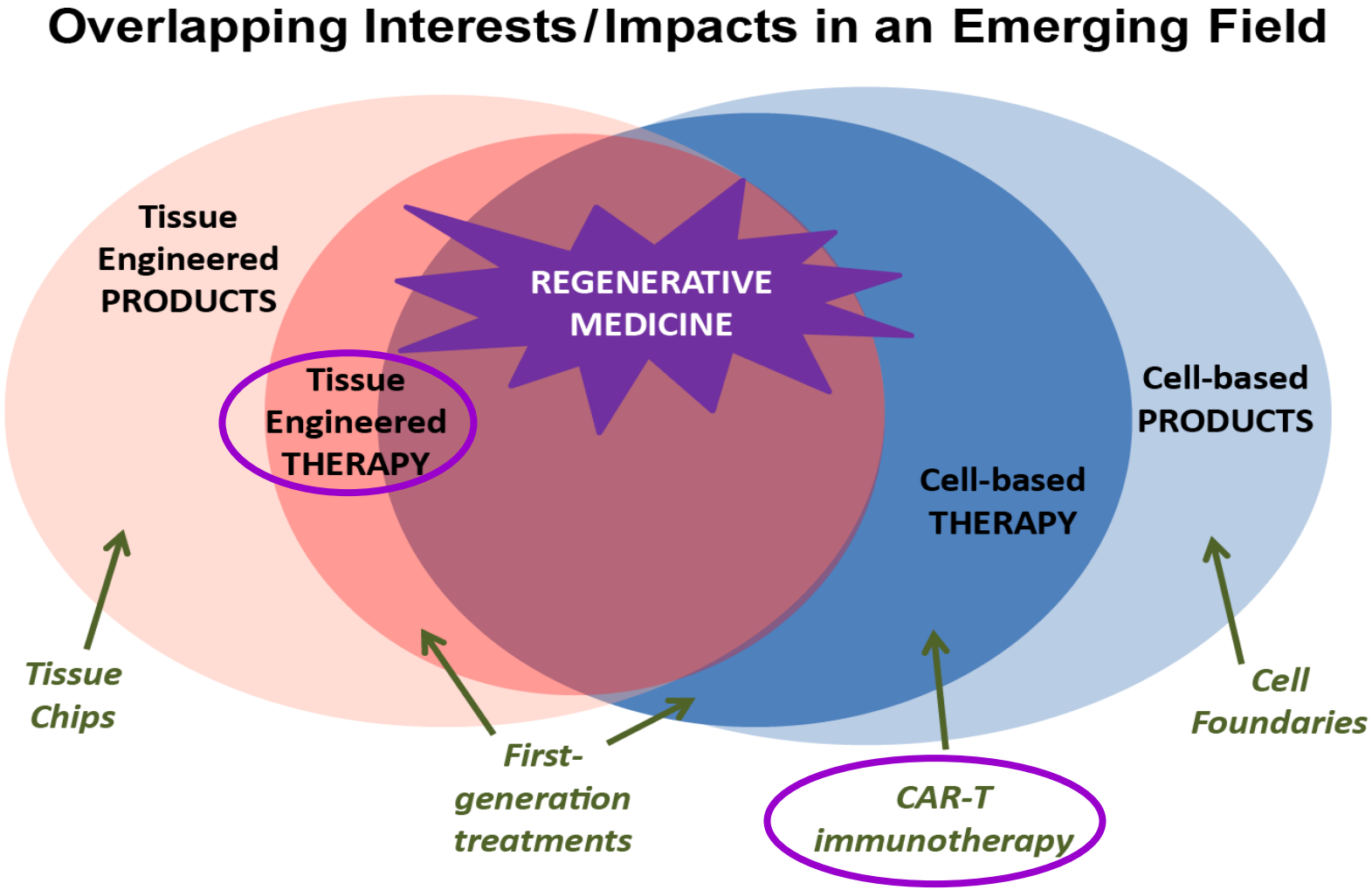
3 groups

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

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

FDA: Regenerative Medicine Advanced Therapy (RMAT)

"cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products"



Advanced therapies are … Gene Therapy

(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, ADDING or DELETING a genetic sequence;

PLUS

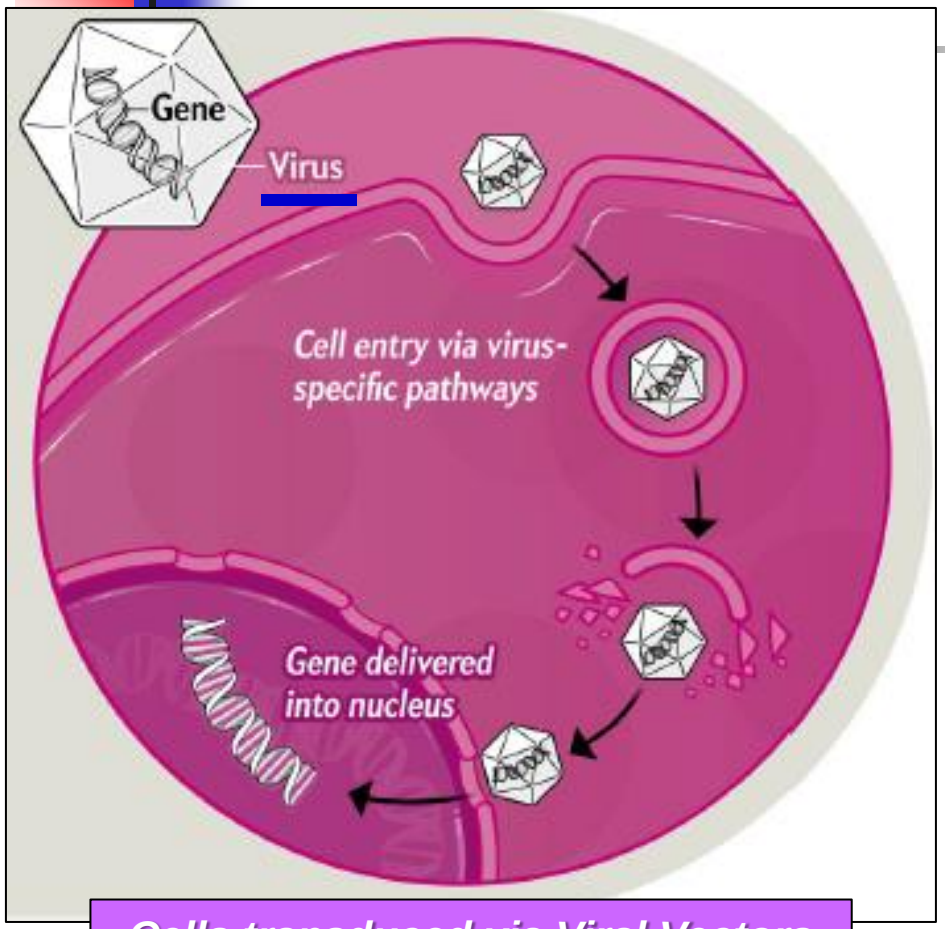
(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence

Gene therapies work by inserting recombinant nucleic acids into human cells:

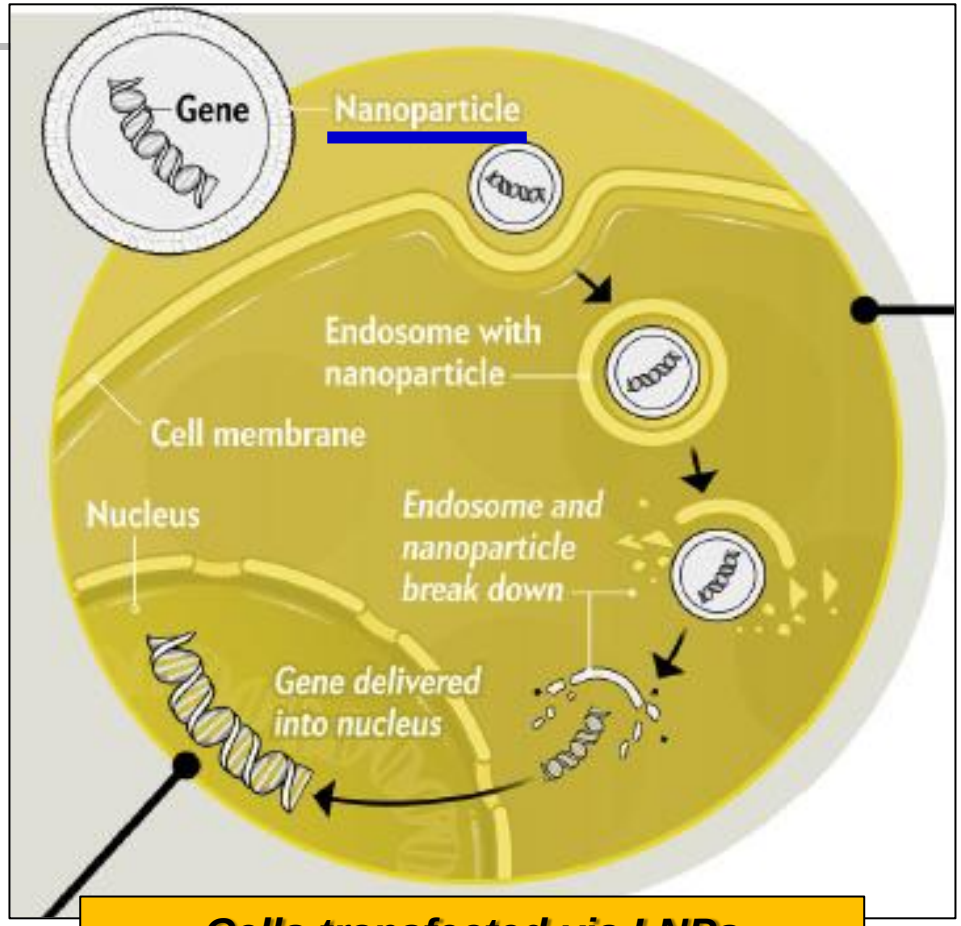
- ***Replacing a malfunctioning gene with a working copy of the gene (gene restoration)***
- ***Addition of a new gene (gene addition)***
- ***Editing a gene that is not functioning properly (gene disabling)***

Gene Therapy – the insertion of DNA/RNA into human cells

(two common insertion approaches)



Cells transduced via Viral Vectors
(AAV or LV containing gene)



Cells transfected via LNPs
(lipid nanoparticles encapsulating gene)

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

Pre-2019	***market approved***
• *Glybera (VISION – rAAV intramuscular – lipoprotein lipase protein → GENE RESTORATION)*	*EMA (2012) (market withdrawn 2017)*
• *Imlygic (MELANOMA – rHSV-1 intralesional – GM-CSF protein → GENE ADDITION)*	*FDA/EMA (2015)*
• *Luxturna (VISION – rAAV intraocular – RPE-65 protein → GENE RESTORATION)*	*FDA/EMA (2017/2018)*

2019 →	***market approved***
• *Zolgensma (SPINAL MUSCULAR ATROPHY - rAAV intraveneous – Survival motor neuron protein (SMN1) → GENE RESTORATION)*	*FDA/EMA (2019/2020)*

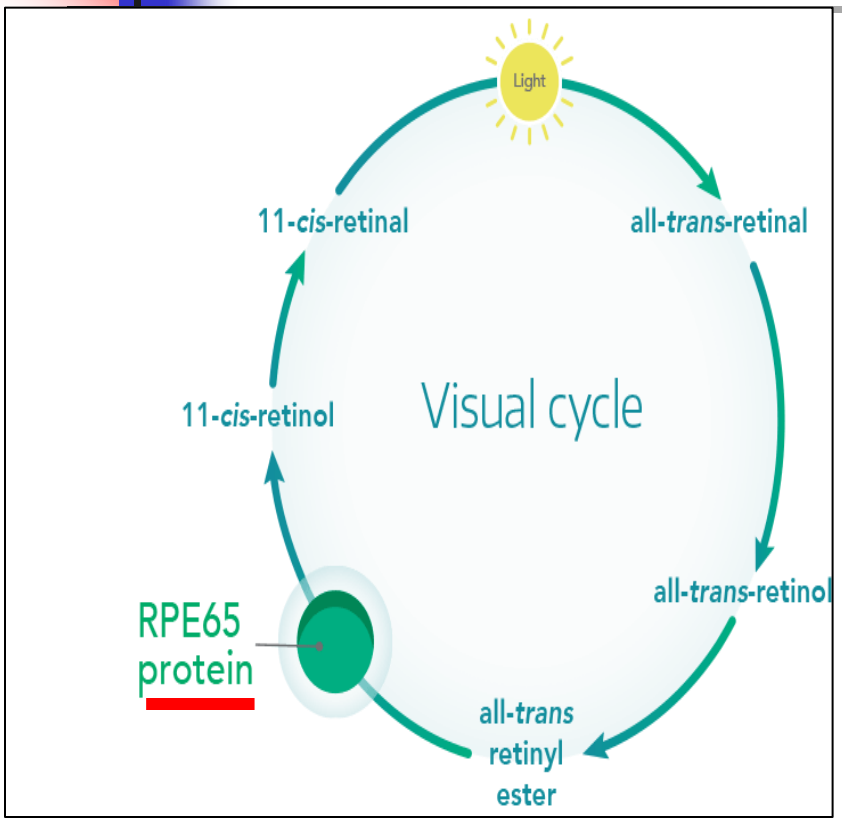
Note, in vivo gene therapy currently relies heavily on genetically engineered adeno-associate virus (rAAV) to deliver genes directly into patients

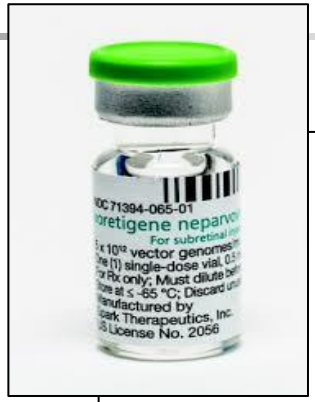
rAAV does not integrate the gene (DNA) into the cell's genome

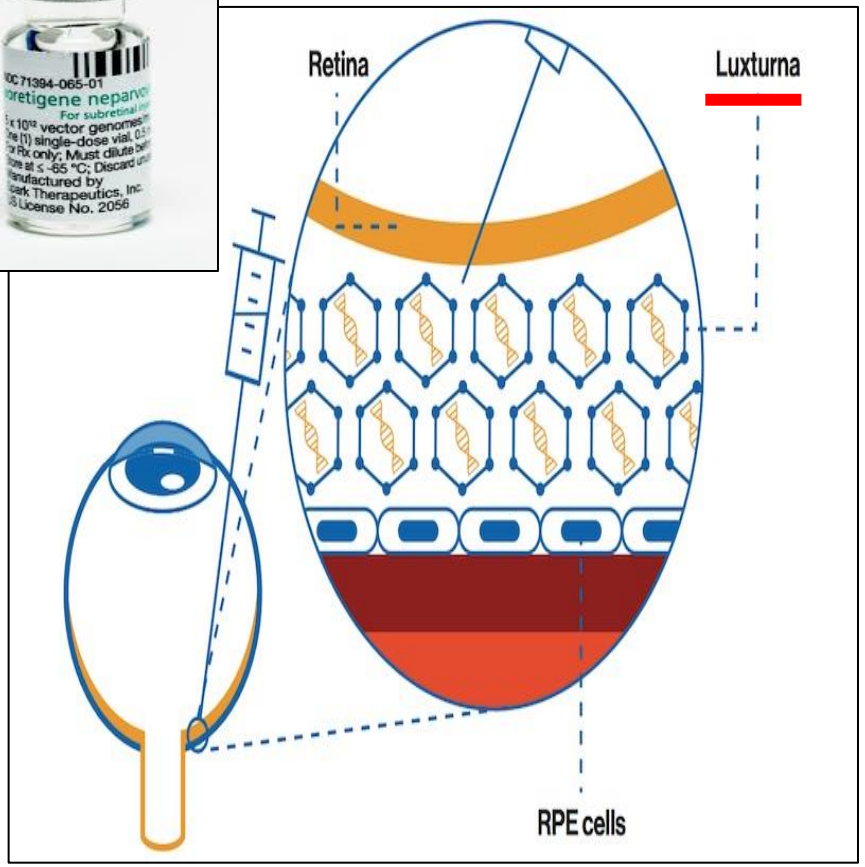
Gene Therapy Example: Recombinant Living Virus (gene restoration)

Spark Therapeutics LUXTERNA

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







Intraocular injection

Note, ~25 genes are associated with loss of vision; RPE65 gene is only one of them

Gene Therapy (EX VIVO) have hit the market …

Name	MOA	Vector	Cells	Market Approval
Strimvelis	Gene restoration – adenosine deaminase enzyme	γretrovirus	HSCs autologous	EMA (2016)
Zalmoxis	Gene addition – herpes simplex thymidine kinase + NGF	retrovirus	T-cells allogeneic	EMA (2016) withdrawn 2020
Kymriah	Gene addition – CAR (CD19)	lentivirus	T-cells autologous	FDA/EMA (2017/2018)
Yescarta	Gene addition – CAR (CD19)	γretrovirus	T-cells autologous	FDA/EMA (2017/2018)
Zynteglo	Gene restoration – β-globulin protein	lentivirus	HSCs autologous	EMA (2019)
Libmeldy	Gene restoration – arylsulfatase A enzyme	lentivirus	HSCs autologous	EMA (2020)
Tecartus	Gene addition – CAR (CD19)	γretrovirus	T-cells autologous	FDA/EMA (2020)

HSCs – hematopoietic stem cells CAR – chimeric antigen receptor

cont.

Gene Therapy (EX VIVO) have hit the market …

Name	MOA	Vector	Cells	Market Approval
Breyanzi	*Gene addition – CAR (CD19)*	*lentivirus*	*T-cells autologous*	*FDA/EMA (2021/2022)*
Abecma	*Gene addition – CAR (B-cell maturation antigen)*	*lentivirus*	*T-cells autologous*	*FDA/EMA (2021)*
Skysona	*Gene restoration – adrenoleukodystrophy protein*	*lentivirus*	*HSCs autologous*	*EMA (2021)*
Carvykti	*Gene addition – CAR (B-cell maturation antigen)*	*lentivirus*	*T-cells autologous*	*FDA/EMA (2022)*

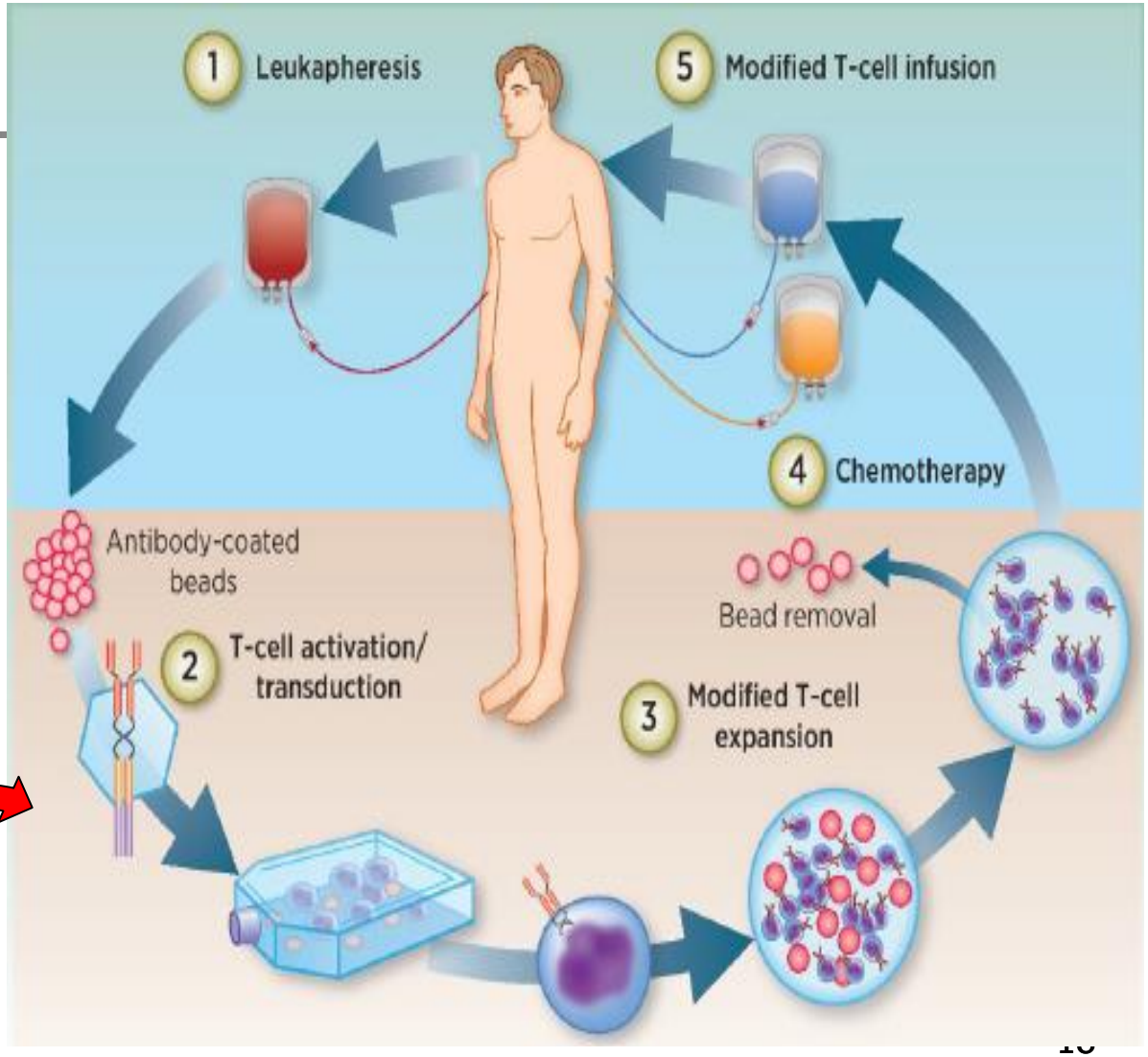
Note, ex vivo gene therapy currently relies heavily on genetically engineered lentivirus (rLV) to deliver genes into patient's cells

rLV integrates the gene (RNA) into the cell's genome

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

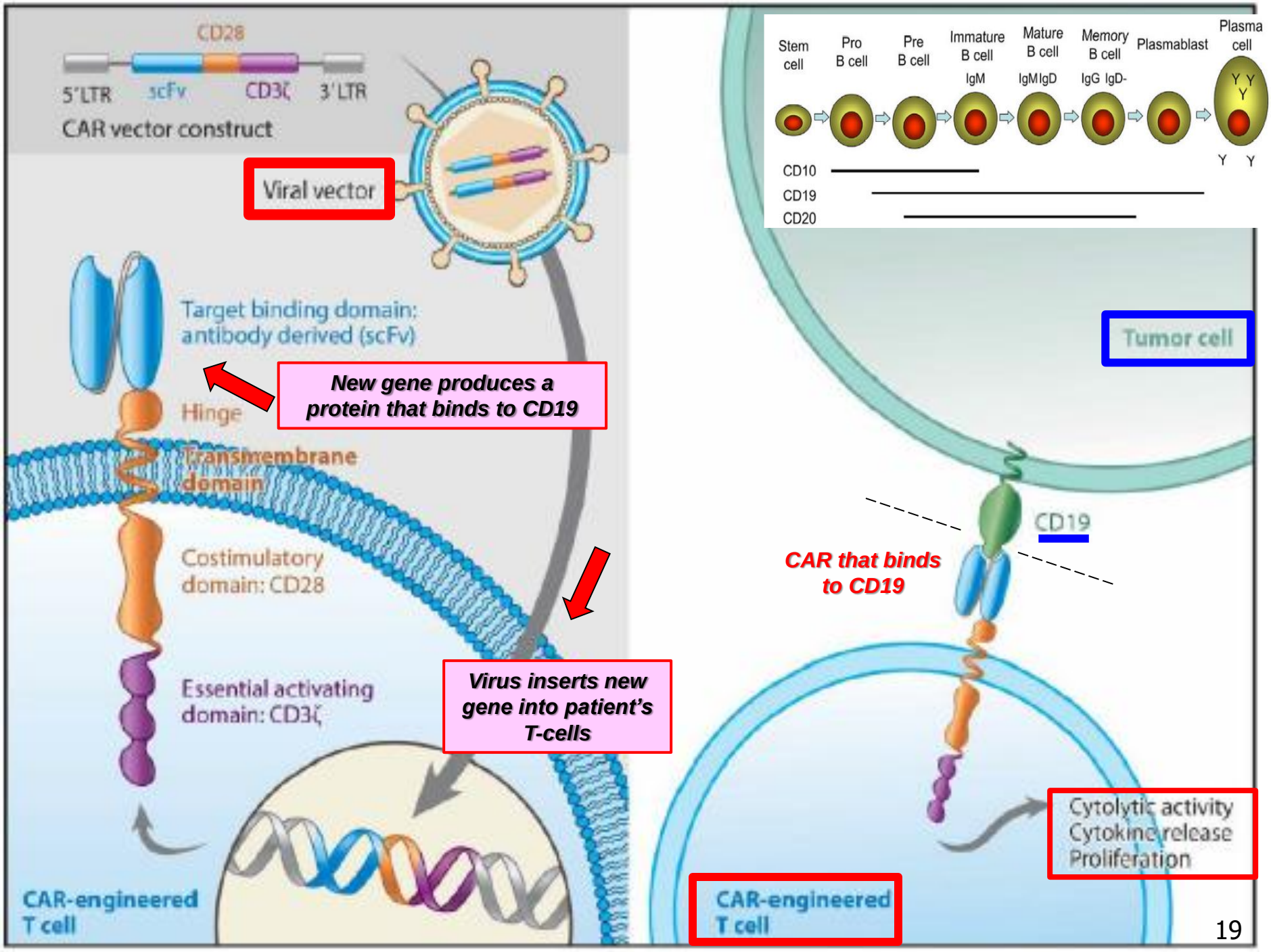
Novartis KYMRIAH
Kite YESCARTA

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



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

see next page


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

Special Note!

"GENETIC VACCINES" are not Gene Therapy Medicines

(but they follow the manufacturing and quality practices of gene therapy)

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

Reflection paper on classification of advanced therapy medicinal products

21 May 2015
EMA/CAT/600280/2010 rev.1

FDA/EMA review "genetic vaccines" as vaccines, not gene therapy products

mRNA COVID-19 Vaccines

Recombinant E. coli bioreactor production of plasmid DNA (contains COVID-19 protein RNA and RNA polymerase promoter) → ***Cell-Free Enzymatic RXN*** ***Linearized pDNA + nucleotide triphosphates + RNA polymerase; enzymatically produce mRNA*** → ***Formulate mRNA LNPs***

Moderna ***Pfizer/BioNTech***

Adenovirus COVID-19 Vaccines

Cell bioreactor production of recombinant virus (contains COVID-19 protein DNA (gene)) → ***Purify recombinant live virus*** → ***Formulate live recombinant virus***

Johnson & Johnson ***AstraZeneca/U of Oxford***

Advanced therapies are … Cellular Therapy

Advanced therapies are … Tissue-Engineered Products

(a) ***contains or consists of cells/tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered,***

FDA: 'more than minimal manipulation'

OR

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

FDA: ' not for homologous use'
'not same surgical procedure'

PLUS

(b) ***CELLS – intended function is to treat, prevent or diagnose a disease via pharmacological, immunological or metabolic action***

TISSUES – intended function is to regenerate, repair or replace a human tissue

EMA category includes the word 'somatic', which is any cell in the body other than sperm/egg

FDAs definition of 'more than minimal manipulation' is poorly explained, but EMA's definition of 'substantial manipulation' is clear

- Substantial manipulation

The cells or tissue(s) have been manipulated during the manufacturing process so that their biological characteristics, physiological functions or structural properties have been modified to be relevant for their intended function. Examples of substantial manipulations include cell expansion (culture), genetic modification of cells, differentiation/activation with growth factors.

Cell culturing leading to expansion is considered substantial manipulation. Induction of proliferation of cells during cell culture has to be regarded as changes of their biological characteristics and structural properties, either because of an immediate change in cell functionality or cell phenotype, or by increasing cell numbers to augment the desired function of the cells. Furthermore, most adherent cells, for example, are impacted by the repeated attachment and detachment cycles. It has been demonstrated that even the techniques applied for cell detachment might lead to different phenotypic changes especially on cell surface proteins (e.g. membrane receptors).

Enzymatic digestion of a tissue to release cells is also considered to be substantial manipulation, when the aim is to dissociate cell-cell contacts and the released cells are administered into patients

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification.

It should be pointed out that this list of non-substantial manipulations is non-exhaustive.

Reflection paper on classification of advanced therapy medicinal products

21 May 2015
EMA/CAT/600280/2010 rev.1

Cellular Therapy – very slowly starting to hit the market …

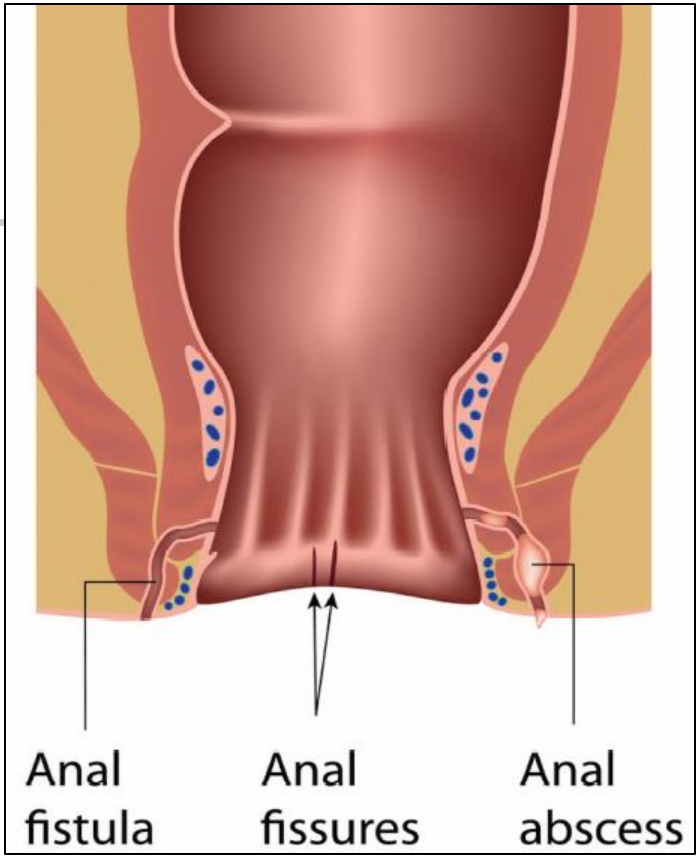
	market approved
• *Provenge (PROSTATE CANCER – intravenous infusion – autologous peripheral blood cells activated with prostatic acid phosphatase, linked to an immune cell activator rGM-CSF)*	*FDA (2010)/EMA (2013) (EMA market withdrawn 2015)*
• *Laviv (SEVERE WRINKLES – Intradermal Injection – skin biopsied expanded autologous skin fibroblast cells)*	*FDA (2011)*
• *Alofisel (PERIANAL FISTULAS – injection into fistula track tissue – liposuctioned expanded allogeneic adipose stem cells)*	*EMA (2017)*

Tissue-Engineered Products – slowly starting to hit the market …

	market approved
• *Gintuit (ORAL WOUNDS – expanded allogeneic keratinocytes and fibroblasts on a polycarbonate sheet)*	*FDA (2012)*
• *Holoclar (CORNEAL SURFACE RESTORATION – expanded autologous corneal epithelial cells containing limbal stem cells on a fibrin sheet)*	*EMA (2015)*
• *Spherox (KNEE CARTILAGE DEFECTS – expanded autologous aggregated articular cartridge cells)*	*EMA (2017)*
• *StrataGraft (THERMAL SKIN WOUNDS – expanded allogeneic keratinocytes and fibroblasts on a polycarbonate sheet)*	*FDA (2021)*
• *Rethymic (CONGENITAL ATHYMIA – expanded allogeneic thymus tissue obtained from infant cardiac surgery, implanted into the quadriceps muscle for T-cell immune restoration)*	*FDA (2021)*

Cellular Therapy (allogeneic)

EMA approved 2017 FDA (in Phase 3 clinical)

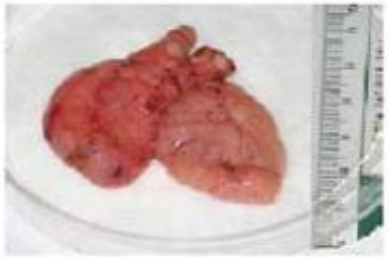


Alofisel is made up of 'mesenchymal stem cells' from the fat tissue of a donor. To make this medicine, the cells are selected and cultivated in the laboratory to increase their number. When injected into the walls of the fistula, these cells can help to reduce inflammation and support the growth of new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

ENZYVANT

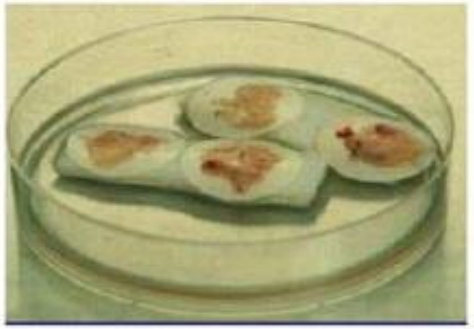
RETHYMIC® (allogeneic processed thymus tissue-agdc),

Thymus tissue is collected as waste tissue leftover from neonate/pediatric cardiac surgery



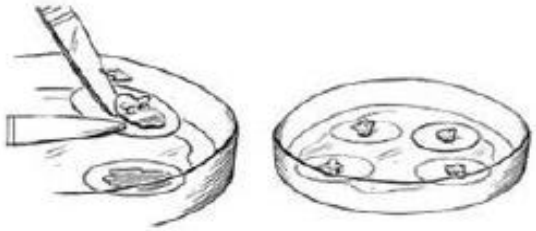
manufacturing is coordinated with availability of donor

Slice manually for culture



Culture on discs for 2 weeks in media to reduce allo T cells

Collect cultures and carry to surgical suite



Directly graft into patient

Regulatory Authority Landscape for Advanced Therapies

(EU and USA to be discussed)

European Pharmaceutical Legislation

European Parliament (only directly-elected EU body)

Final approval of pharmaceutical legislation

European Commission (EC)

Proposes new pharmaceutical legislation (regulations/directives)

Implements legislation approved by the European Parliament

Final market approval of EMA recommended medicines

European Medicines Agency (EMA)

Scientific review/evaluation of commercial medicines

Recommends approvals of medicines to EC

Committee for Advanced Therapies (CAT)

Enforcement of GMP legislation

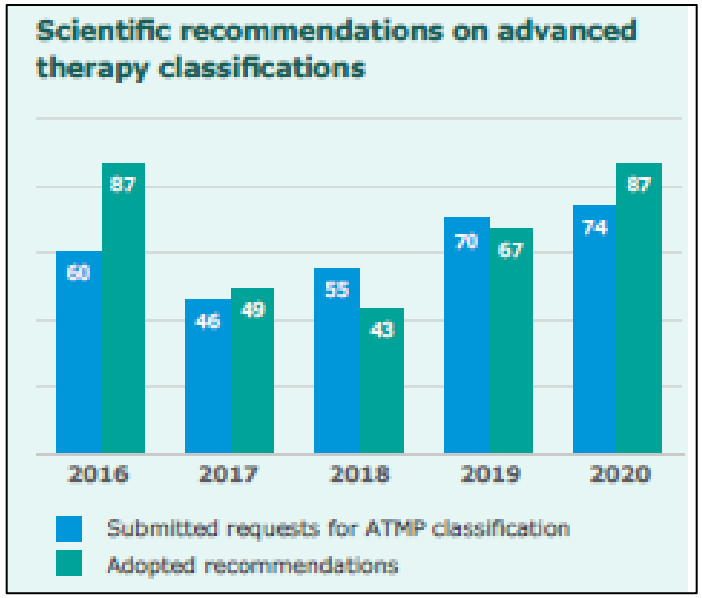
Issues guidelines

National Competent Authorities (NCAs) regulate clinical trials

Committee for Advanced Therapies (CAT)

- participates in certifying quality and non-clinical data for small and medium-sized enterprises developing ATMPs; *provide scientific certainty that ATMP development is on track*
- participates in providing scientific recommendations on the classification of ATMPs;
- contributes to scientific advice, in cooperation with the Scientific Advice Working Party (SAWP);
- takes part in any procedure delivering advice on the conduct of efficacy follow-up, pharmacovigilance or risk-management systems for ATMPs;
- advises the CHMP on any medicinal product that may require expertise in ATMPs for the evaluation of its quality, safety or efficacy;
- assists scientifically in developing any documents relating to the objectives of the Regulation on ATMPs;

https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ANNUAL REPORT 2020

Pathway to Commercialization for Medicines in EU

all medicines including ATMPs

Clinical Trial Application (CTA)

[human clinical studies]

CMC format: Investigational Medicinal Product Dossier (IMPD)

Marketing Authorisation Application (MAA)

[market approval]

CMC format: eCTD Module 3

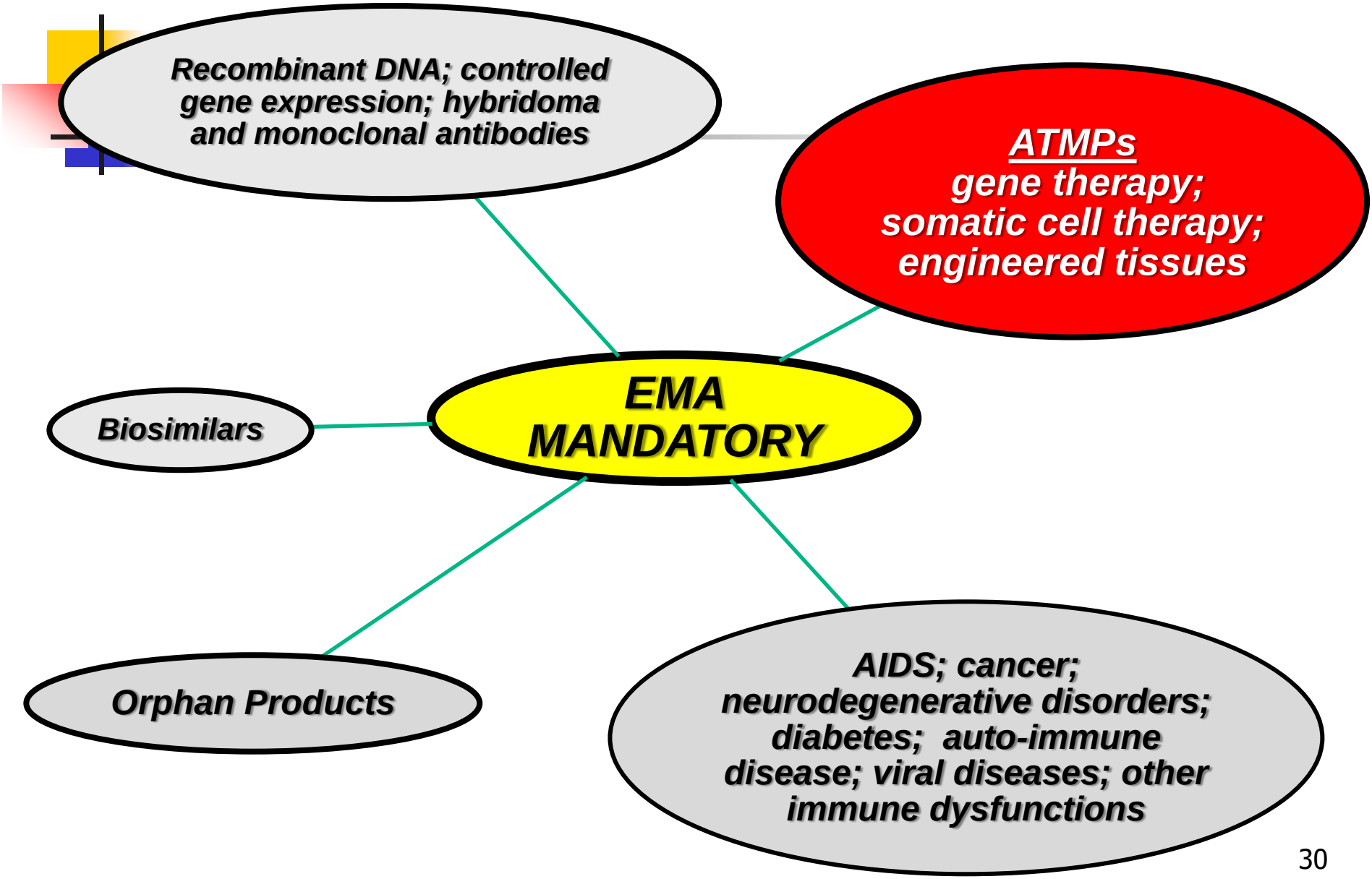
NCAs regulate
(country-by-country review)

EMA regulates
(centralized review)

Directive 2001/20/EC allows each country to choose how to implement the act

Clinical Trial Regulation (536/2014) in transition until 2023

Regulation EC 726/2004 a binding legislative act; must be uniformly applied across EU


Recombinant DNA; controlled gene expression; hybridoma and monoclonal antibodies
ATMPs
gene therapy; somatic cell therapy; engineered tissues
EMA MANDATORY
Biosimilars
Orphan Products
AIDS; cancer; neurodegenerative disorders; diabetes; auto-immune disease; viral diseases; other immune dysfunctions

EU Hospital Exemption for ATMPs

(individual patients, non-routine, limited basis, hospital setting)

The article 28 (2) of the Advanced Therapy Medicinal Products (ATMP) Regulation[1] modified the Directive 2001/83/EC[2] by adding the article 3(7), referred to as the 'hospital exemption' (HE), according to which it is permitted to use an ATMP without a marketing authorization under certain circumstances. This clause applies only to custom-made ATMPs used in a hospital setting for an individual patient. Such products must be produced at the request of a physician and should only be used within the Member State where they are produced. In addition, the approach of using the HE to treat patients with an ATMP needs to be authorized by the competent authority of the Member State and in accordance with Reg 1394/2007, should comply with the same general requirements for quality, traceability and pharmacovigilance as for authorized medicinal products.

Similar to FDA expanded access ('compassion use') provision, but in EU controlled by each country

EU GMO Legislation for Gene Therapy

(country-by country considerations)

MEDICINAL PRODUCTS FOR HUMAN USE CONTAINING OR CONSISTING OF GMOS: INTERPLAY BETWEEN THE EU LEGISLATION ON MEDICINAL PRODUCTS AND GMOS[1]

VERSION 3
October 2019

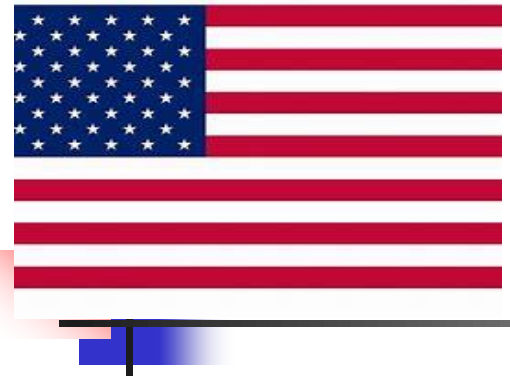
Human cells cannot proliferate in the environment as they can only survive inside the human body or under *in vitro* culture conditions. However, viruses that are used to modify the human cells are organisms that could proliferate in the environment. Therefore, investigational human cells genetically modified with viral vectors are to be regulated under the GMO legal framework focusing the assessment thereof on the viral vector.

Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified [1]

VERSION 5
November 2021

Manufacturing requirements and containment levels (BSL-1, BSL-2)
Environmental Risk Assessment (ERA)

[FDA categorical exclusion from Environmental Assessment 21 CFR 25.31]



United States Pharmaceutical Legislation

U.S. Congress
passes/amends a pharmaceutical law

Executive Branch (President → HHS → FDA)
implements the intent of a pharmaceutical law

FDA proposes regulations to enforce the law
publishes their intent in the Federal Register (FR)

much public debate;
but 'after dust settles'

FDA publishes guidances ('recommendations') to explain in greater detail how to follow the regulations

FDA publishes final regulations in the Code of Federal Regulations (CFR) Title 21

1944 Public Health Services (PHS) Act

Pathway to Commercialization for Biologicals in PHS Act

Biologic License Application (BLA) Pathway

Investigational New Drug (IND)		Biologic License Application (BLA)
21 CFR 312	→	21 CFR 600-680*
[human clinical studies]		[market approval]
FDA regulates		FDA regulates
CMC format <u>today</u>: eCTD Module 3		CMC format <u>today</u>: eCTD Module 3

*[* PHS Act is linked to FD&C Act 21 CFR 211 (cGMPs) and 21 CFR 314 (administrative procedures)]*

Biological product defined by 'specific product type'

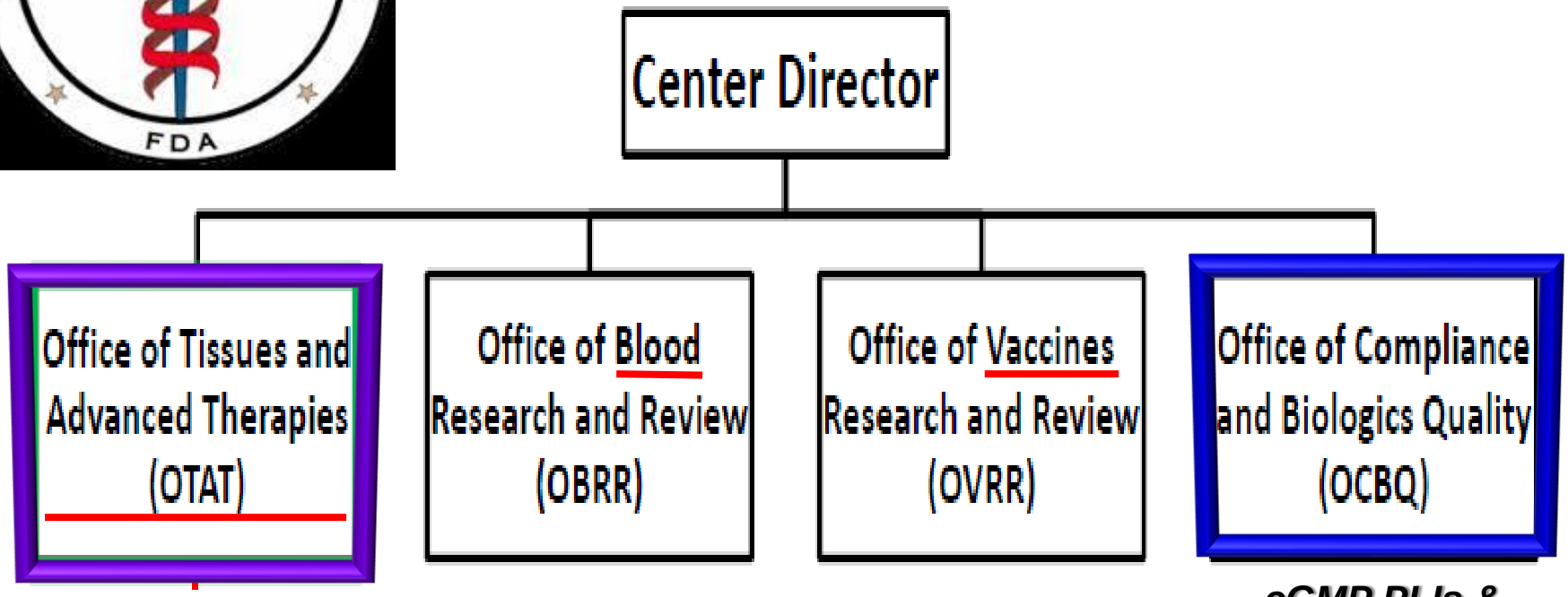
CFR changes in biological product type over time

- ***1944:** 'a virus, therapeutic serum, toxin, antitoxin or analogous product or arsphenamine'*
- ***1970 added:** 'vaccine, blood, blood component or derivative, allergenic products'*
- ***2010 added:** 'protein (except any chemically synthesized polypeptide)'*
- ***2020 changed:** 'protein ~~(except any chemically synthesized polypeptide)~~'*

So where do CGTPs fit?** **'analogous products'

Analogous = comparable in certain respects

Center for Biologics Evaluation & Research (CBER)



CMC review

cGMP PLIs & other inspections

Center for Devices & Radiological Health (CDRH)
regulates devices used with biologics, including CGTPs

PHS Act: Biologic License Application (BLA) Pathway

Three (3) Unique Requirements – Applicable to Commercial CGTPs

1) ***extra test requirement to release commercial batches***
2) ***FDA can require pre-release review of commercial batches***
3) ***FDA can add a bioqualifier to commercial INN***

1) Extra test requirement to release commercial batches

21 CFR 610.14 Identity.
The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.

a physical or chemical or biological or immunological content test – after labelling!

LEGALLY REQUIRED FOR ALL BIOLOGICALS

all rproteins/mAbs/vaccines

In Vivo Gene Therapy
Ex Vivo Gene Therapy
Cellular Therapy
Tissue-Engineered Products

Case Example (mAb)

Trogarzo (Ibalizumab-uiyk) – FDA Approval History, Letters, Reviews and Related Documents – Administrative and Correspondence Documents – Meeting Minutes Mid-Cycle Communication (August 18, 2017)

The BLA submission does not contain information regarding identity testing of labeled ibalizumab drug product vials. 21 CFR 610.14 requires that identity testing be performed on each filled DP lot after all labeling operations have been completed. The identity test method for the labeled drug product should be appropriately validated for its intended use. Update your BLA with the following information:

- a description of the identity test method for the labelled drug product
- appropriate method validation, or if applicable, method transfer data
- revise FDA-356h form to include testing facility information
- revise Section 3.2.P.3.1 of Module 3 to include the testing facility information.

Note: not a FD&C Act requirement

Note: not an EMA requirement

2) FDA can require pre-release review of commercial batches

§ 610.2 Requests for samples and protocols; official release.

(a) *Licensed biological products regulated by CBER*. Samples of any lot of any licensed product together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Center for Biologics Evaluation and Research (see mailing addresses in § 600.2 of this chapter). Upon notification by the Director, Center for Biologics Evaluation and Research, a manufacturer shall not distribute a lot of a product until the lot is released by the Director, Center for Biologics Evaluation and Research:

(not a FD&C Act requirement)

Varies by biological product type →

FDA pre-release of Commercial In Vivo Gene Therapy required for all!

LUXTURNA (voretigene neparvovec-rzyl) **December 19, 2017**

You are required to submit lot release protocols for future lots of voretigene neparvovec-rzyl to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

ZOLGENSMA® (onasemnogene abeparvovec-xioi) May 24, 2019

Please submit protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

as stated in CBER market approval letters

(not an EMA requirement)

FDA team internal discussion on why pre-release

ZOLGENSMA TEAM MEETING SUMMARY

In vivo gene therapy – AAV virus

Application number: 125694/0 **Meeting date & time:** April 10, 2019

Product name: onasemnogene abeparvovec-xioi

Andrew Byrnes explained DCGT's preference for quarterly surveillance instead of lot release due to the large number of lots (approximately 1 per week) and the risk to commercial supply that could be caused by delays in release. Andrew explained that given the relatively short shelf life (effectively only 8 months), routine lot release could delay distribution of the product.

Jay Eltermann expressed that all products are subject to lot release, but case by case exemptions have been granted, e.g., CAR-T cells. Jay explained that this product has attributes that support the need for routine lot release - it is not a patient specific product, it is a novel product from a manufacturer with little experience, and there appear to be testing issues. It therefore cannot be under surveillance. AveXis will need to establish an acceptable lot release history (longer than 5 years), accumulate stability data, and demonstrate the manufacturing process is well controlled before submitting a supplement to request surveillance as an alternative to routine lot release.

Maryna Eichelberger explained that lot release would give CBER confidence with the product, and regardless if the protocols are electronic or paper, they come to DPMQ/PRB. They are reviewed by the Product Office (PO) and DBSQC reviewers. Paper protocols are physically routed to sequential reviewers and therefore if paper protocols are submitted, it could delay the release. AveXis could send electronic protocols after BLA approval. The Testing Plan (TP), a CBER internal document, determines the LRS routing. There are no PDUFA time lines for lot release. However, the Lot Release Branch (LRB) is committed to releasing lots within 30 business days of protocol receipt. Jay mentioned that LRS captures tests which are released, but no test data is captured in LRS.

FDA pre-release of Commercial Ex Vivo Gene Therapy & Cellular Therapy & Tissue-Engineered Products

waived on a case-by-case basis!

typically single patient batches

TECARTUS™ (brexucabtagene autoleucel) July 24, 2020

You are not currently required to submit samples or protocols of future lots of brexucabtagene autoleucel to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

RETHYMIC (Allogeneic processed thymus tissue–agdc) October 8, 2021

You are not currently required to submit samples or protocols of future lots of allogeneic processed thymus tissue-agdc to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

as stated in CBER market approval letters

3) FDA can add a bioqualifier to the commercial INN

World Health Organization

INN – international nonproprietary name – assigned by WHO

each INN is a unique name assigned to an active pharmaceutical ingredient (API)

BIOLOGICAL BIOQUALIFIER – a FDA-designated suffix (4 lowercase letters)

This guidance describes FDA's current thinking on the need for biological products licensed under the Public Health Service Act (PHS Act) to bear a *nonproprietary name*[2] that includes an FDA-designated suffix. Under this naming convention, the nonproprietary name designated for each *originator biological product*, *related biological product*, and *biosimilar product* will be a proper name that is a combination of the *core name* and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters.[3] The suffix format described in this guidance is applicable to originator biological products, related biological products, and biosimilar products previously licensed and newly licensed under section 351(a) or 351(k) of the PHS Act.

Nonproprietary Naming of Biological Products **January 2017**

An applicant should propose a suffix composed of four lowercase letters for use as the distinguishing identifier included in the proper name designated by FDA at the time of licensure (see section VI of this guidance). Such submissions can be made during the investigational new drug application (IND) phase[16] or at the time of BLA submission. An applicant should submit up to 10 proposed suffixes, as described in this section, in the order of the applicant's preference.

FDA	EMA
Zolgensma (in vivo gene therapy virus)	
onasemnogene abeparvovec-xioi	***onasemnogene abeparvovec***
Abecma (ex vivo gene therapy cells)	
idecabtagene vicleucel	***idecabtagene vicleucel***
(cellular therapy)	
Stratagraft (tissue-engineered product)	
allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat	

***not** applied to chemical drugs or generics*

***always** applied to recombinant proteins and monoclonal antibodies*

***not** applied by EMA*

CONFUSED YET!

- ATMP
- Directive Regulation
- EMA CAT
- substantial manipulation
- not same essential function
- CGTP
- FD&C Act PHS Act
- CBER OTAT
- more than minimal manipulation
- not for homologous use

- pre-release lot-by-lot or not
- bioqualifiers or not

QUESTIONS??

Course Outline

2. Advanced Therapy Product GMP and Quality Risk Consequences

- ***Adapting knowledge from established regulatory guidances and experiences (e.g., mAbs, recombinant viral vaccines, etc.)***
- ***What minefields might occur if improperly adapted***

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

Patients cannot check the quality of their medicines

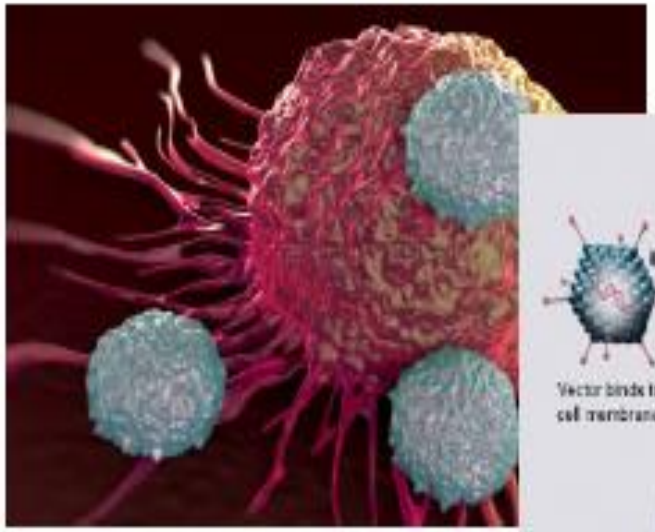
Patients therefore are dependent upon an effective GMP & Quality System!
(facility, process, staff, product – "all doing what is right")

Unsafe or poor quality medicines can harm patients

The Regulatory Authority Challenge

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

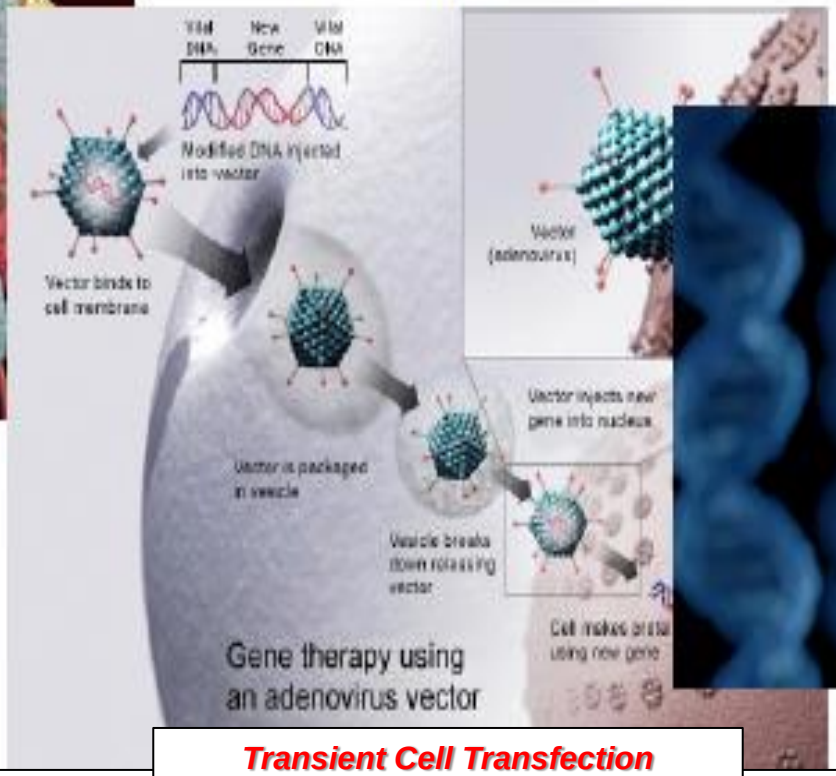
Cell-based Therapeutics



Stem Cells
T-Cells

Autologous
Allogeneic

Gene Therapy Products



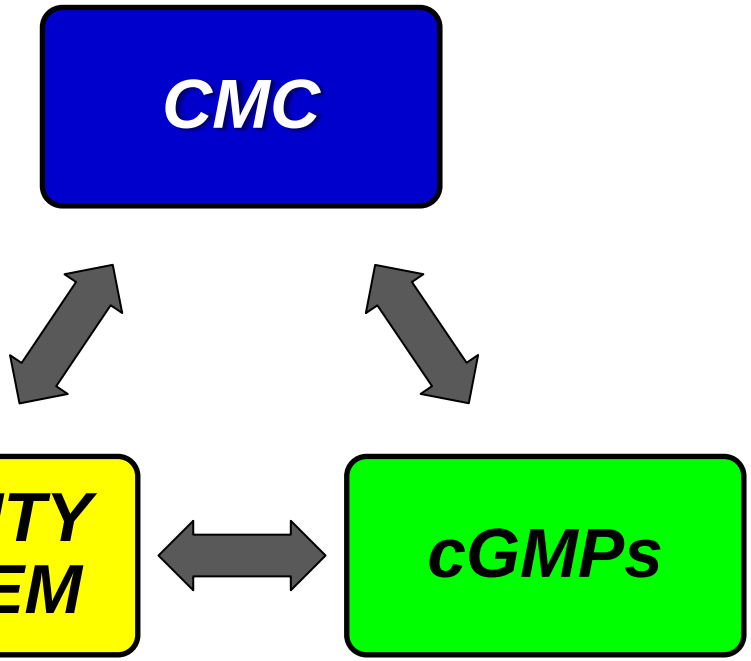
Transient Cell Transfection
Transient Cell Transduction
Virus Producer Cells
mRNA LNPs
Electroporation

Gene Editing

CRISPR-Cas
TALEN

3 interactive components to protect patients

Regulatory authority criteria to be met by Manufacturing & Quality 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

CMC

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

Applies to all medicines seeking market approval

Manufacturing Process Control & Product Quality	
Drug Substance (DS, API)	**Drug Product (DP)**
Manufacturer	Manufacturer
Manufacturing Process Definition	Manufacturing Process Definition
Manufacturing Process Control	Manufacturing Process Control
Source Material	Excipients
Characterization of Product	Formulation
Release of DS Product	Release of DP Product
Stability of DS Product	Stability of DP Product
Adventitious Agent Control (TSE, Virus, Mycoplasma, Microbial)	

(increasing knowledge and understanding of the manufacturing process and the product over time while in clinical development)

THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: QUALITY

QUALITY OVERALL SUMMARY OF MODULE 2

MODULE 3 : QUALITY

ICH M4Q(R1)

EMA CMC Regulatory Guidances for ATMPs

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

PIC/S

- *Guide to Good Manufacturing Practice for Medicinal Products Annexes – Annex 2A ATMPs (2022)*

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

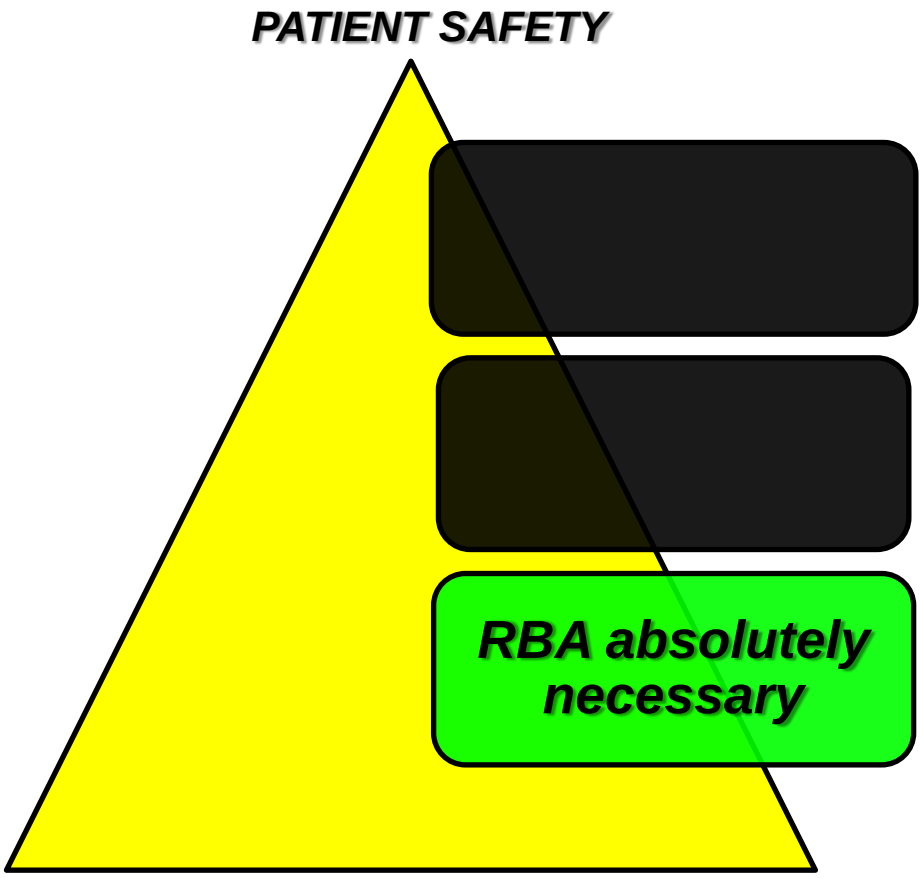
FDA CMC Regulatory Guidances for CGTPs

- ***Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (IND) (2008)***
- ***Guidance for Industry: CGMP for Phase 1 Investigational Drugs (2008)***
- ***Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (2011)***
- ***Guidance for Industry: Recommendations for Microbial Vectors Used for Gene Therapy (2016)***
- ***Guidance for Industry: Evaluation of Devices Used with Regenerative Medicine Advanced Therapies (2019)***
- ***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: Chemistry, Manufacturing & Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (2020)***
- ***Guidance for Industry: Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial (2021)***
- ***Guidance for Industry: Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations (2021)***
- ***Guidance for Industry: Chemistry, Manufacturing and Controls Changes to an Approved Application – Certain Biological Products (2021)***
- ***Guidance for Industry (draft): Human Gene Therapy Products Incorporating Human Genome Editing (2022)***
- ***Guidance for Industry (draft): Considerations for the Development of Chimeric Antigen Receptor 1 (CAR) T Cell Products (2022)***

CMC

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

Risk-Based Approach (RBA)



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

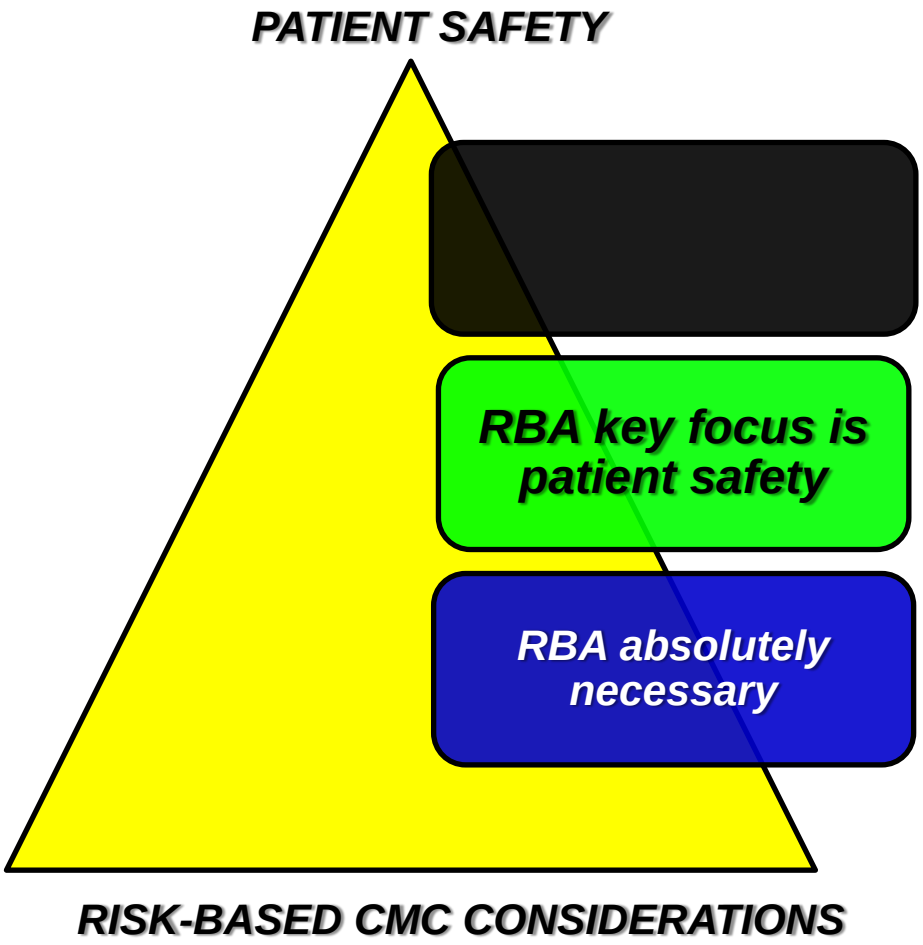
2.13. The risk-based approach ("RBA") is applicable to all type of ATMPS. It applies in an equal fashion to all type of settings. The quality, safety and efficacy attributes of the ATMPs and compliance with GMP should be ensured for all ATMPs, regardless of whether they are developed in a hospital, academic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

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

CMC

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

Risk-Based Approach (RBA)



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.

EUROPEAN MEDICINES AGENCY

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

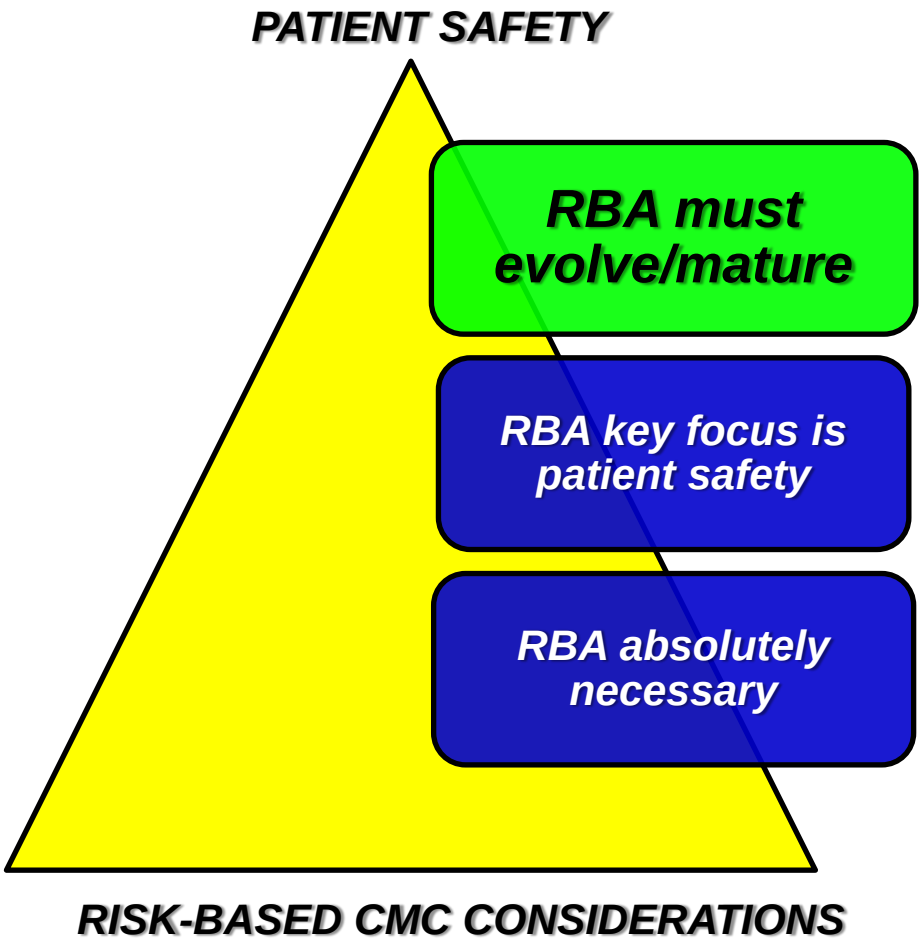
31 January 2019
EMA/CAT/852602/2018

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

CMC

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

Risk-Based Approach (RBA)



The risk-base approach must evolve/mature!

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

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

Risk-Based Approach to manage the "MINIMUM CMC regulatory compliance CONTINUUM"

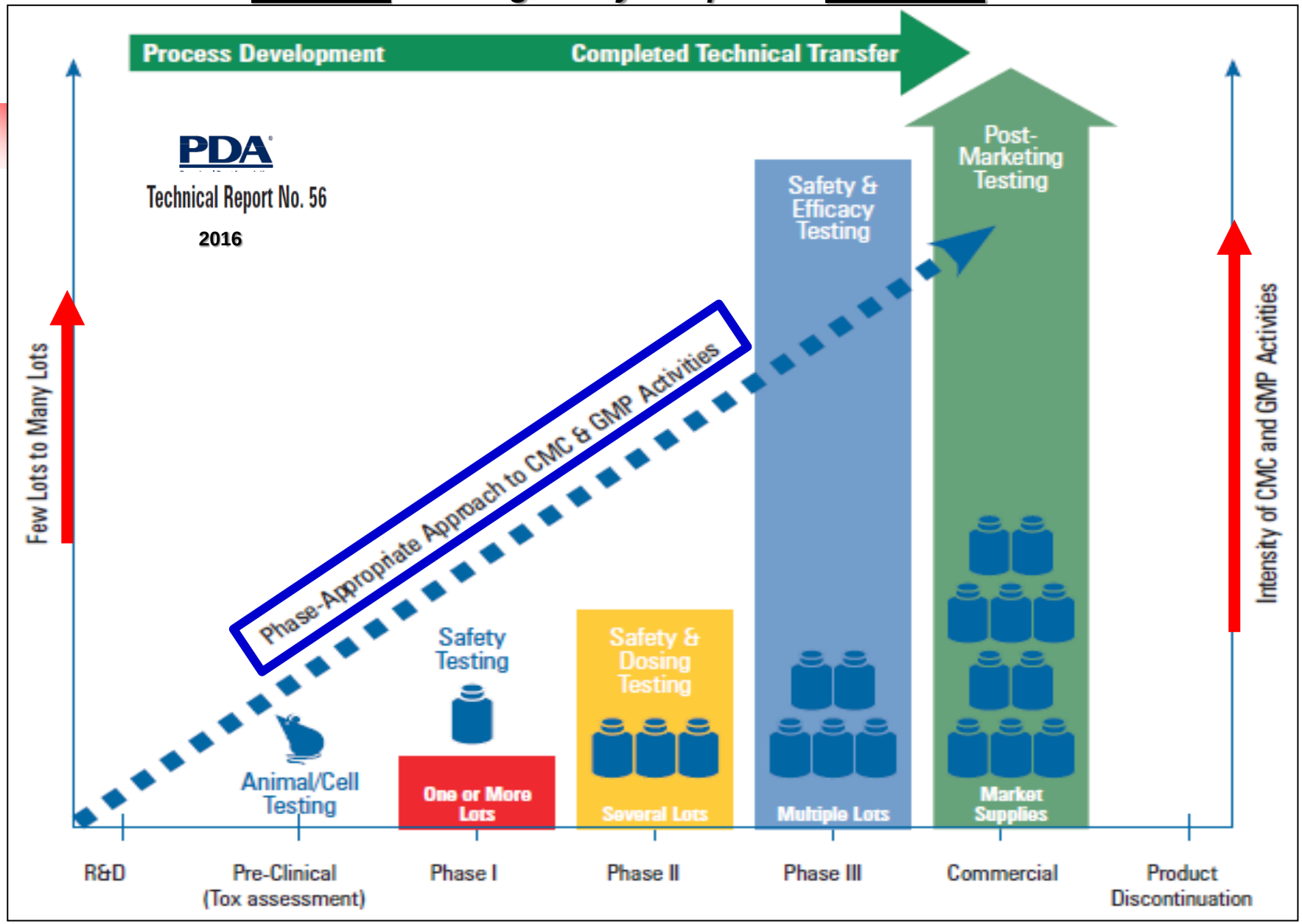
"minimum" – the threshold of CMC regulatory compliance that must be achieved – cannot go below

"continuum" – that threshold of CMC regulatory compliance keeps rising as clinical development advances

- ***Early clinical stage focus → product safety for patient***
- ***Later clinical stage focus → product safety for patient***
  + manufacturing process consistency to achieve the necessary quality biologic product

***APPLIED* across the pharmaceutical industry**

'minimum CMC regulatory compliance continuum'



***ACKNOWLEDGED* by regulatory authorities for CGTPs**

'minimum CMC regulatory compliance continuum'

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**
EUROPEAN MEDICINES AGENCY	Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials	31 January 2019 EMA/CAT/852602/2018
U.S. FOOD & DRUG ADMINISTRATION	**Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products**	**Food and Drug Administration** **Center for Biologics Evaluation and Research** **March 2022**

'minimum CMC regulatory compliance continuum' — *acknowledged by regulatory authorities*

IND/IMPD CMC Section		FDA GTs	EMA ATMPs
S.2.2 P.3.3	Description of Manufacturing Process	We acknowledge that information on process controls may be limited early in development and recommend that sponsors provide additional information and updates as product development proceeds.	During development, as process knowledge is gained, further details of in-process testing should be provided and acceptance criteria reviewed. As development proceeds, manufacturing consistency needs to be demonstrated.
S.2.4 P.3.4	Control of Critical Steps	The Agency acknowledges that this information may be limited in the early phases of development and recommends that sponsors provide additional information and updates as product development proceeds.	Critical steps in the manufacturing process should be identified as appropriate for the stage of development and all available data and acceptance criteria should be provided. It is acknowledged that due to limited data at an early stage of development complete information may not be available.
S.2.5 P.3.5	Process Validation	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.	Process characterisation/evaluation data should be collected throughout the development.

'minimum CMC regulatory compliance continuum' ***acknowledged by regulatory authorities***

IND/IMPD CMC Section		FDA GTs	EMA ATMPs
S.4.1 P.5.1	Specification	For products in the early stages of clinical development, very few specifications are finalized, and some tests may still be under development.	During early phases of clinical development specification can include wider acceptance criteria based on the current knowledge of the risks. As the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature preliminary and need to be subject to review during development.
S.4.3 P.5.3	Validation of Analytical Procedures	Validation of analytical procedures is usually not required for original IND submissions for Phase 1 studies; however, you should demonstrate that test methods are appropriately controlled.	Validation of analytical procedures during clinical development is an evolving process. An appropriate degree of method qualification should be applied at each stage to demonstrate the methods are suitable for their intended use at that time.

'minimum CMC regulatory compliance continuum' — *acknowledged by regulatory authorities*

IND/IMPD CMC Section		FDA GTs	EMA ATMPs
S.4.5 P.5.6	Justification of Specification	We recognize that acceptance criteria may be adjusted throughout the product development stages, based on both manufacturing and clinical experience. For early stage clinical studies, assays used to characterize production lots may be more variable than those used in later phase investigations.	It is acknowledged that during early clinical development when there is only limited experience, the acceptance criteria may be wide. Further refinement is expected as knowledge increases and data become available.
P.2	Pharmaceutical Development	The Agency acknowledges that this information may be limited in the early phases of development and recommends that sponsors provide additional information and updates as product development proceeds.	For early development there may be only limited information to include in this section.
S.7 P.8	Stability	Please note that stability studies may evolve with product development, …	The increase of available data and improved knowledge about the stability of the active substance will need to be demonstrated during the different phases of clinical development.

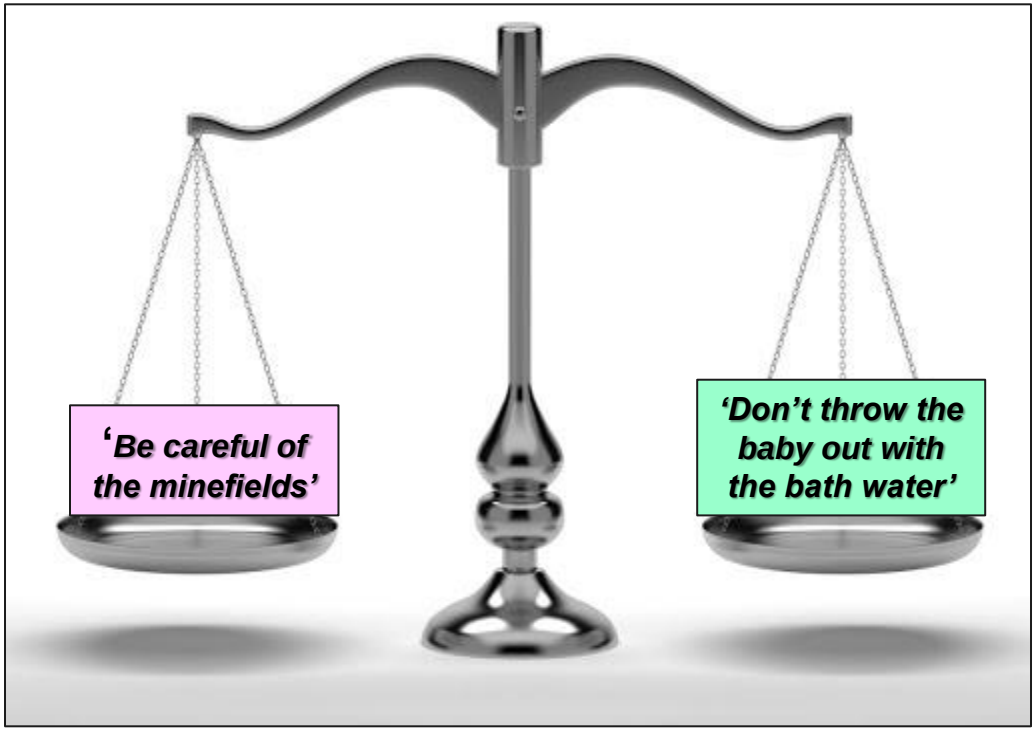
FDA on 'Minimum CMC Regulatory Compliance Continuum'

CAR T-Cell Manufacturing

The emphasis for CMC in all phases of development is product safety and manufacturing control. We recommend that CAR T cells be developed following a life cycle approach where information may be gathered over the course of product development and submitted in a stage-appropriate manner. The amount of CMC information to be submitted in your IND depends on the phase and the scope of the clinical investigation proposed (21 CFR 312.23(a)(7)). Therefore, you may not need to complete all CTD sections in your original IND submission. Similarly, CAR T cells and vectors are to be manufactured under Good Manufacturing Practice (GMP) conditions that are appropriate for the stage of development (section 501(a) (2) (B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 351(a)(2)(B)) (see also Ref. 17). Additional CMC information may be needed to align product development with the clinical development, especially when the latter is rapidly progressing under an expedited development program.

For CAR T cells in the early stages of clinical development, very few specifications are finalized, and some tests may still be under development (section V.A.4.a of the GT CMC Guidance (Ref. 3)). Cellular characterization data collected during early studies can inform release criteria used in later development to ensure product and process consistency. Thus, characterization studies are crucial to support product development and comparability assessments. For studies in which a primary objective is to gather meaningful data about product efficacy, we recommend that acceptance criteria be refined to ensure batches are well-defined and consistently manufactured.

Lessons Learned from Across the Biological Industry



CMC Does Not Apply Equally
across the different biological product types!

Many CMC regulatory compliance similarities across the biological industry …

Recombinant Proteins/mAbs		Gene & Cellular Therapy
Development Genetics	Genetic engineering of genes	Development Genetics
Starting Material	Cell bank preparation and maintenance	Starting Material
Cell Expansion	adherent/suspension cells	Cell Expansion
DS → DP	Formulation; filling into container closure	DS → DP

… but, extra CMC regulatory compliance challenges for ATMPs

"The Process is the Product"

For Chemical Drugs

the synthesized chemical drug can be uncoupled from the manufacturing process
(i.e., different pathways to a chemical generic provided quality is maintained)

large manufactured batch sizes – many patients

For Recombinant Proteins/mAbs

the biosynthesized biologic can be slightly uncoupled from the manufacturing process
(i.e., slightly different pathways to a biosimilar provided quality is highly similar)

large manufactured batch sizes – many patients

For CGTPs

the biosynthesized biologic is linked to the manufacturing process
(i.e., the process controls the quality of the biologic product)

small manufactured batch sizes – many times patient-specific

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

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

water resistant vs waterproof

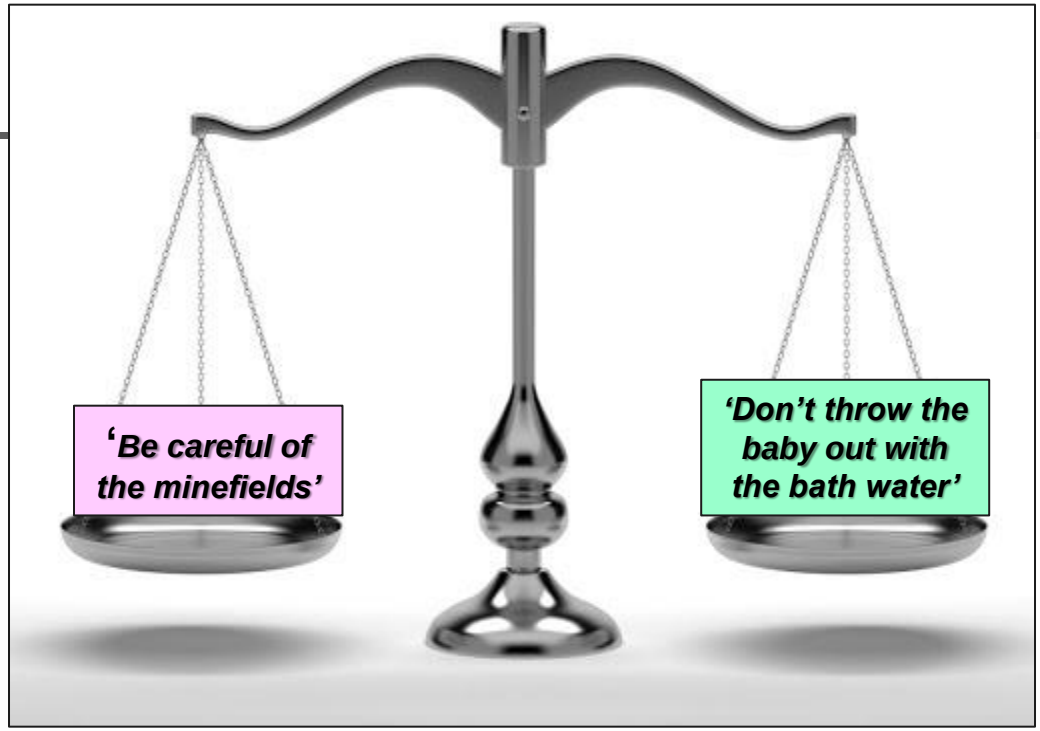
QUESTIONS??

Course Outline

3. Regulatory Authority Expectations During Clinical Development

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

Lessons Learned from Across the Biological Industry



cGMP and Quality System <u>Applies Equally</u> across the different biological product types!

Quality Unit Oversight; auditing, deviation handling, CAPA, documentation (SOPs, PBRs, QC records); training

cGMPs and Quality System must be in place from FIH!

1.1. Scope

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

… and, cGMPs and Quality System must increase in 'adequate and appropriate control' over clinical development!

- ***Facility***
- ***Process Equipment***
- ***Aseptic Processing***
- ***Process Design → Process Validation***
- ***Quality Unit***
- ***Training***

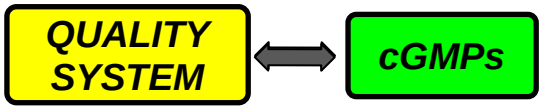
risk-based continuum of increased control

"investigational ATMPs" used over 50 times

QUALITY SYSTEM ⟷ cGMPs

risk-based acknowledged by regulatory authorities

Guidance		Level of GMP Manufacturing Process Control & Maturity of the Quality System for INVESTIGATIONAL ATMPs
2.12	Why flexibility is needed for GMPs	It follows that, in laying down the GMP requirements applicable to ATMPs, it is necessary to recognise a certain level of flexibility …. This is particularly important in the case of investigational ATMPs, especially in early phases of clinical trials (phase I and phase I/II), due to the often incomplete knowledge about the product (e.g. potency) as well as the evolving nature of the routines (in order to adjust the manufacturing process to the increased knowledge of the product).
2.20	Why GMPs are Necessary	The application of GMP to investigational ATMPs is intended to protect the clinical trial subjects and it is also important for the reliability of the results of the clinical trial …
2.21 2.22	Quality System	It is important to ensure that data obtained from the early phases of a clinical trial can be used in subsequent phases of development. Therefore, a functional quality system should be in place for the manufacturing of investigational ATMPs. The quality and safety of the product needs to be ensured from the first stages of development. Nevertheless, it is acknowledged that there is a gradual increase in the knowledge of the product and that the level of effort in the design and implementation of the strategy to ensure quality will step up gradually.
2.51	Facilities & Equipment Control	In early phases of clinical research (clinical trial phases I and I/II) when the manufacturing activity is very low, calibration, maintenance activities, inspection or checking of facilities and equipment should be performed at appropriate intervals, which may be based on a risk-analysis. The suitability for use of all equipment should be verified before it is used.



risk-based acknowledged by regulatory authorities

Guidance		Level of cGMP Manufacturing Process Control & Maturity of the Quality System for INVESTIGATIONAL ATMPs
2.52	Documentation	The level of formality and detail for the documentation can be adapted to the stage of development. The traceability requirements should however be implemented in full.
6.32	Retention of Documents	For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used.
9.11	Controls for Manufacturing Process	In case of investigational ATMPs, the knowledge and understanding of the product may be limited, particularly for early phases of clinical trials (phase I and I/II). It is therefore acknowledged that the manufacturing process (including quality controls) may need to be adapted as the knowledge of the process increases. In the early phases of development, it is critical to carefully control and document the manufacturing process. It is expected that the manufacturing process and quality controls become more refined as development progresses.
10.14	Air Quality System	For investigational ATMPs, it is expected that at least the suitability of the air quality system (in accordance with ISO 14644-1 and ISO 14664-2) and the suitability of the premises to adequately control the risk of microbial and nonviable particle contamination is verified.
10.35	Cleaning Validation	For investigational ATMPs, cleaning verification is acceptable. In such cases, there should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.

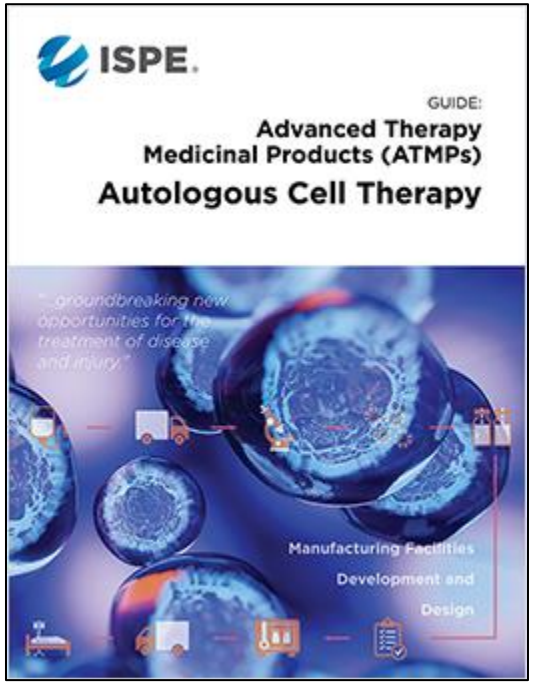
4. Premises

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***
- ***Cleaning, maintenance and repair programs***
- ***Lighting, temperature, humidity, ventilation controls***
- ***Room cleanliness classification***
- ***Environmental monitoring (air pressure differentials; viable/non-viable air; viable surface/personnel, etc.)***
- ***Pest control***
- ***Prevention of entry of unauthorized personnel***
- ***Restrictions on what operations are allowed in facility***



Nov 2021

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***
- ***Non-reactive product-contact surfaces***
- ***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***

Aseptic Processing Simulation Mandatory

FIH and through all clinical development – proper training & confirmation

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

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products
22.11.2017

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

EUROPEAN MEDICINES AGENCY

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

31 January 2019
EMA/CAT/852602/2018

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

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

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

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

Process Equipment of the FUTURE for Gene Therapy Cell and Cellular Therapy Processes

Manufacturing Major Desires

- ***More closed operational steps** – less open transfer steps*
- ***Increased automation** – less manual human manipulations*
- ***Parallel manufacturing in same room** – Point of Care (POC)*

the future

Lonza video


LONZA – COCOON 4 min

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.

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

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.

Trained personnel a necessity!

3.1. General principles

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

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

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products

3 training 'Rights' for GMP personnel

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

3.2. Training

4 areas

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. 1

3.13. There should be appropriate (and periodic) training in the requirements specific to the manufacturing, testing, and traceability of the product. 2

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

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. 4 Personnel handling genetically modified organisms ("GMOs") require additional training to prevent cross-contamination risks and potential environmental impacts.

The challenge of finding experienced personnel!

On-the-Job training becomes critical!

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

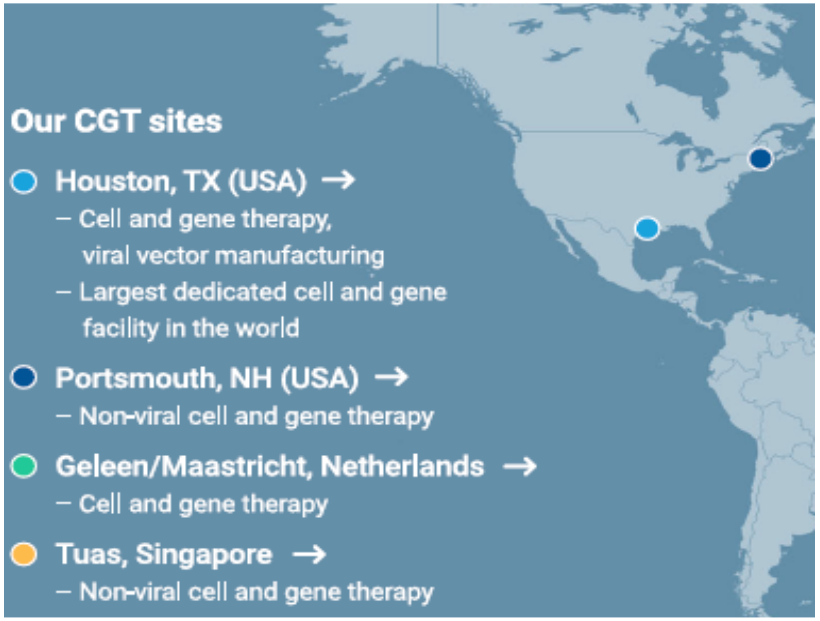
PwC Health Research Institute

Beyond the hype

September 2019

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

Lonza ~100 positions advertised (March 2022)



Take CMC, cGMP and Quality Systems seriously!

Patients must always be protected

ERA The Netherlands B.V.

Manufacturer for cellular therapy – MAA filed

GMP non-compliance – suspension of manufacturing

Emergent BioSolutions

BDS manufacturer for genetically engineered viruses for COVID vaccine

GMP non-compliance – suspension of multiproduct facility manufacturing

June 2020 filed MAA for Cellular Therapy triggering inspection Feb 2021

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

The competent authority of Netherlands confirms the following:

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

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

STATEMENT OF NON-COMPLIANCE WITH GMP

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

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

(still on suspension Jan 2022)

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

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

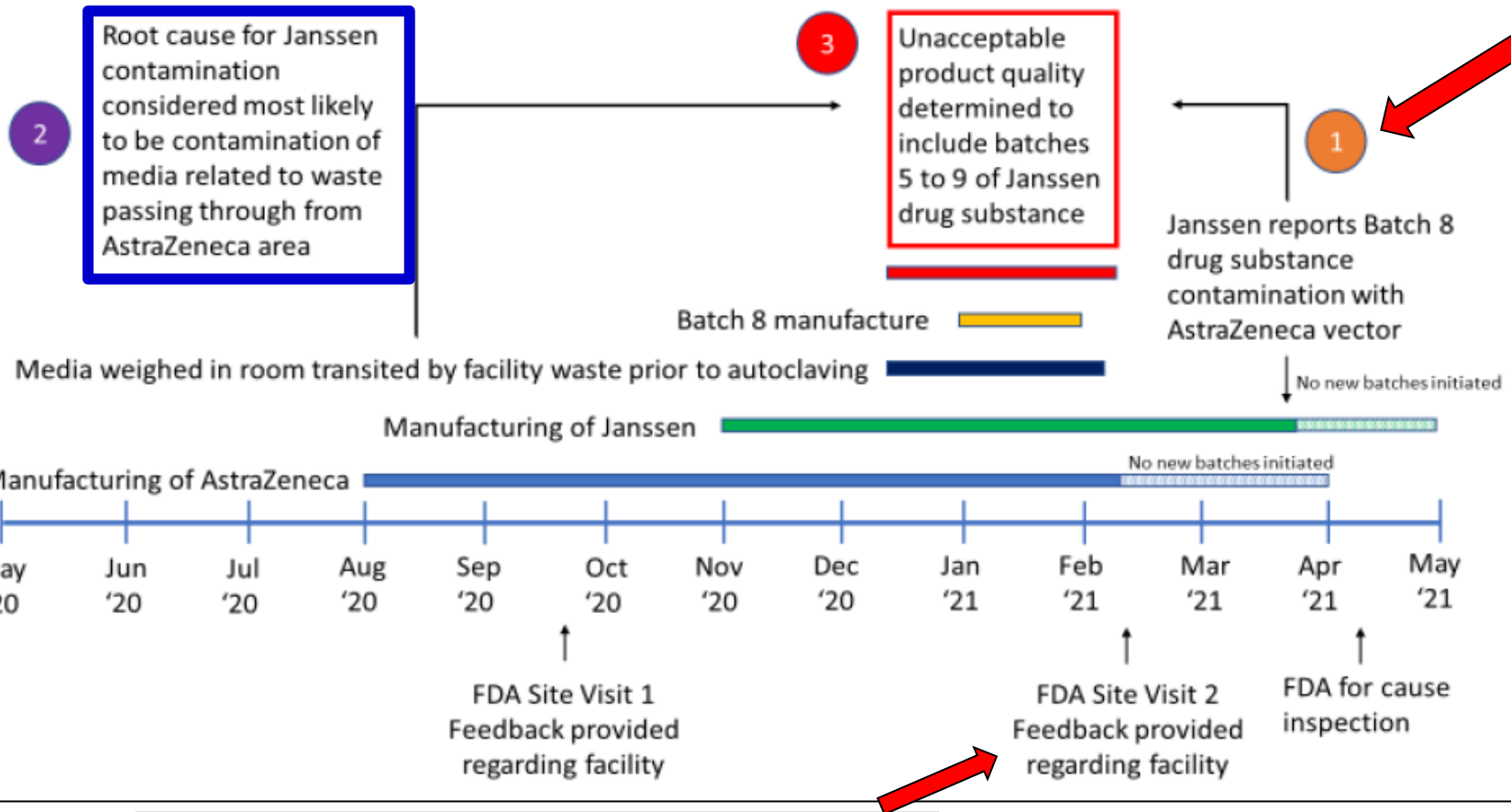
Gliovac – cancer cells and other tumoral components freshly collected from the patient(s) tissue)

How bad can it get …

J&J – human adenovirus
AZ – chimpanzee adenovirus

FDA tells J&J to scrap 60 million vaccine doses made at troubled plant

Figure 1: Timeline Related to Batches GMP 5 through 9



FDA Feb 2021 – GMP flags – many new hires, changing procedures, not following GMPs

Risk-Based Approach Applied by the Industry: ICH

not mandatory, but highly recommended ('expected') – <u>including ATMPs!</u>

ICH harmonisation for better health

ICH Q8(R2) Quality by Design (QbD) 2006

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.

How important are the Process Development and Analytical Development groups in the development of the nucleic acid-based pharmaceuticals?

Cell line development → transgene selection/modification
Cell culture optimization → transfection/transduction of transgene
Process purification design → residual process impurity reduction
Characterization of the transduced patient's cells → functionality/therapeutic activity

<u>Does Development fully understand</u> that what they do impacts successful entry into clinical development and/or successful market approval?

ICH Q9 Quality Risk Management (QRM) 2006

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 Q9 (R1) at step 2 (2022)

mitigation/control of risks that could impact the development of the CGTP

QRM ***project management tools***	***QRM*** ***statistical analysis tools***
Risk Ranking and Filtering (RRF) ***Failure Mode Effects Analysis (FMEA)*** ***Preliminary Hazard Analysis (PHA)***	***Control Charts (Shewhart)*** ***Process Capability Analysis (Cpk)*** ***Design of Experiments (DOE)***

QbD, QRM – not mandatory, but expected!

proven invaluable across the entire biological manufacturing field

Quality by Design (QbD) elements

Quality Risk Management (QRM) tools for prioritization

QTPP • Quality Target Product Profile

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

(why the product is so great; why you should invest in the company)

↓ **(changeable by executive management)**

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.

(direction on what needs to be done to achieve the TPP for the company)

The QTPP is the target to be shared across all team disciplines

(Development, QC, QA, Manufacturing, RA)

QbD/QRM - the language of communicating with regulatory authorities

during clinical development

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

CQA

CPP

EUROPEAN MEDICINES AGENCY

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31 January 2019
EMA/CAT/852602/2018

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

CQA

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

QbD/QRM - the language of communicating with regulatory authorities

for market approval (ex vivo gene therapy)

Abecma

Idecabtagene vicleucel (ide-cel) is a gene therapy product consisting of modified autologous T cells transduced with an anti-BCMA02 chimeric antigen receptor (CAR) lentiviral vector (LVV). The

Lentiviral Vector (LVV Starting Material)

An evaluation of product quality attributes for LVV was conducted following quality risk management principles. LVV quality attributes are categorised as CQAs and non-CQAs based on the predicted severity of impact to patient safety and finished product efficacy. The determination of quality attributes seems reasonable. — **CQA**

The single steps of the LVV manufacturing process are sufficiently described. Acceptable ranges/action limits are defined for critical process parameters (CPPs) and in-process controls (IPCs) and listed for each unit operation. In addition to action limits and acceptance criteria, ongoing process verification (OPV) establishes and assesses internal control limits for process monitoring across multiple lots indicating that the manufacturing process is performing in a state of control. The OPV programme is — **CPP**

The overall control strategy including in-process controls and testing of starting materials is adequate to control the process resulting in an LVV of consistent quality. — **CS**

Transduced Cells

Critical quality attributes were identified according to ICH Q8, Q9, and Q10 utilising a risk-based approach to assess and categorise product quality attributes. Justifications for each attribute's designation are provided. — **CQA**

Performance parameters for ide-cel manufacturing are classified as critical process parameter (CPP) or non-critical process parameter (nCPP) and are evaluated as controllable within PARs. — **CPP**

CQA • Critical Quality Attributes

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

impact on patient safety ↕ **(changeable, not static, as scientific understanding about the product increases)**

ICH Q8(R2)

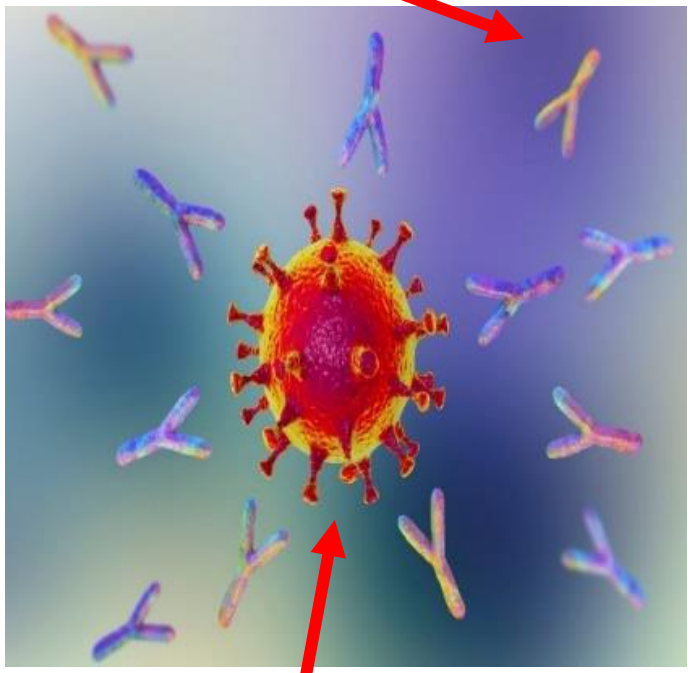
> **Critical Quality Attribute (CQA):**
>
> A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

CQAs commonly have 'specifications' but also can be controlled through process validation

CQAs force the focus onto those properties or characteristics of the product that are most important – especially those that are related to patient safety

But what a challenge for ATMPs!

***Protein** (10 nm)*



***Virus** (25 nm – 100 nm)*

proteins + nucleic acids

***Cell** (10,000-100,000 nm)*

~20,000 genes

Challenge of CQA Determination for ATMPs

more complex molecules
limited test methods (but additional QC methods upcoming)
less and more variable batches (for setting specifications)

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

Example of CQA determination: Cellular Therapy

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

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

Risk Ranking & Filtering (RRF): severity x uncertainty

Failure Mode and Effects Analysis (FMEA): severity x occurrence x detection

Example of CQAs for In Vivo AAV

Table 13

Example of a routine quality control testing for selected CQAs of an AAV process based on [45, 44, 46]. (SEC: Size Exclusion Chromatography, DLS: Dynamic Light Scattering, ELISA: Enzyme-linked immunosorbent assay, TEM: Transmission Electron Microscopy, AUC: Analytical Ultracentrifugation, MS: Mass Spectrometry, qPCR: quantitative Polymerase Chain Reaction, HPLC: High-Pressure Liquid Chromatography, LAL: Limulus Amebocyte Lysate).

	Quality Attribute	Test Strategy	Test Method	Specification
	Noninfectious AAV	Lot-release testing	AD-dependent infectivity in susceptible cells	Product-specific
Product-Related Impurity	Deamidated AAV	Lot-release testing	SEC, DLS	Product-specific
	Glycosylated AAV	Lot-release testing	SEC, DLS	Product-specific
	Aggregated AAV	Lot-release testing	SEC, DLS, light microscopy, TEM, AUC	Product-specific, eg. > 95% monomeric AAV
	Empty capsids	Lot-release testing	ELISA/qPCR, HPLC, MS, TEM, AUC	Product-specific
	Encapsidated host cell DNA	Lot-release testing	qPCR	< 10 ng/dose, ≤ 200 bp
	Encapsidated helper DNA	Lot-release testing	qPCR	Product-specific, eg. < 0.1% VG DNA
	Replication competent rcAAV	Lot-release testing	in vitro assay of cell lines permissive to infection	<1 rcAAV in 10^8 vg

Process-Related Impurity	Residual host cell DNA/RNA	Lot-release testing	qPCR, Picogreen, DNA Threshold assay	< 10 ng/dose , < 200 bp
	Residual host cell protein	Lot-release testing	ELISA, SDS-PAGE, HPLC, TEM	Product-specific, eg. < 1% VP protein
	Residual plasmid DNA	Lot-release testing	qPCR	Product-specific, eg. < 0.1% VG DNA
	Residual helper viruses	Lot-release testing	qPCR, infectious titer or ELISA for virus proteins	Negative
	Residual animal-derived CC medium components (BSA)	Lot-release testing	ELISA	Product-specific, eg. < 1% VP Protein
	Detachment enzyme	Lot-release testing	Various commercially available assays	Product-specific
	Detergents	Lot-release testing	MS, chromatography, TEM	Product-specific
	Leachables *	Lot-release testing	LC/MS, GC/MS [47]	Product-specific (eg. 1.5 µg total daily intake for genotoxic impurities)
	Nuclease	Lot-release testing	ELISA	< 0.1% by mass or < 1 pg/ 10^9 VG

list dependent upon what was actually used in the manufacturing process

(* typically tested once at later clinical stages)

Adventitious Agents	Endotoxin	In-process testing / Lot-release testing	LAL (EP 2.6.14 [48], USP <85> [49], JP 17th Ed. 4.01 [50])	< 2 EU/dose
	Bioburden	In-process testing / Lot-release Testing	Sterility testing (EP 2.6.1 [48], USP <71> [51], JP 17th Ed. 4.06 [50])	Negative
	Myoplasma / spiroplasma	In-process testing / Lot-release testing	Cell based assay according to 21 CFR and alternative methods, eg. PCR (Ph. Eur. 2.6.7, Ph. Eur 2.6.21 [48], ICH Q2A (R1) [52])	Negative
	Adventitious viruses	In-process testing	*In vivo* and *in vitro* cellular assay according to 21 CRF (ICH Q5A [53])	Not detected
Potency	Functional AAV titer	In-process testing	ELISA, ddPCR, optical density (UV A260:280)	Product-specific
		Lot-release testing	ZOLGENSMA has a nominal concentration of 2.0×10^{13} vg/mL.	

(potency)

PALL

Quality by Design (QbD) for Adeno-Associated Virus (AAV) 2021

+ Identity of Vector (HPLC/MS of Capsid) and Integrity/Identity of Transgene (DNA Sequence)

+ Pharmacopeia Requirements (Appearance; pH; Particulate Matter; Extractable Volume; etc.)

CPP • Critical Process Parameters

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

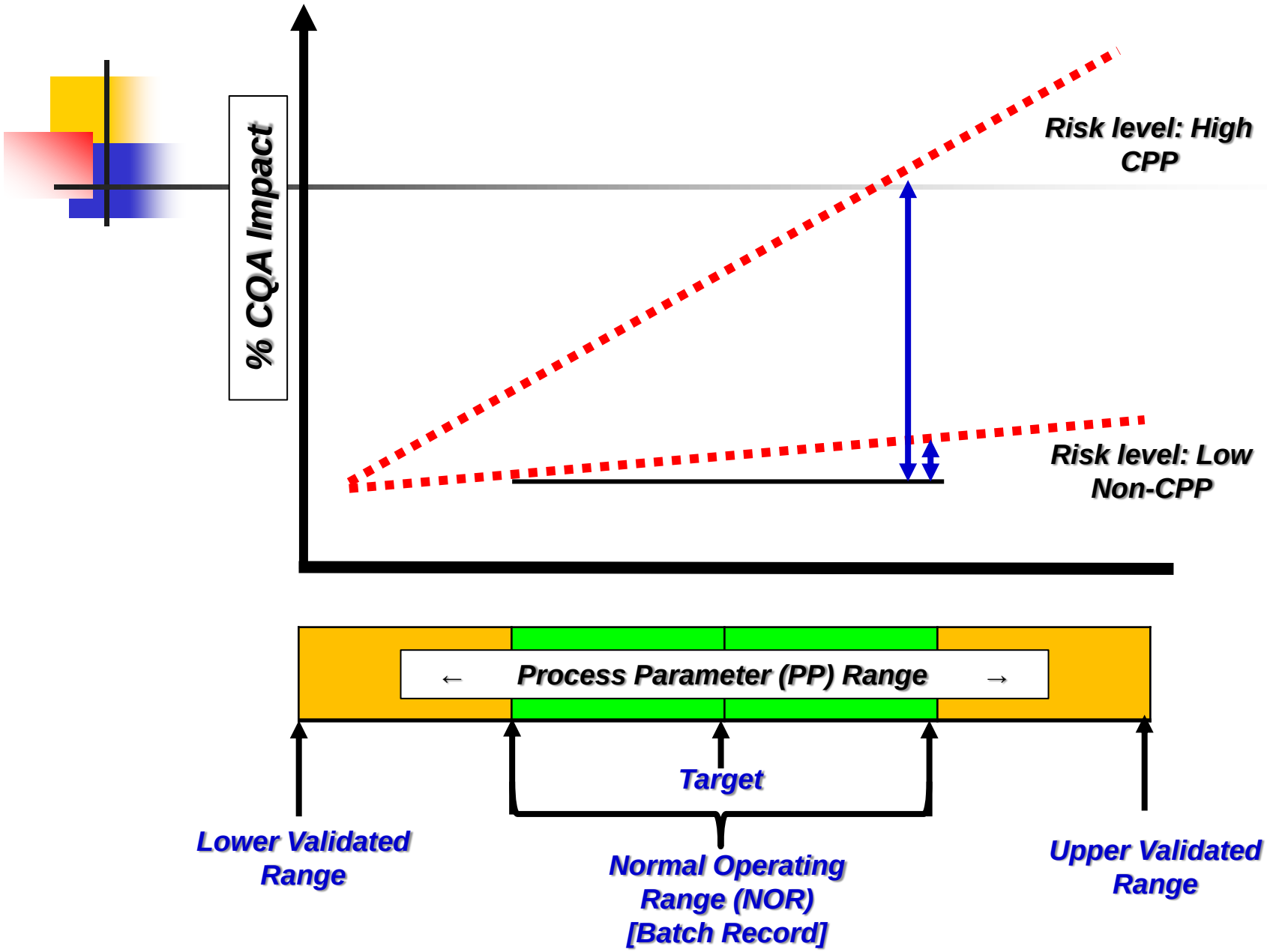
impact on CQAs ↕ ***(changeable, not static, as scientific understanding about the process increases)***

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.

ATMP manufacturing processes have MANY PPs! ***which ones will be CPPs?*** →

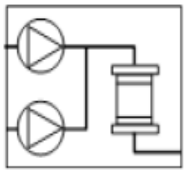
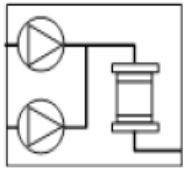
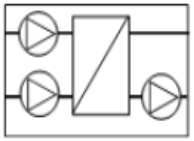
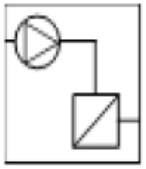
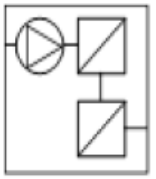

% CQA Impact
Risk level: High
CPP
Risk level: Low
Non-CPP
← Process Parameter (PP) Range →
Target
Lower Validated
Range
Normal Operating
Range (NOR)
[Batch Record]
Upper Validated
Range

Example of CPP determination: Cellular Therapy

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

	CQA					
PP	Safety	Identity	Dose	Purity	Potency	CPP: Parameter had no impact on CQA Parameter had a moderate impact on CQA Non-CPP: Parameter had severe impact on CQA
Incubation time for each expansion						Incubation time is linked to cell yield for each expansion step. The longer the incubation, the higher the yield. However, if the incubation time exceeds a defined threshold, the phenotype of the cells and their chondrogenic potential is compromised.
Incubation temperature for each expansion						Temperature significantly impacts the cell cycle. If temperature drops below 35 °C, cell metabolism will slow down and eventually "pause" at 25 °C. On the other hand, temperature higher than 37 °C will trigger the production of heat-shock proteins and, eventually, lead to cell death.
% CO_2 during expansion						CO_2 is used in combination with bicarbonate present in the medium to keep the pH constant. Chondrocytes grow well at pH 7.4. Higher pH (7.4-7.7) leads to proliferation of fibroblasts, which tend to prefer slightly basic environments. Lower pH leads to cell death.

Example of CPPs for In Vivo AAV

Product- and Process-Related Impurities	Affinity Chromatogr.	Polishing Chromatogr.	UFDF	Virus Filtration	Sterile Filtration
					
Noninfectious AAV			N/A	N/A	N/A
Deamidated AAV			N/A	N/A	N/A
Aggregated AAV					
Empty capsids			N/A	N/A	N/A
Encapsidated host DNA			N/A	N/A	N/A
Encapsidated helper DNA			N/A	N/A	N/A
Residual host cell DNA				N/A	N/A
Residual host cell protein				N/A	N/A
Residual helper viruses	N/A		N/A	N/A	N/A

- Profound data basis proves that the unit operation impacts the CQA
- Few data and solid expert opinion indicate that the unit operation impacts the CQA
- Expert knowledge without data support suggest that the unit operation impacts the CQA

CPP

N/A Not applicable: the unit operation does not impact the CQA

Non-CPP

PALL®

Quality by Design (QbD) for Adeno-Associated Virus (AAV) 2021

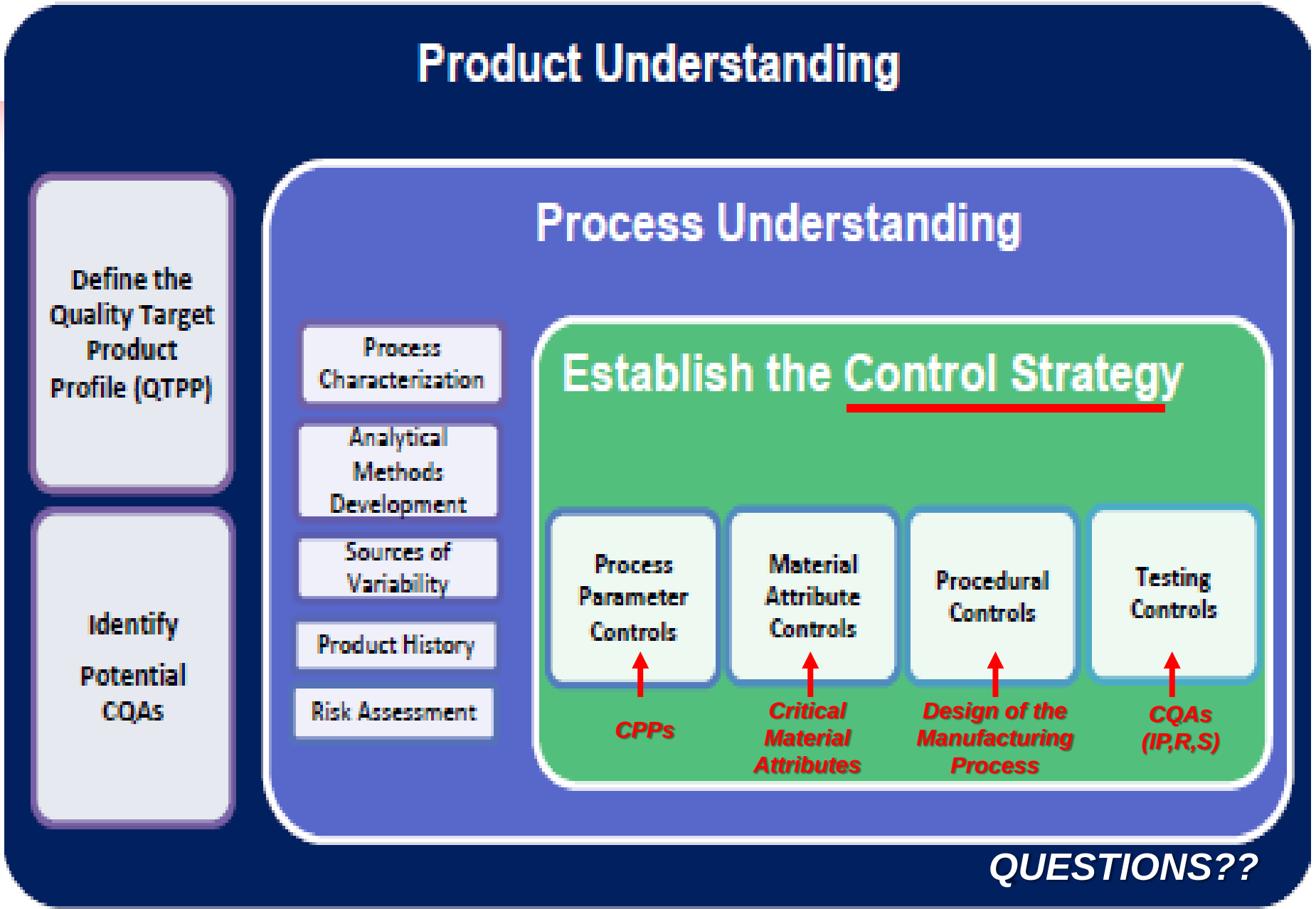
CS • Control Strategy

ICH Q8(R2)

Control Strategy:

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

The Control strategy is much more than just product release specifications!


Product Understanding
Define the Quality Target Product Profile (QTPP)
Identify Potential CQAs
Process Understanding
Process Characterization
Analytical Methods Development
Sources of Variability
Product History
Risk Assessment
Establish the Control Strategy
Process Parameter Controls
Material Attribute Controls
Procedural Controls
Testing Controls
CPPs
Critical Material Attributes
Design of the Manufacturing Process
CQAs (IP,R,S)

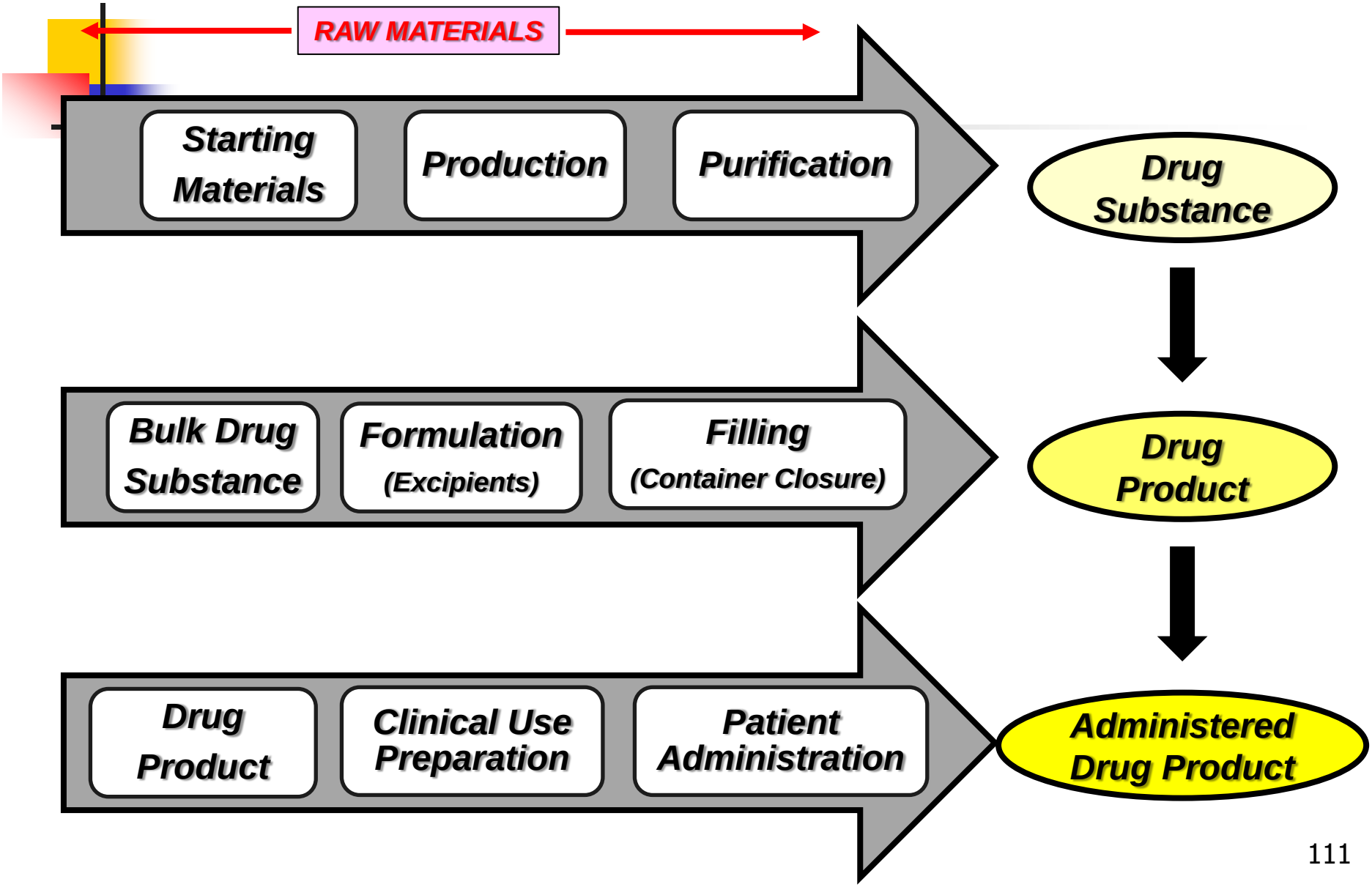
QUESTIONS??

Course Outline

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

- ***Applied risk-based strategy across the entire manufacturing process from starting materials → production → purification → bulk drug substance → formulation → drug product → administered drug***

Applied Risk-Management Across the Manufacturing Process



RAW MATERIALS

Raw materials are the reagents and components that come in contact with the CGTP during manufacturing, but are <u>not</u> part of the final product

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

- ***Up-Stream Process (USP)***
  - *Culture media components for cell expansion*
  - *Cationic lipids for transfecting plasmids into cells*
  - *Antibody-coated beads to activate T-cells*
  - *Surfactant/nuclease to lyse cells for release of virus*
  - *…*
- ***Down-Stream Process (DSP)***
  - *Solution and buffer components used in purification*
  - *Resins in the purification columns*
  - *Nanofilters*
  - *…*

Major CMC Regulatory Compliance Concerns of Raw Materials

***Impact* from raw material *batch-to-batch variation* on the the *consistency* of the manufactured cell and gene therapy products!**

***Patient safety concerns* from *contaminants* introduced into the manufacturing process by the raw materials**

***Patient safety concerns* from the raw material *residuals* remaining in the final product!**

Explains why raw materials for CGTPs receive so much attention from regulatory authorities

EMA Raw Material Expectations and Recommendations

(during clinical development)

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

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

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

EUROPEAN MEDICINES AGENCY

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

31 January 2019
EMA/CAT/852602/2018

FDA Raw Material Expectations and Recommendations

(during clinical development)

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

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

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

We recommend that you consider using non-animal-derived reagents if possible (e.g., serum-free tissue culture media and recombinant proteases).

Other Guidance on Assessing Raw Material Risk

European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

European Pharmacopeia

General Chapter 5.2.12.

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

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

(definition, production, identification, tests, assay)

United States Pharmacopeia

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

ISO Technical Committee 276 Biotechnology, Working Group 4 Bioprocessing

ISO/DIS 20399
Biotechnology — Ancillary materials

(updating under development)

Treat critical raw materials seriously with advanced therapy products!

Patients must always be protected

Case Example What can happen when there is missing CMC documentation in a submission for a critical raw material

MARKER THERAPEUTICS

Cellular Therapy

Phase 2 AML trial of MT-401

(MT-401 (zelenoleucel) is an allogeneic multi-tumor-associated antigen (MultiTAA)-specific T cell product using donor-derived T cells obtained from apheresis.)

(30 month delay)

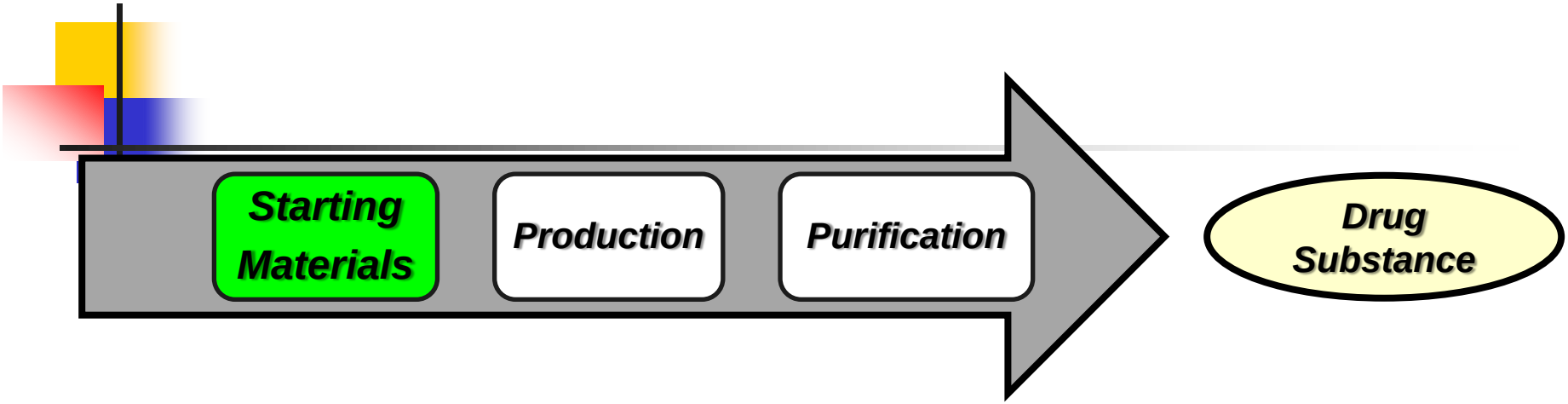
Press Releases

Nov 12, 2019: FDA partial clinical hold – "FDA requested additional information and technical specifications for two legacy reagents supplied by third parties…. 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."

Nov 09, 2020: "The company received the remaining reagent from the alternate supplier in Q3 2020 and is currently conducting the comparability analysis between the previous and new reagents, as required by the FDA. Market intends to submit all required data to FDA by Q1 2021"

Jan 05, 2021: "FDA lifted partial clinical hold on Phase 2 AML clinical trial"

Applied Risk-Management Across the Manufacturing Process



Starting materials dependent upon type of ATMP manufacturing process

Starting Materials		
In Vivo Gene Therapy	**Ex Vivo Gene Therapy**	**Cellular/Tissue Therapy**
Cell/Seed Banks	Cell/Seed Banks	Patient's Cells
Plasmids/LNPs	Plasmids/LNPs	
	Patient's Cells	

Starting Materials: 'Principles of GMP' vs GMP

EUROPEAN MEDICINES AGENCY

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

24 February 2021
EMA/246400/2021

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

2. What does principles of GMP mean?

GMP requirements for ATMP active substances (drug substances) and ATMP finished products are described in Part IV of the GMP Guide. Some requirements of part IV can also be relevant for the starting materials.

However, the main differences with regard to the starting materials are:

- Not all GMP aspects described in Part IV of the GMP Guide are required.
- According to the current legal framework, neither recurring inspections nor GMP certifications by the responsible authorities are required.

As a result of this situation, the ATMP manufacturers have the responsibility to verify that appropriate GMP requirements are implemented for the manufacturing/testing of the starting materials according to the methodology described in the questions 4 and 5 of the document.

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

i. transmissible spongiform encephalopathy; *TSE*

ii. potential for viral contamination and cross contamination with other vectors or other genetical material;

iii. replication competent virus (in case of replication-deficient viral vector). It should be demonstrated the absence of formation of replication competent virus at the level of the viral production system used[5];

iv. potential for microbiological (e.g. Mycoplasma) or endotoxin/pyrogen contamination;

v. potential, in general, for any impurity originating from the raw materials, or generated as part of the process and carried over;

vi. sterility assurance for materials claimed to be sterile;

vii. potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities (for instance residual DNA (antibiotic resistance gene, residual DNA from potentially tumorigenic cell lines etc.), substance of animal origin, antibiotic etc.);

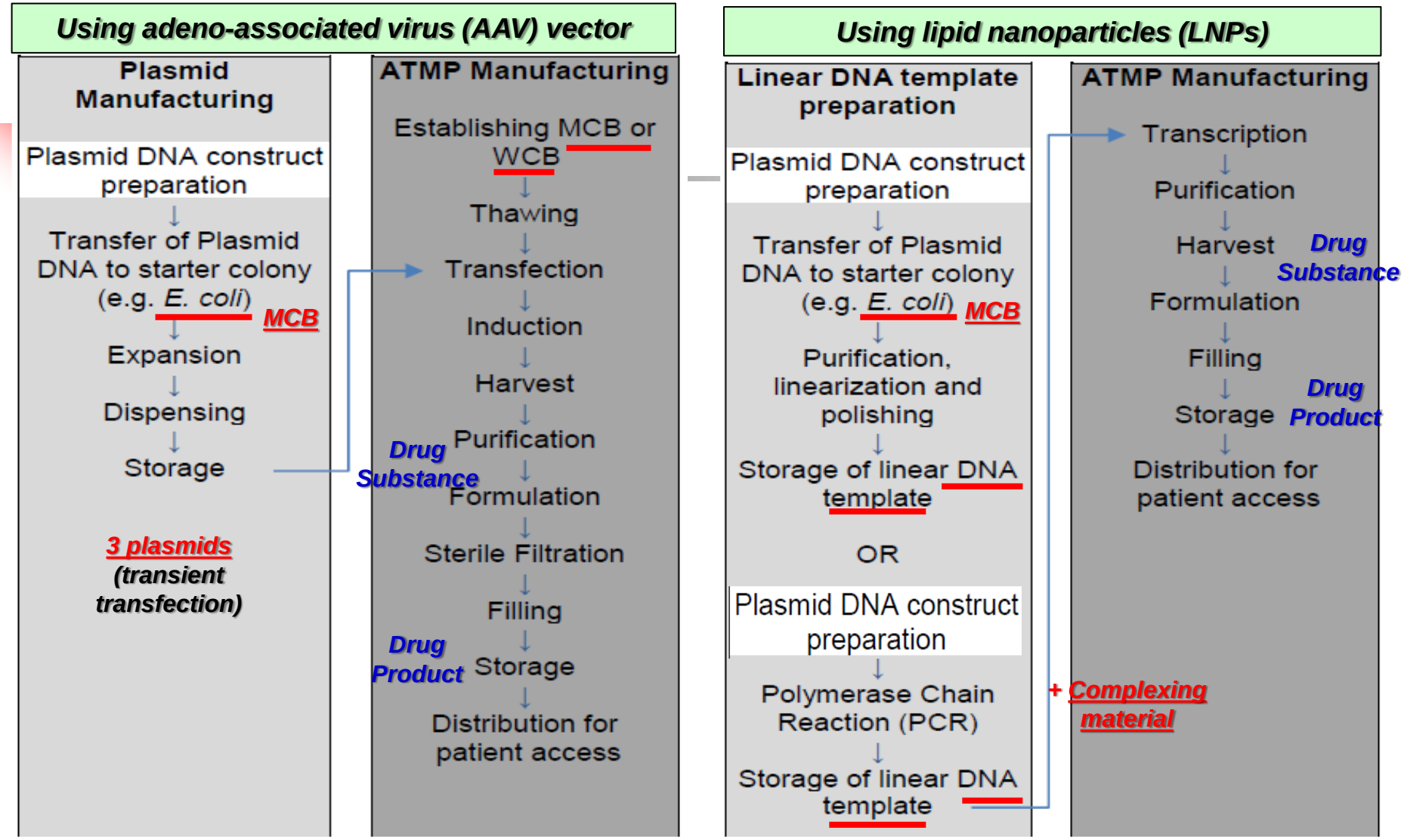
viii. environmental control and storage/transportation conditions including cold chain management if appropriate;

ix. stability;

x. supply chain complexity and integrity of packages.

In case that significant risks to the product are identified, measures for risk control and mitigation should be defined and implemented.

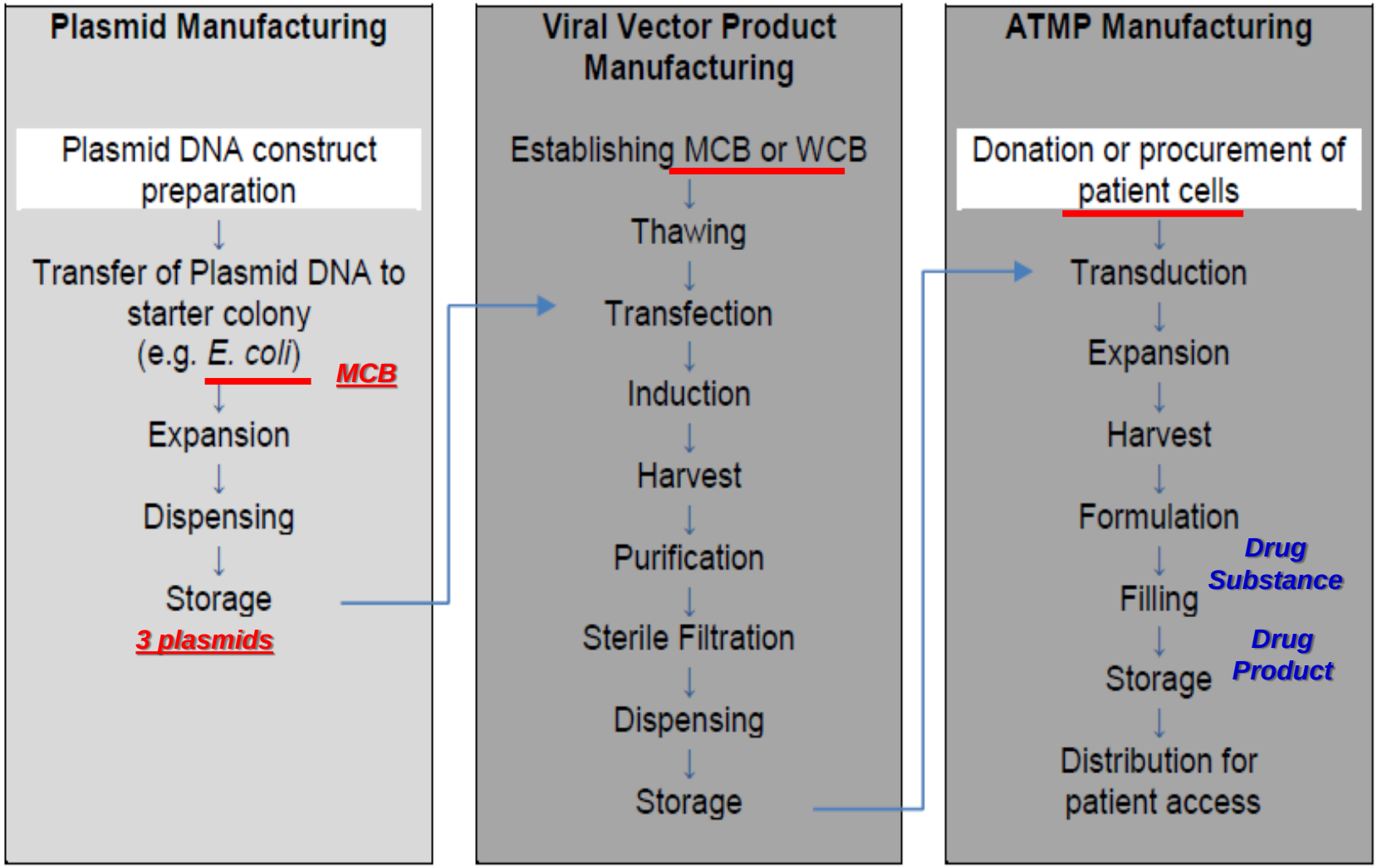
In Vivo Gene Therapy Manufacturing Processes — *Starting Materials* ____



Box Color: ***White – outside GMPs*** | ***Light Grey – Principles of GMP*** | ***Dark Grey - GMPs***

Ex Vivo Gene Therapy Manufacturing Processes

Starting Materials



Box Color: | ***White – outside GMPs*** | ***Light Grey – Principles of GMP*** | ***Dark Grey - GMPs***

Regulatory Compliance Expectations

- ***All starting materials used for manufacture of the active substance should be listed and information on the source, quality and control of these materials must be provided.***
- ***The establishment of bacterial/cell/virus seed or bank(s) is expected for starting materials which are bankable. The source and history of the cells or bacterial or virus seeds used for generation of the respective banks should be described and genetic stability of the parent material demonstrated.***
- ***All starting materials, including master and working cell banks and viral seeds should be appropriately characterised and monitored (e.g. according to the concepts outlined in ICH guideline Q5D).***
- ***Where applicable, genetic stability of the starting materials should be demonstrated at the beginning and the end of the culturing process.***

EUROPEAN MEDICINES AGENCY

Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products

22 March 2018
EMA/CAT/80183/2014

Regulatory Compliance Expectations

Ex Vivo

4.1.1. Starting materials

Genetically modified cells can be produced by *ex vivo* gene transfer or via *ex vivo* genome editing technologies. For both procedures, different categories of starting materials are used. These include the human or animal cells and the tools (e.g. vectors, mRNA) used to genetically modify them. The latter might be different and will depend on the procedure for genetic manipulation used, as presented below.

For *ex vivo* gene transfer, the tools used to genetically modify the cells shall be, as appropriate, the vector (e.g. viral or non-viral vector) and the components to produce them. Principles of good manufacturing practice (GMP) shall apply from the bank system used to produce the vector onwards.

For genome editing approaches, the tools used to genetically modify the cells shall be, as appropriate, the vector (viral or non-viral vector) carrying the nucleic acid sequences encoding the modifying enzyme, the mRNA expressing the modifying enzyme, the modifying enzyme itself, the genetic sequence for modification of the cell genome (e.g. a regulatory guide RNA) or a ribonucleoprotein (e.g. Cas9 protein pre-complexed with gRNA), the repair template (e.g. linear DNA fragment or a plasmid), and the components to produce them. When vectors, mRNA or proteins are used, the principles of GMP shall apply from the bank system used to produce these materials onwards.

For combined ATMP containing genetically modified cells, additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with the manipulated cells, of which they form an integral part, shall be considered as starting materials, even if not of biological origin (definition as laid down in 2009/120/EC directive). They should be qualified for their intended use as recommended in the guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006).

Starting materials used for the production of genetically modified cells and genome edited products shall be carefully qualified to assure a consistent manufacturing process. The amount of data to be provided for each starting material is the same as required for, respectively, the drug substance of a cell-based medicinal product and the drug substance of an *in vivo* gene therapy medicinal product. ★

EUROPEAN MEDICINES AGENCY

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

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

CASE EXAMPLE: Level of Plasmid Detail for the viral vector used in Ex Vivo Gene Therapy

A multi-plasmid system, consisting of a transfer plasmid (pLBP100) that carries the *ABCD1* (ATP-binding cassette, sub-family D, member 1) gene, which encodes the human adrenoleukodystrophy protein (ALDP), and packaging plasmids is used to manufacture Lenti-D LVV by transient transfection of HEK293T cells. Expression of the *ABCD1* transgene is controlled by an internal enhancer/promoter derived from the unique 3' region of murine myeloproliferative sarcoma virus (MPSV) with a negative control region deletion (i.e., an internal MNDU3 enhancer/promoter). Information on the structural elements, associated plasmid maps and full sequence information for the plasmids is provided.

The plasmid production site is qualified and managed by the applicant, in accordance with their quality management system and the plasmids are manufactured according to the applicant's specifications. Adherence to principles of GMP is ensured by the quality system in place, including audits being performed regularly.

A flow diagram and brief narrative description of the plasmid manufacturing process have been provided, including information of process parameters and in-process controls. Individual WCBs are used for the manufacture of each of the plasmids. The manufacturing process consists of fermentation and harvest, a downstream purification process, ending up with final filtration, filling and storage. Stability has been verified for the proposed shelf-life.

The manufacturing process performance has been evaluated with regards to process control and consistency, aseptic manufacturing, sterilising grade filter validation, cleaning validation, and shipping validation.

The information provided on the manufacturer and the manufacturing process is considered adequate.

Regulatory Compliance Expectations

The Patient's Cells for Ex Vivo Gene Therapy

The nature of the cells used as starting material may be critical for CAR T cell quality and function. Due to patient or donor variability, the cellular starting material can represent a major source of lot-to-lot variability. Here, we describe considerations for cellular starting material, using starting material obtained from leukapheresis (referred to as "leukapheresis starting material") as an example. The recommendations in this section may be applicable to other types of cellular starting material as well.

We recommend that procedures used for handling the leukapheresis starting material from collection to the start of the manufacturing process are described as discussed in section V.A.2.c.ii of the GT CMC Guidance (Ref. 3). This description should include any wash steps or cryopreservation procedures. We recommend these procedures be in place at all leukapheresis collection sites to ensure quality of the process, including handling of the cells and shipment to the manufacturing site. You should have appropriate procedures in place to ensure adequate control of the leukapheresis starting material during shipping to the manufacturing facility (e.g., temperature control), and information regarding shipping containers and temperature monitoring should be provided. Validation of the shipping process and any hold or cryopreservation steps, including assessment of leukapheresis starting material stability under the intended conditions, should be included for licensure.

The probability of manufacturing success may be increased by establishing acceptance criteria for the leukapheresis starting material used in CAR T cell manufacturing. For example, you may specify a minimum cell number, viability, and percent CD3+ cells. We recommend that you test the leukapheresis starting material for microbial contamination (e.g., sterility or bioburden) prior to initiating CAR T cell manufacturing or that you retain a sample for post hoc testing in the event of a DP sterility test failure. Additional characterization of the leukapheresis starting material (e.g., for percent and absolute number of CD4+ and CD8+ T cells, NK cells, monocytes, B cells) may inform the CAR T cell manufacturing process as these characteristics may influence T cell selection and expansion and final CAR T cell quality (Refs. 20, 21, 22).

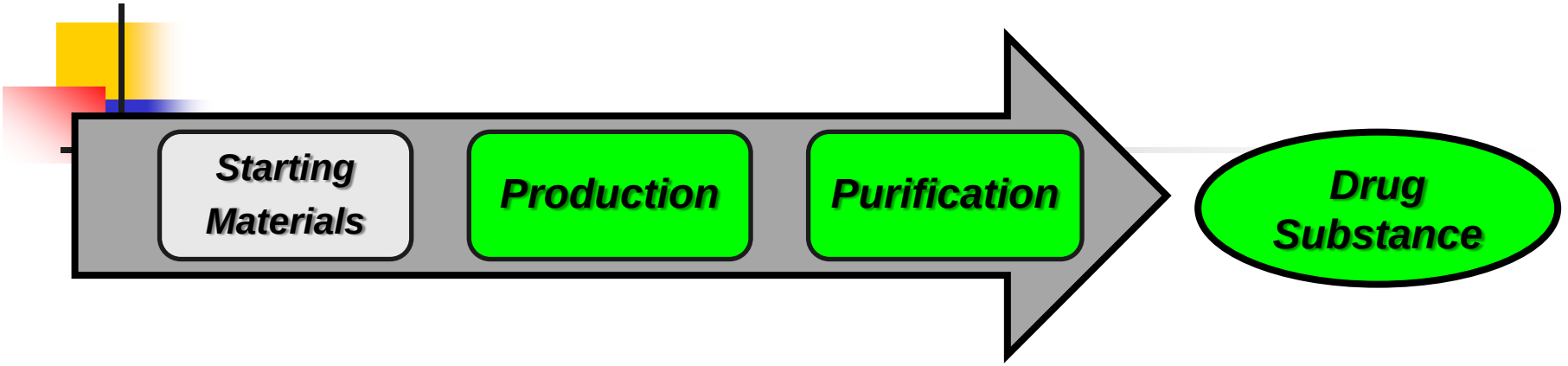
Regulatory Compliance Expectations

The Patient's Cells for Cellular Therapy

You should describe the following information in your IND:

- Cell source: tissue and cell type (e.g., colon, hematopoietic, neuronal, T-cells);
- Mobilization protocol: document whether or not donor cells are mobilized or activated in vivo in the donor:
- Collection or recovery method: state the procedure used to obtain cells (e.g., surgery or leukapheresis indicating the device used if possible), the name and location of the collection facility, and transport conditions if shipped to a processing facility for further manufacturing; and
- Donor screening and testing: the donor screening and testing that is performed to determine donor eligibility. Requirements for screening and testing donors of human cells and tissues are described in 21 CFR Part 1271 (see final rule, "Eligibility Determination for Donors of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps)") (Ref. 3). When appropriate, you should document the donor safety testing that is performed.

Applied Risk-Management Across the Manufacturing Process



Regulatory Compliance Control Strategy dependent upon type of CGTP Manufacturing Process

- ***In Vivo Gene Therapy using rAAV*** →
- ***Ex Vivo Gene Therapy using rLV***
- ***Cellular Therapy***

In Vivo Gene Therapy using rAAV

Commonality of Upstream Manufacturing Processes

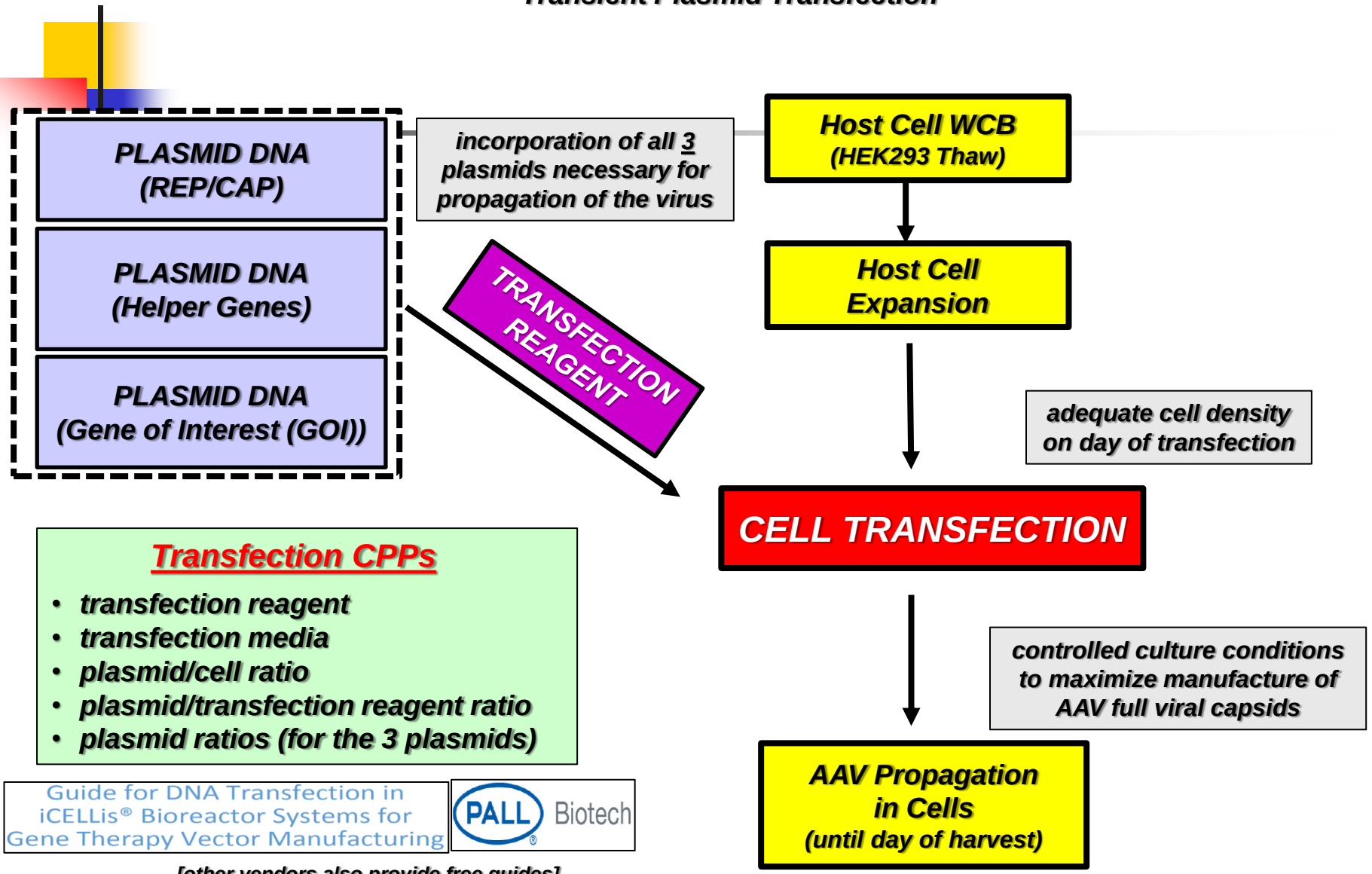
Recombinant Protein/mAb	Gene Therapy Recombinant Virus
Recombinant WCB Thaw	Host Cell WCB HEK293 Thaw
Recombinant Cell Expansion	Host Cell Expansion
Protein Induction (Temperature Shift)	Cell Transfection (Plasmid Transfection)
Protein Expression	Virus Propagation

suspension cell culture
(common for protein production)

adherent cell culture
(common for virus production)

Critical Drug Substance Upstream Manufacturing Process Step (USP)

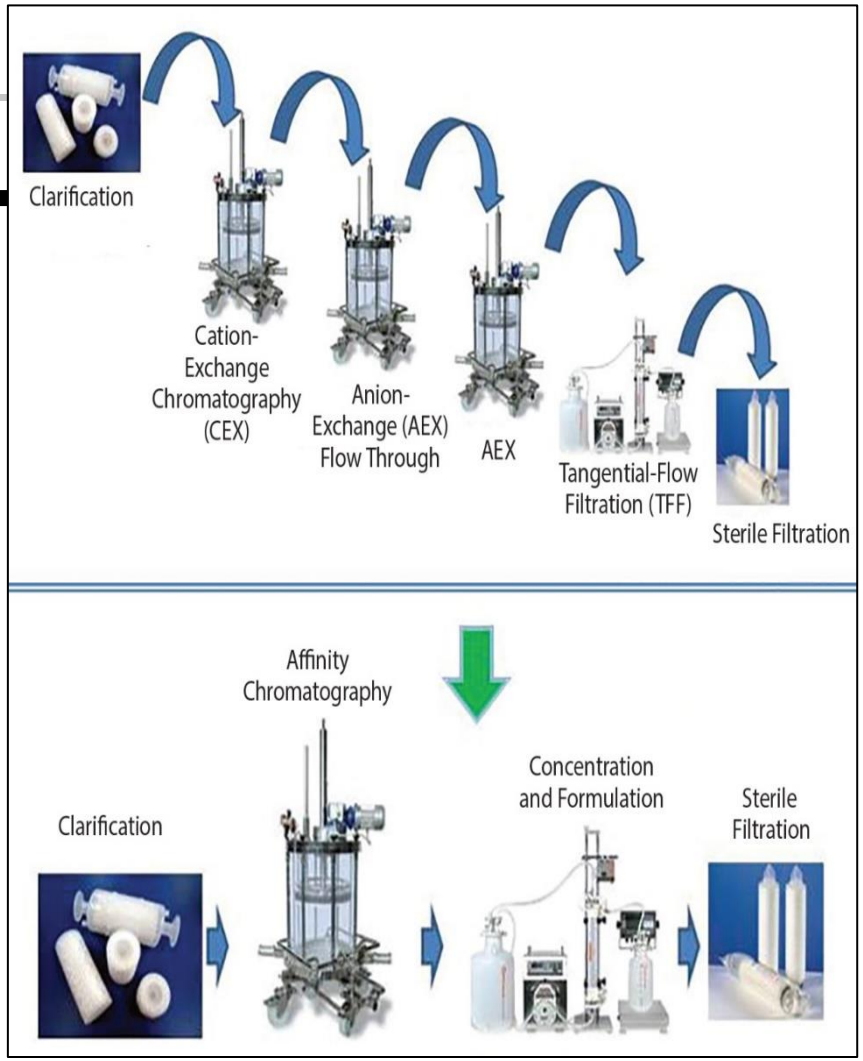
Transient Plasmid Transfection



[other vendors also provide free guides]

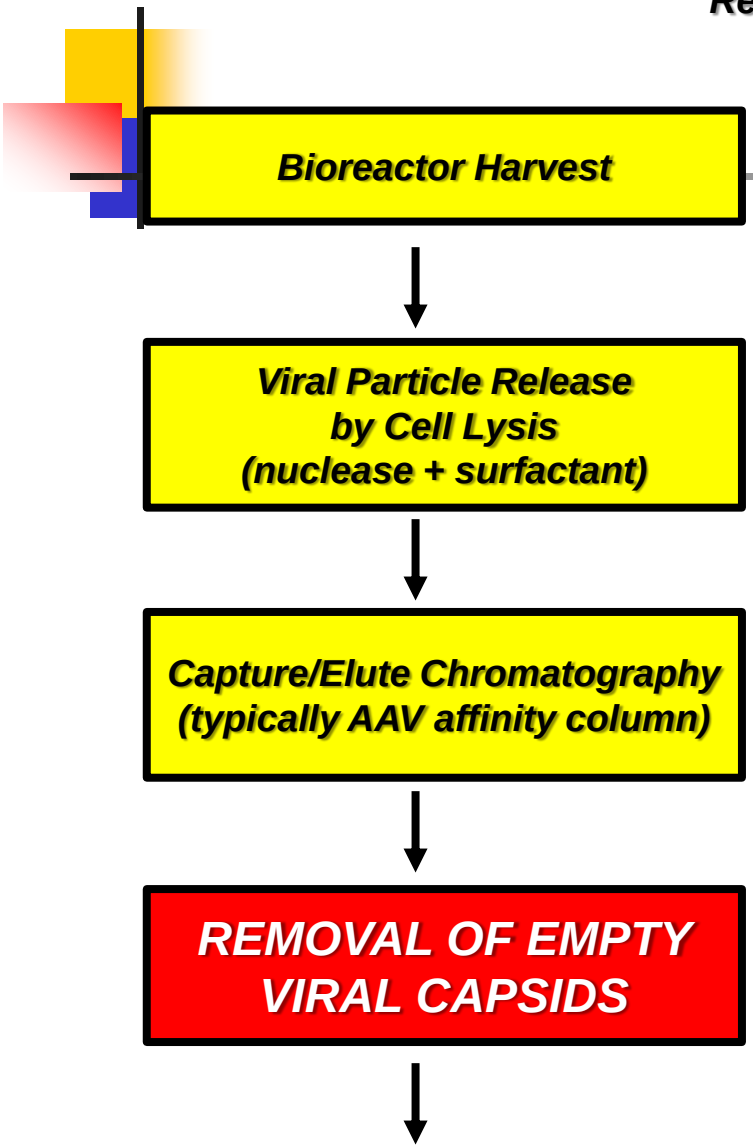
Commonality of Downstream Manufacturing Processes

Recombinant Protein/mAb	Gene Therapy Recombinant Virus
Release/Clarification (Removal of Cells/Debris)	Release/Clarification (Removal of Cells/Debris)
Multiple Purification Process Steps	Multiple Purification Process Steps
TFF (buffer exchange, concentration)	TFF (buffer exchange, concentration)
0.2µ Bioburden Filtration	0.2µ Sterile Filtration
API (Purified Protein)	API (Purified Virus)



Critical Drug Substance Downstream Manufacturing Process Step (DSP)

Removal of Empty Virus Capsids



Empty capsids increase overall antigenic load and potentially exacerbate capsid-triggered innate and adaptive immune responses.

AAV empty capsids may compete with full capsids for receptor binding on target cells, which could necessitate an increase in the required vector dose.

Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy

Food and Drug Administration (FDA)

Cellular, Tissue, and Gene Therapies Advisory Committee

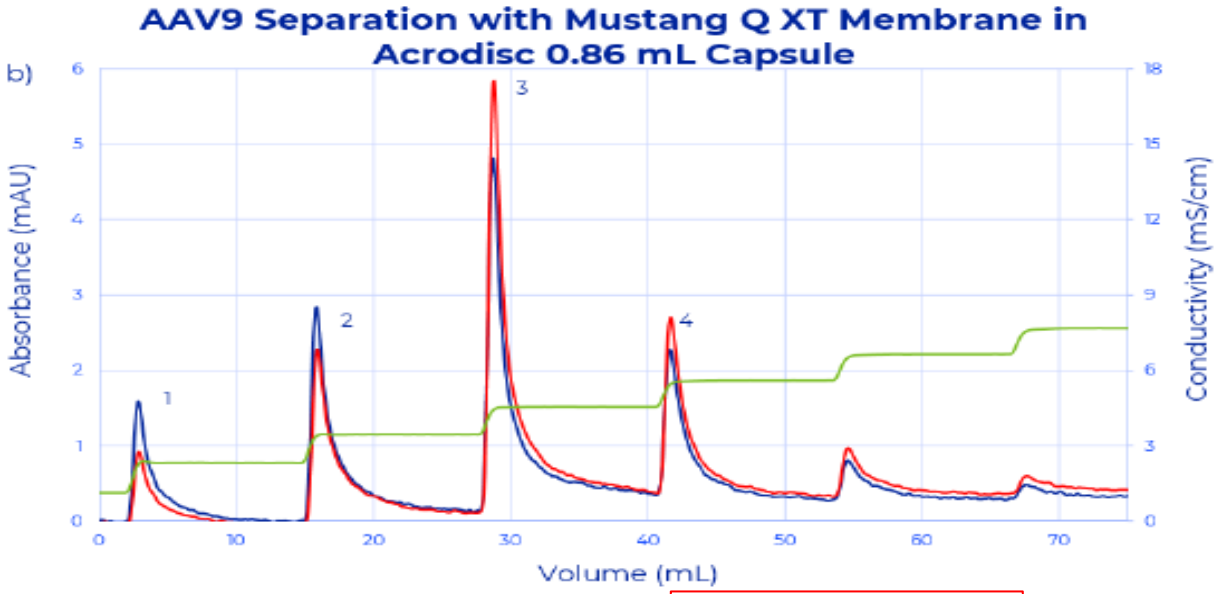
(CTGTAC) Meeting #70 **September 2-3, 2021**

This polishing step is the major downstream challenge.

Even after optimization of the anion exchange chromatography step, the peaks that represent the full and empty capsids typically overlap to some degree, which means some undesired materials remain.

Depending on how the full capsid fraction is collected, viral genome titer will be lost.

Anion Exchange Chromatography Capture/Elute



When viral capsids have a much higher A260 than A280 signal – capsids are considered full; vice versa for empty capsids

selected peaks

Sample	Load	Peak 1	Peak 2	Peak 3	Peak 4	4 Peak Yield
Total GC [1x10^{11}]	45	0.2	13	20	6.2	95%
Total Capsids [1x10^{11}]	90	10	20	20	10	66%
GC/Capsids [%]	50	2.0	66	~100	62	N/A

GC – virus genome copies (by ddPCR)

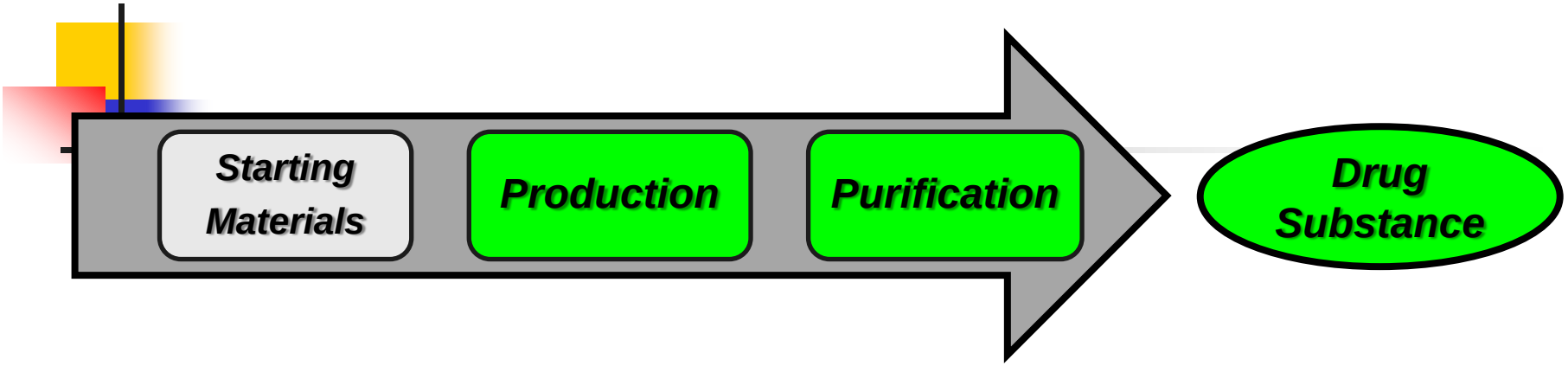
Total capsids (by ELISA)

% full capsids (gene containing)

PALL

Full Adeno Associated Virus (AAV) Capsid Enrichment Using Mustang® Q Membrane

Applied Risk-Management Across the Manufacturing Process

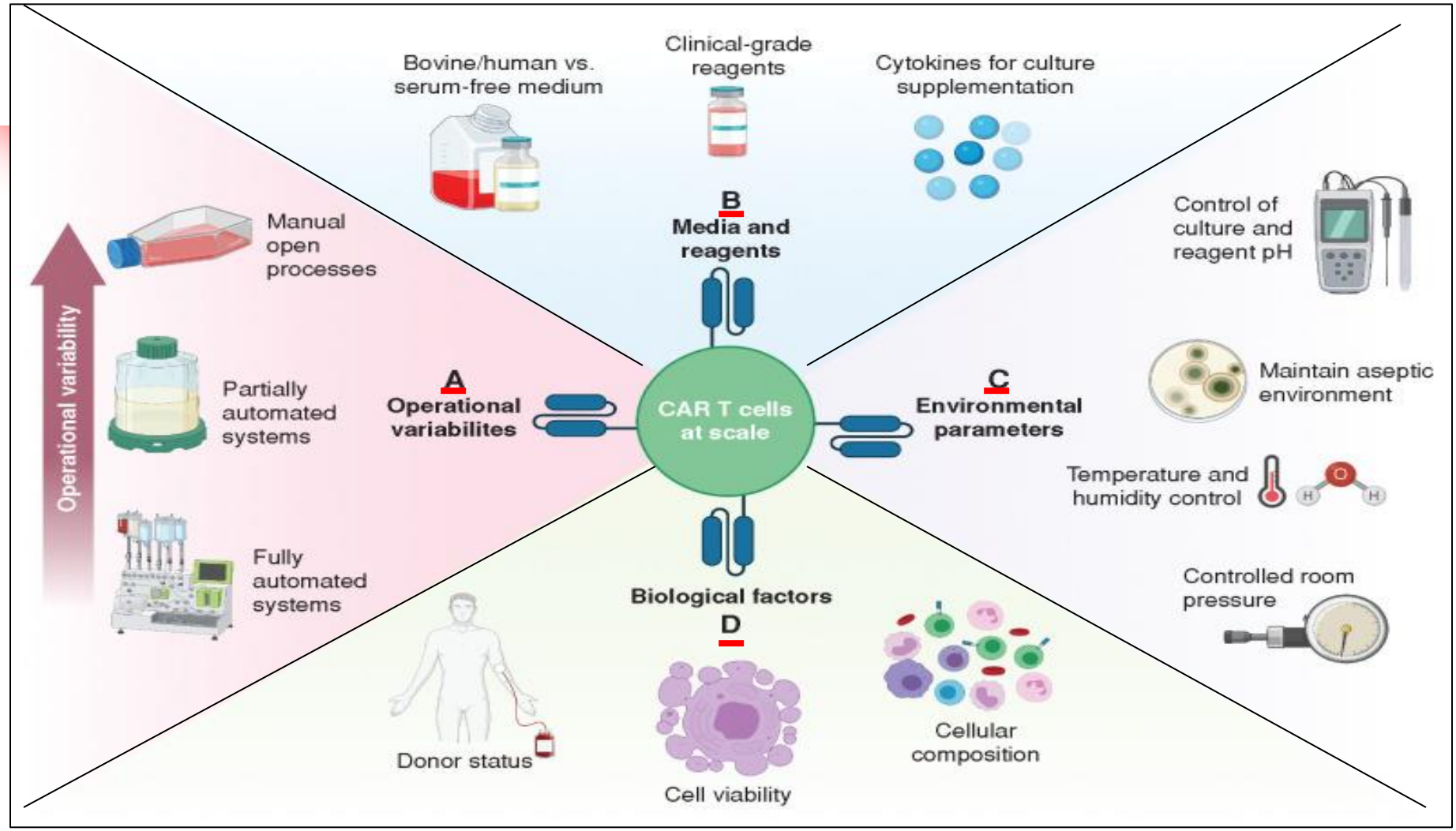


Regulatory Compliance Control Strategy dependent upon type of CGTP Manufacturing Process

- *In Vivo Gene Therapy using rAAV*
- ***Ex Vivo Gene Therapy using rLV*** →
- *Cellular Therapy*

Manufacture of Transduced Cells (Takeda) ***3 min***

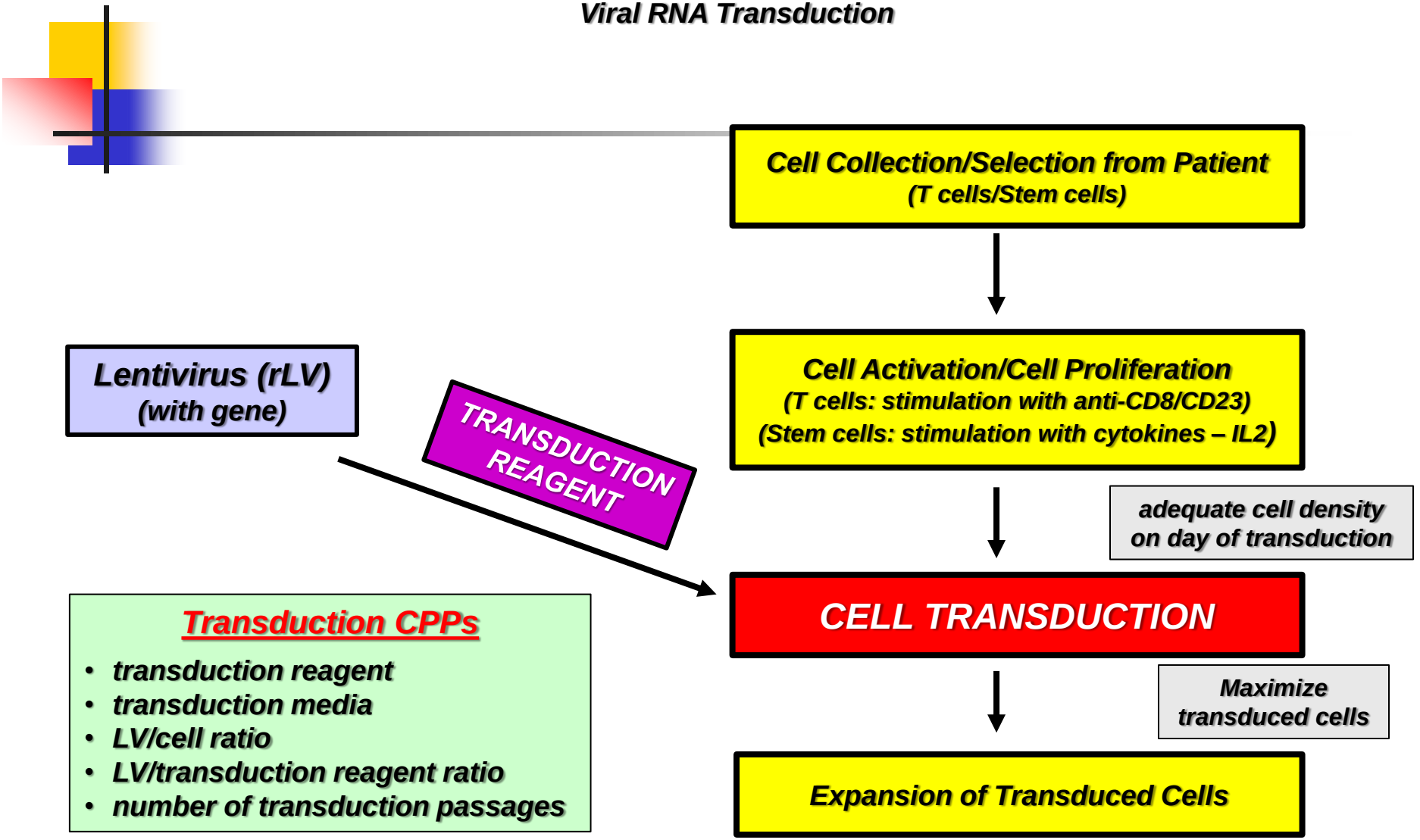
Many sources of variability in manufacturing for Ex Vivo Gene Therapy



A – Operational (methods, personnel, equipment)
B – Raw Materials (sera, media, growth factors)
C – Environmental (temperatures, pH, humidity)
D – Biological (patient starting material quality/composition, gene vector)

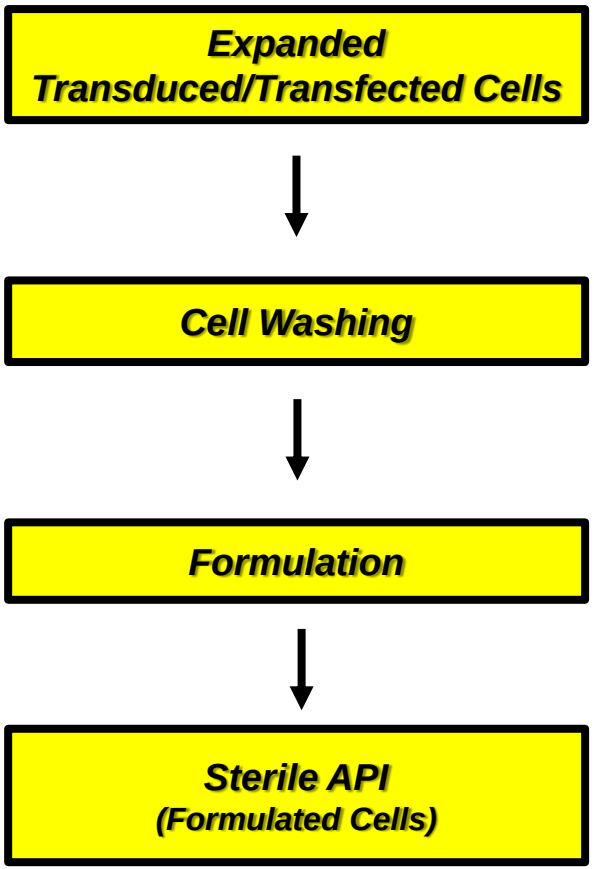
Critical Drug Substance Manufacturing Process Step

Viral RNA Transduction



Critical Downstream Manufacturing Process Step

Limited Options!



Since there is no cell separation, the % of transduced/transfected cells needs to be maximized

Cells cannot pass through chromatography resins – so washing is only 'purification'!

(explains why product-related and process-related impurities receive so much concern)

Cells cannot pass through 0.2µ filters – so no sterile filtration step

(explains why aseptic processing is so critical for cell-based processes)

Step 1. A tisagenlecleucel batch is produced for each patient from one leukapheresis material batch.

Step 2. Enrichment and activation

At Day 0, T cell enrichment is performed based on the cellular composition of the patient leukapheresis material. Percentage of monocytes and percentage of B lineage cells are measured by flow cytometry. The percentage of monocytes and B lineage cells dictates the choice of pathway for T cell enrichment.

The stimulation of T cells is performed using immunomagnetic beads bearing anti-CD3/CD28 monoclonal antibodies, Dynabeads® CD3/CD28 Cell Therapy Systems (CTS)™.

The cell-bead suspension then undergoes magnetic separation, retaining the bead-bound $CD3^+/CD45^+$ T cell fraction.

Step 3. Transduction

The bead-bound cells in this positive fraction are advanced to lentiviral vector transduction. Lentiviral vector transduction utilizes a self-inactivating minimal lentiviral vector that encodes the CD19-targeting CAR; transduction is performed twice, over 2 successive days. (Note: vector is produced by a third-party provider.)

Step 4. Expansion

On Day 3, following the second incubation period, the cell culture is washed to remove non-integrated vector and residual vector particles. The washed cells are seeded into a disposable culture system. The culture is continued over a period of several days until the cell number is sufficient to enable harvest.

When the cell count reaches the required minimum number of total viable cells, the cells are separated from the beads using a magnetic separation device, harvested, and washed.

CASE EXAMPLE:
Manufacture of CAR T cell Ex Vivo Gene Therapy

NOVARTIS

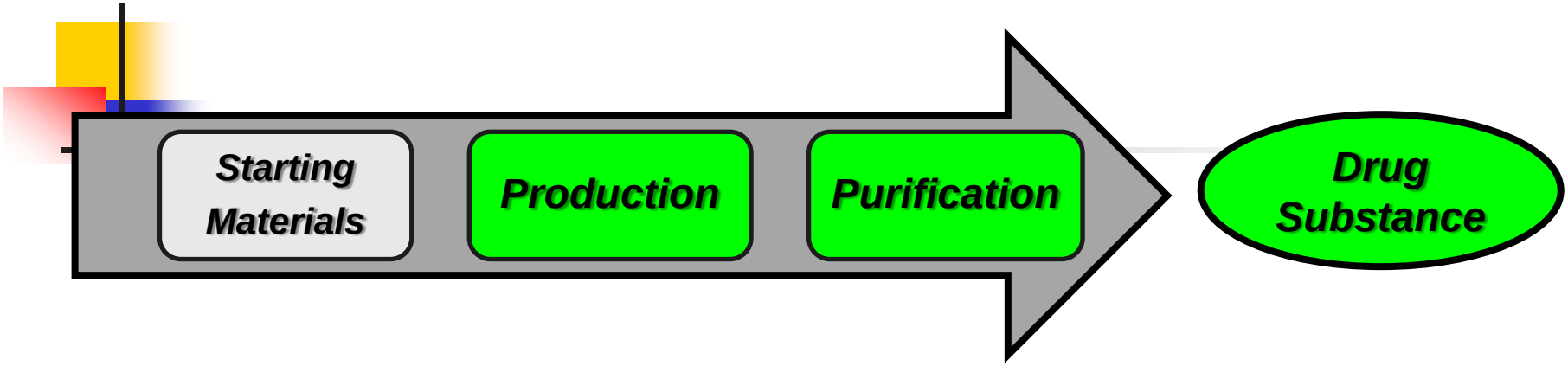
KYMRIAH

Tisagenlecleucel

FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting

12-Jul-2017

Applied Risk-Management Across the Manufacturing Process

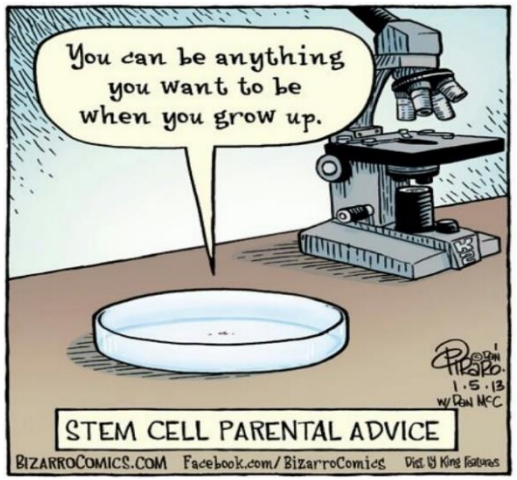


Regulatory Compliance Control Strategy dependent upon type of CGTP Manufacturing Process

- *In Vivo Gene Therapy using rAAV*
- *Ex Vivo Gene Therapy using rLV*
- ***Cellular Therapy*** →

Cellular Therapy

- ***Hematopoietic Stem Cells (HSCs)*** – *isolated from bone marrow or umbilical cord blood*
- ***Mesenchymal Stem Cells (MSCs)*** – *isolated from bone marrow or umbilical cords (WJ) or adipose tissue*



Cell/Tissue Collection from Patient/Donor

↓

Cell Selection Tissue Digestion

↓

Cell Expansion (Culturing)

'significant manipulation'

↓

Cell Washing

↓

Formulation

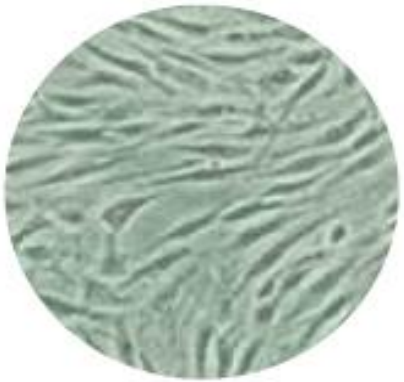
↓

Sterile API (Formulated Cells)

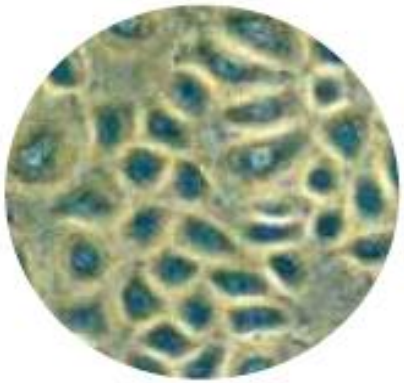
Concern for 'drifting' in cellular properties

- *morphology*
- *phenotype* →
- *genotype*
- *expressed antigens*
- *viability*
- *life span (senescence)*

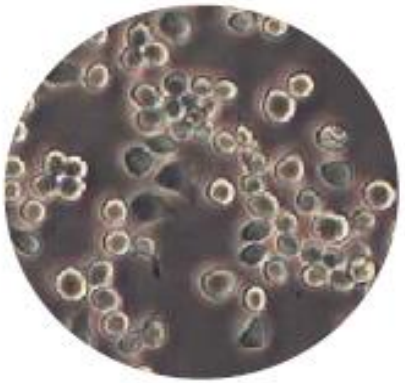
cell morphologies



Fibroblastic (or fibroblast-like) cells are bipolar or multipolar, have elongated shapes, and grow attached to a substrate.



Epithelial-like cells are polygonal in shape with more regular dimensions, and grow attached to a substrate in discrete patches.

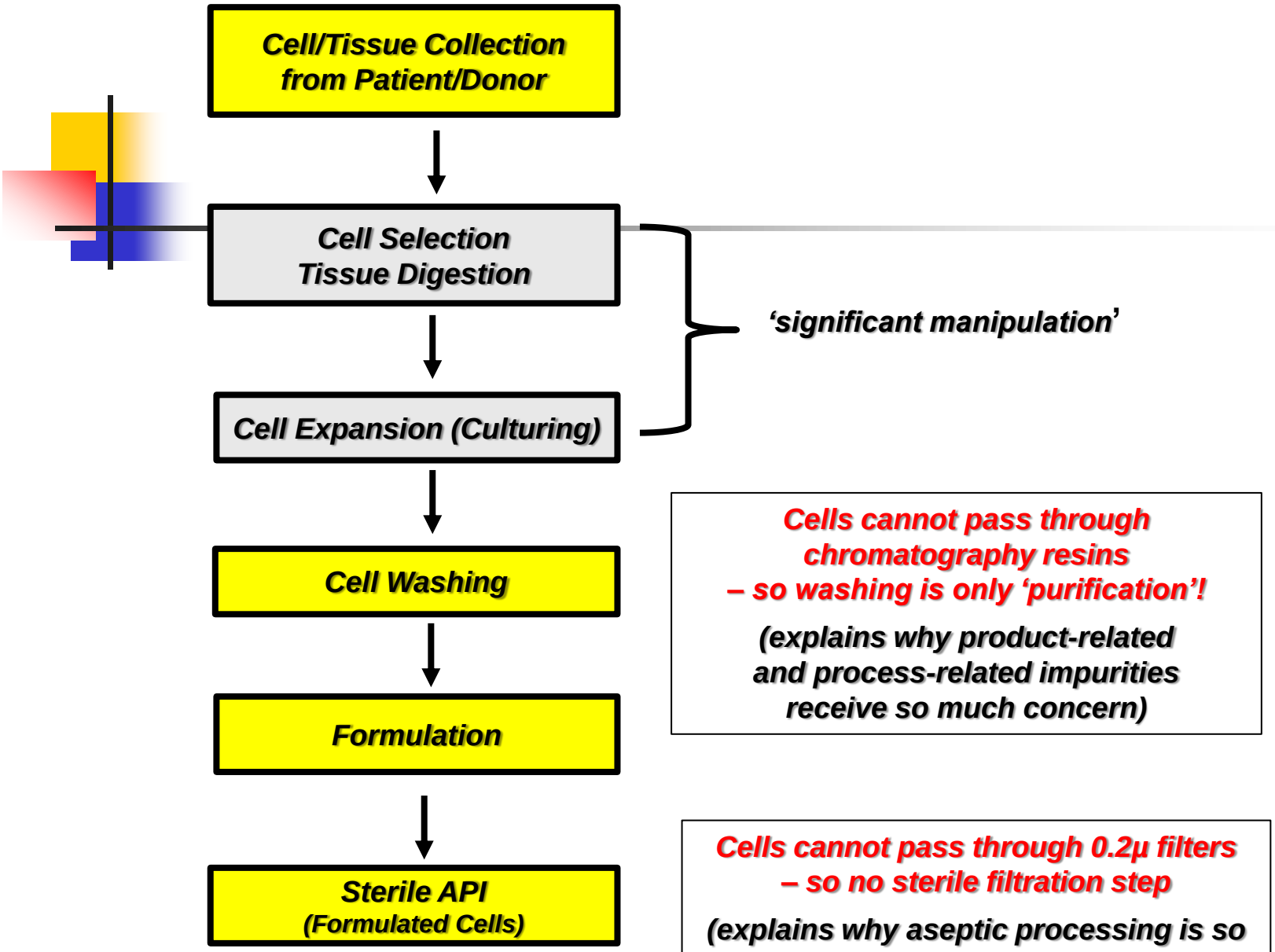


Lymphoblast-like cells are spherical in shape and usually grow in suspension without attaching to a surface.

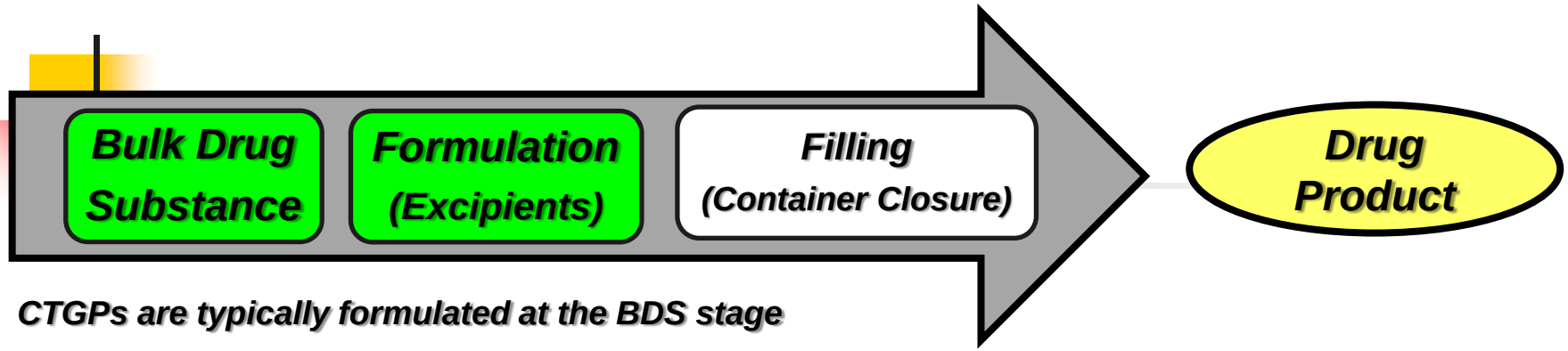
cell surface phenotypes (markers)

'Cluster of Differentiation'

CD4
CD8
CD19
CD…


Cell/Tissue Collection from Patient/Donor
Cell Selection Tissue Digestion
Cell Expansion (Culturing)
'significant manipulation'
Cell Washing
Formulation
Sterile API (Formulated Cells)
Cells cannot pass through chromatography resins – so washing is only 'purification'!
(explains why product-related and process-related impurities receive so much concern)
Cells cannot pass through 0.2µ filters – so no sterile filtration step
(explains why aseptic processing is so critical for cell-based processes)

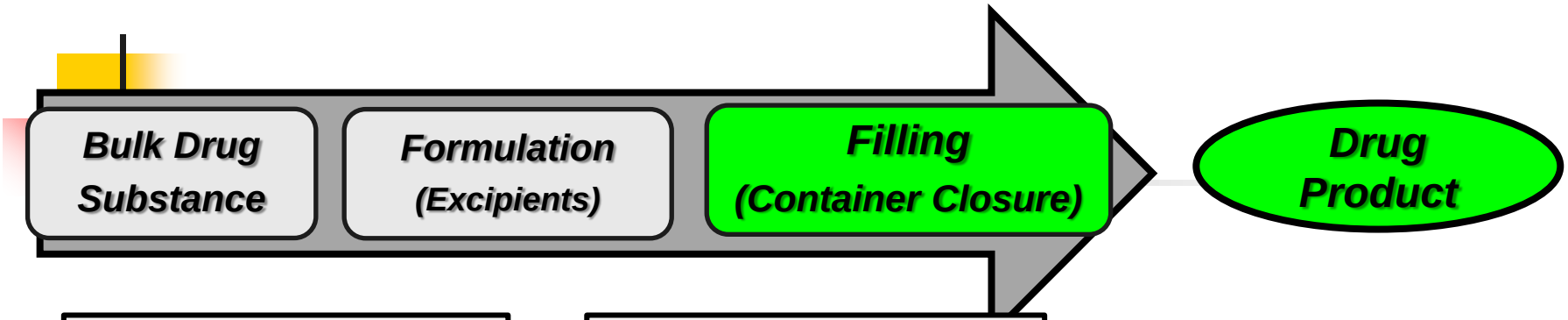
Applied Risk-Management Across the Manufacturing Process



CTGPs are typically formulated at the BDS stage

Frozen rAAV BDS	CAR T Cell BDS	Cellular Therapy
ZOLGENSMA	ZYNTEGLO	ALOFISEL
20 mM Tris (pH 8.0), 200 mM NaCl 1 mM $MgCl_2$, 0.005% poloxamer 188	TECARTUS	DMEM (isotonic buffer) 20% HSA
LUXTURNA	Cryoformulation CryoStor (5% DMSO)	PROVENGE
10 mM Na_3PO_4 (pH 7.3), 180 mM NaCl, 0.001% poloxamer 188)		Lactate Ringer's Injection

Applied Risk-Management Across the Manufacturing Process

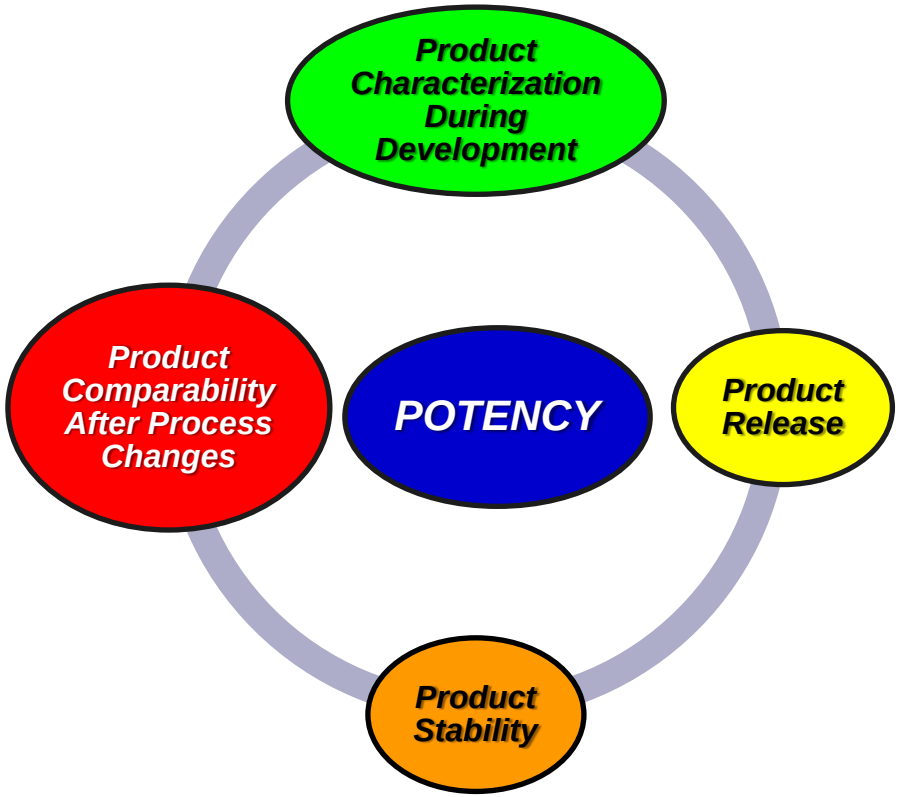


rAAV In Vivo Gene Therapy	CAR T Cell Ex Vivo Gene Therapy	Cellular Therapy
ZOLGENSMA	ZYNTEGLO	ALOFISEL
LUXTURNA	Aseptic Filling into Plastic Fluorinated Ethylene Propylene (FEP) Cryopreservation Bag Freeze < -140°C	Type I Glass Vial, with Rubber Stopper
Thaw Frozen BDS		
↓		
Sterile Filtration		PROVENGE
↓	TECARTUS	Plastic Infusion Bag
Fill into Crystal Zenith Vial with Chlorobutyl Stopper	Aseptic Filling into Plastic Ethylene Vinyl Acetate (EVA) Cryopreservation Bag Freeze < -150°C	
↓		
Freeze < -60°C		

Important Comment on CQAs for ATMPs

Critically important to identify CQAs sooner than later

Especially for Potency!



The cornerstone of a strong control strategy!

Potency Assay: Early Development is Critical!

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

Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer

21 July 2016
EMA/CHMP/BWP/271475/2006 rev.1

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

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

31 January 2019
EMA/CAT/852602/2018

Potency Assay: Early Development is Critical!

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

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

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

2. Later phase product development:

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

Press Release

IOVANCE BIOTHERAPEUTICS

FDA input obtained during pre-BLA meeting for their cellular therapy product

Iovance Biotherapeutics Provides Regulatory Update for Lifileucel Potency Assays

May 18, 2021

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

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

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

Follow-up Press Release

IOVANCE BIOTHERAPEUTICS

Iovance Biotherapeutics Announces Regulatory and Clinical Updates for Lifileucel in Melanoma

April 05, 2022 16:05 ET

SAN CARLOS, Calif., April 05, 2022 (GLOBE NEWSWIRE) -- Iovance Biotherapeutics, Inc. (NASDAQ: IOVA), a late-stage biotechnology company developing novel T cell-based cancer immunotherapies, today announced that the U.S. Food and Drug Administration (FDA) has provided feedback on April 1, 2022 regarding Iovance's proposed matrix of potency assays for its upcoming Biologics License Application (BLA) for lifileucel in metastatic melanoma. Iovance received positive feedback from the FDA on both its potency assay matrix and its proprietary cell co-culture assay included in the potency assay matrix. Based on this response, Iovance expects to request a pre-BLA meeting in July 2022 and to complete a BLA submission for lifileucel by August 2022.

1.5+ year CMC delay in filing BLA

FDA U.S. FOOD & DRUG ADMINISTRATION

ODAC Briefing Document

BLA 125706
Remestemcel-L
Applicant: Mesoblast

mesoblast

August 13, 2020

BLA filed February 2020 → Advisory Committee Meeting August 2020

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

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

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

Ryoncil

BLA not resubmitted as on April 2022 – 18+ month CMC delay

Don't under-estimate the amount of effort and time to develop adequate and appropriate assays for ATMP CQAs!

'Cell and gene therapy developers haven't always done a good job constructing tests early on that allow them to consistently measure their products as they move from early testing into larger clinical trials and, eventually, to the FDA'

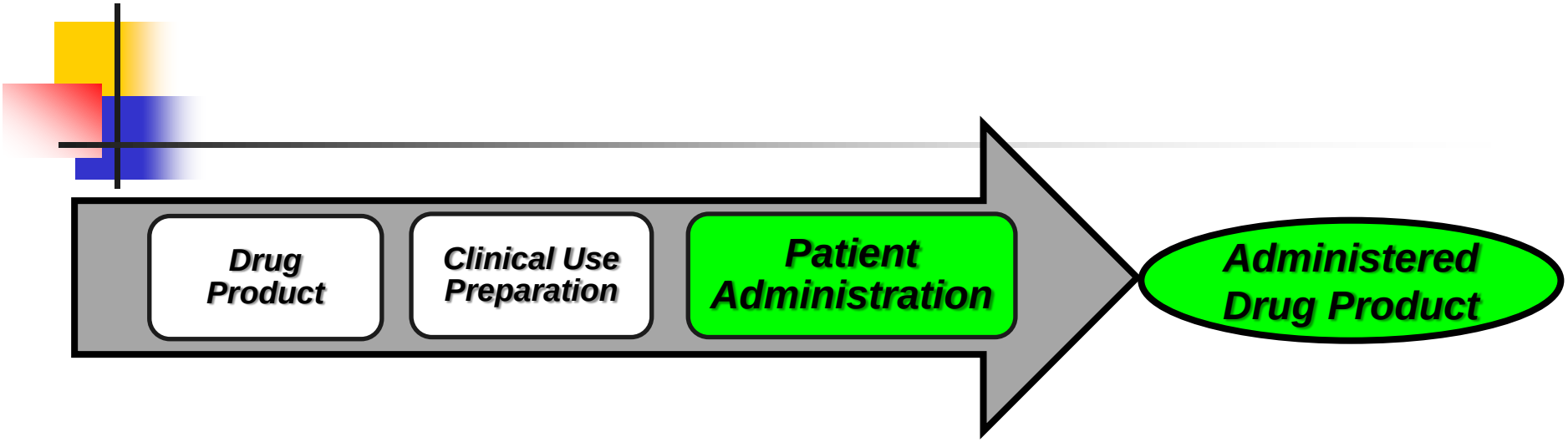
'It sounds almost sing-songy, but many times developers get very excited about the fact that their product produces an important effect that they don't worry as much about reproducibly making that product'

'In addition, as many of the cell and gene therapies now in clinical testing are among the first of their type developed, it's not always clear from the beginning what characteristics or attributes are most important for reliably assessing clinical effect. But, developers still need to try.

Peter Marks, M.D., Ph.D.
Director CBER, FDA

Presentation at the
World Medical Innovation Forum
May 2021

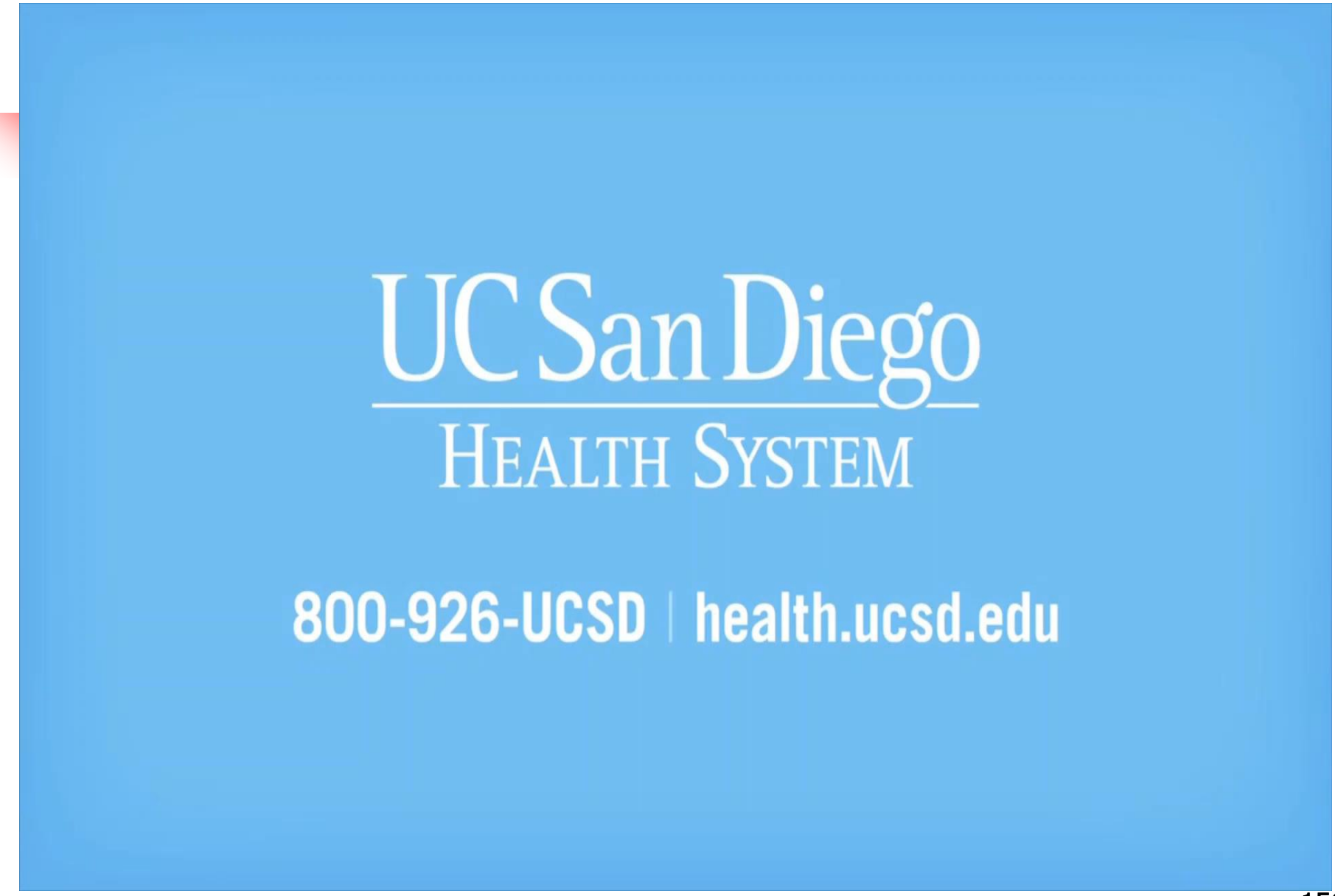
Applied Risk-Management Across the Manufacturing Process



- **Concerns for the delivery device**
  - Impact of the product on the device
  - Impact of the device on the product

Not always by injection into a vein!

Direct delivery of a gene therapy virus into the brain



Patient Administration of Cell & Gene Therapy Products

FDA CMC Expectations for Devices

f. Compatibility (3.2.P.2.6)

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

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

!! ***FDA caution***

PassageBio

Case Example: Patient Safety Concerns

FDA Phase 1 placed on Clinical Hold (June 2020)

in vivo virus gene therapy (gene replacement) directly into the brain

Received feedback from U.S. Food and Drug Administration (FDA) on Investigational New Drug (IND) application for PBGM01 – In June 2020, Passage Bio submitted its first ever IND for PBGM01 for the treatment of GM1 gangliosidosis to the FDA in collaboration with the University of Pennsylvania's Gene Therapy Program. Following this submission, the Company was notified that the IND was placed on clinical hold pending additional risk assessments of the biocompatibility of the proposed ICM delivery device. The ICM route of administration delivers PBGM01 directly to the brain into the cisterna magna, a space within the lower portion of the brain, with techniques and delivery devices commonly used both in current medical practice and other clinical trials, including those for gene therapy. The Company is evaluating options for conducting additional risk assessments while it awaits official written feedback from the FDA. During the IND review, the Company addressed specific clinical and protocol questions raised by the FDA, and the agency confirmed that there are no further clinical information requests. As a result of the clinical hold, the Company now expects to initiate dosing of its Phase 1/2 trial late in the fourth quarter of 2020 or early in the first quarter of 2021 and remains on track to report initial 30 day safety and biomarker data late in the first half of 2021.

IND Clinical Hold lifted January 2021

(6 month delay)

Deficient CLINICAL PLAN causes TERMINATIONS

Explains why senior management spends so much focus on the Clinical Plan, but …

Deficient CMC, cGMP, Quality System causes DELAYS

… but delays are costly also to a manufacturer!

QUESTIONS??

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

Course Summary

- ✓ **Overview of the ATMP Landscape**

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

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

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

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

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

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

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

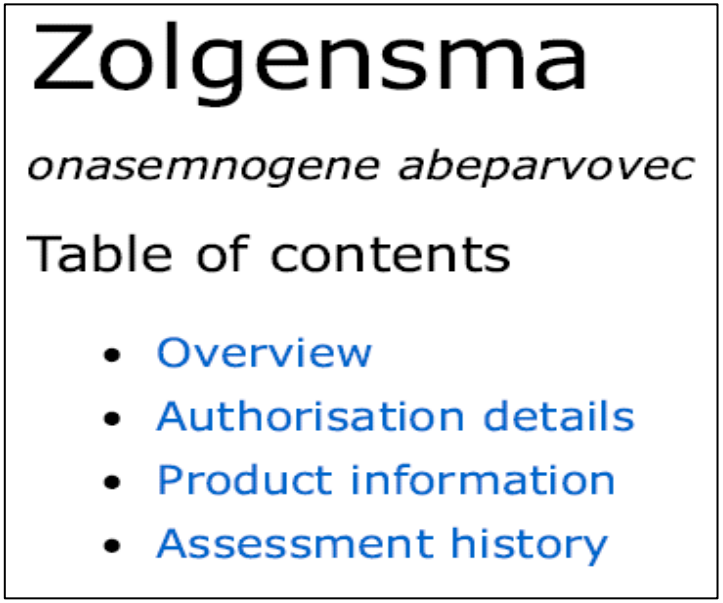
Thank you

RESOURCES

ATMPs approved by EMA (www.EMA.Europa.EU)

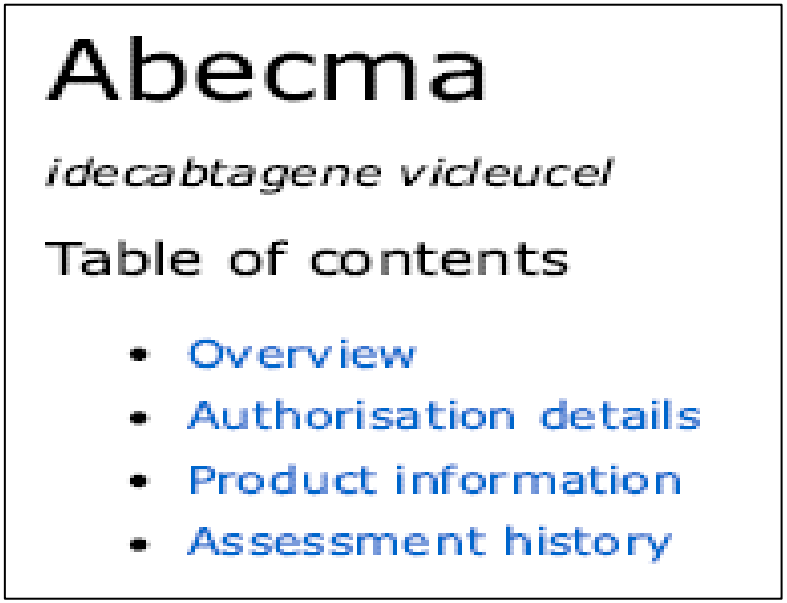
Google Search: EMA EPAR name of ATMP

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



EPAR – Assessment Report

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



EPAR – Assessment Report

CGTPs approved by FDA CBER

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

Search alphabetically by proper name

[Biologic]

Approval History, Letters, Reviews, and Related Documents

Product Information ZOLGENSMA

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

Supporting Documents

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

100 documents

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

Product Information ABECMA

- Package Insert - ABECMA

Supporting Documents

- Summary Basis for Regulatory Action - ABECMA
- March 26, 2021 Approval Letter - ABECMA
- Approved Risk Evaluation and Mitigation Strategies (REMS) - ABECMA
- Approval History, Letters, Reviews and Related Documents - ABECMA

17 documents

www.fda.gov/vaccines-blood-biologics/abecma-idecabtagene-vicleucel

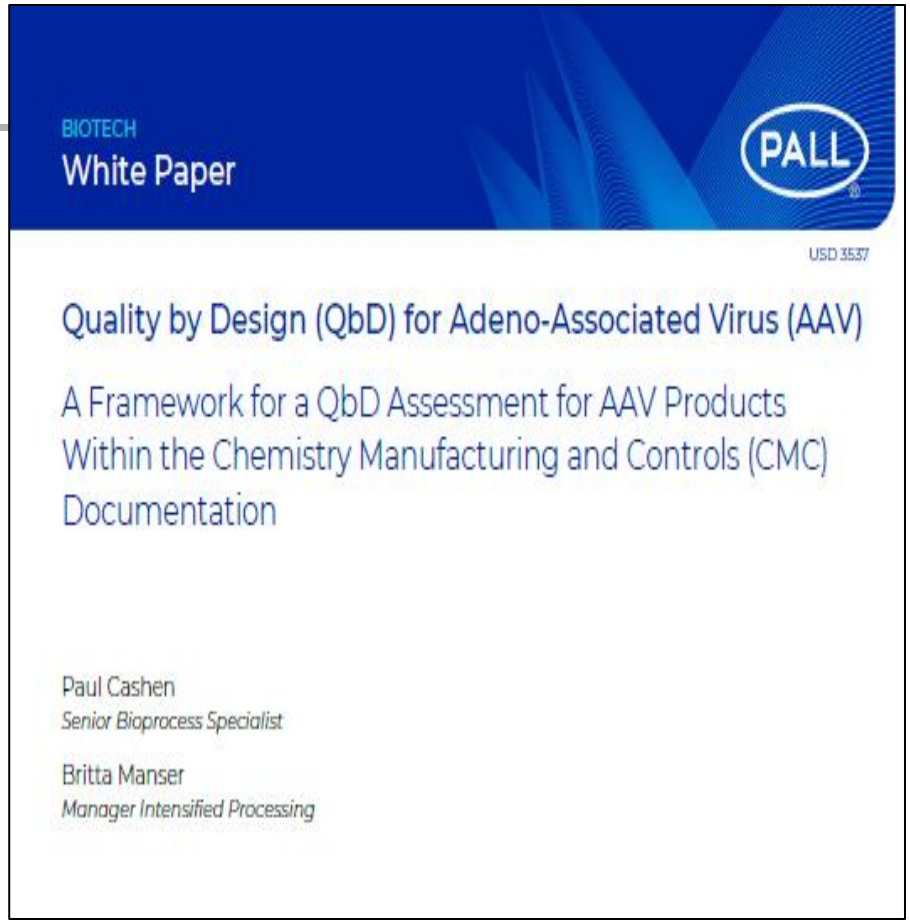
Cell & Gene Therapy Products – Annual Meetings

- **Past, Present, and Future State of Mycoplasma Testing**
  Speaker Presentation Tai Kenneth, Kite, a Gilead Company, 2021
- **Global CMC Convergence: an FDA Perspective**
  Speaker Presentation Schultz Kimberly, CBER, FDA, 2021
- **Potency Assay Development Cell-based Therapy for Cartilage Repair**
  Speaker Presentation Roël Giulietta, CO.DON AG, 2021
- **Product Structural Characterization for AAV-based Gene Therapy Development**
  Speaker Presentation Pu Yi, Biogen, 2021
- **Autologous Cell Therapy Phase Appropriate Control Strategies from Early Clinical Development to Commercialization**
  Speaker Presentation Polson Nolan, Bristol-Myers Squibb Company, 2021
- **Facilitating Advanced Technologies in Cell and Gene Therapies**
  Speaker Presentation Oh Steven, CBER, FDA, 2021
- **BLA Post-Approval Case Studies for Oncolutic Virus, IMYGIC® (TALIMONGENE LAHERPAREPVEC)**
  Speaker Presentation McQueen Jocelyn, Amgen Inc., 2021
- **Overcoming the Challenges Getting ATMPs Approved in the European Union**
  Speaker Presentation Celis Patrick, European Medicines Agency (EMA), 2021

free, downloadable presentations at www.CASSS.org

(for a limited time after the meeting is held)

Cell & Gene Therapy Products – free information



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

much free literature and webinars from vendors and CMOs!