Practical Application of Phase-Appropriate GMPs & Quality to Clinical Development of ATMPs

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

PDA Parenteral Drug Association

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Practical Application of Phase-Appropriate GMPs & Quality to Clinical Development of ATMPs

Course Outline

1. **Quick Overview of ATMPs (CGTPs)**
   - ✓ Critical terminology landscape (e.g., CAT, OTAT, RMAT)
   - ✓ Diversity of ATMPs challenge the application of GMPs and Quality
2. **ATMP GMPs and Quality Risk Consequences**
   - ✓ Necessity of a risk-based approach
   - ✓ Limitations of adapting from guidelines for rproteins and mAbs
3. **ATMP GMPs and Quality Specific Guidelines During Clinical Development**
   - ✓ EMA/FDA
   - ✓ PDA and industry practice

Goal

not just give a list of what to do or not to do,
but how to approach/think about what to do,
for these diverse type of medicinal products!

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

"If you are humble, nothing will touch you, neither praise nor disgrace, because you know what you are"

Mother Teresa, Missionaries of Charity in Calcutta India, 1910-1997

- ***40+ years experience in Chemistry, Manufacturing & Control (CMC) strategies for the clinical development and commercialization of biopharmaceutical recombinant proteins and monoclonal antibodies***
- ***Senior CMC Expert and Vice President Quality in the industry (IDEC Pharmaceuticals, Immunex)***
- ***Immediate Past Chair PDA Biopharmaceutical Advisory Board***
- ***15+ years as a CMC regulatory consultant to the biopharmaceutical industry: recombinant proteins, monoclonal antibodies, biosimilars, cellular and gene therapy (ATMP) medicines***

Who are you?

- ***My name is …. And I work for ….***
- ***My experience with ATMPs is ….***
- ***My interest in taking this course is ….***

What a difference a year has made for ATMPs!

(since course taught last June at this conference)

2017/2018 — **market approved**

- ***Kymriah (cancer treatment CAR T-cell gene therapy)*** — ***FDA/EMA***
- ***Yescarta (cancer treatment CAR T-cell gene therapy)*** — ***FDA/EMA***
- ***Luxturna (vision restoration gene therapy virus)*** — ***FDA/EMA***

2018/2019

autologous CD34+ cell enriched population that contains hematopoietic stem cells transduced with lentiglobin BB305 lentiviral vector encoding the beta-A-T87Q-globin gene

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

On 28 March 2019, the Committee for Medicinal Products for Human Use (CHMP) on the basis of the draft Committee for Advanced Therapies opinion, adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Zynteglo, intended for the treatment of transfusion-dependent β-thalassaemia (TDT).

As Zynteglo is an advanced therapy medicinal product, the CHMP's positive opinion is based on an assessment by the Committee for Advanced Therapies. Zynteglo was designated as an orphan medicinal product on 24 January 2013 and was reviewed under EMA's accelerated assessment programme. The applicant for this medicinal product is bluebird bio (Netherlands) B.V.

To eliminate blood transfusions due to severe anemia

ATMPs becoming a game-changer in the industry

Kite, A GILEAD Company

GILEAD

~$12 billion

Spark THERAPEUTICS

Roche

~$5 billion

PARAGON BIOSERVICES

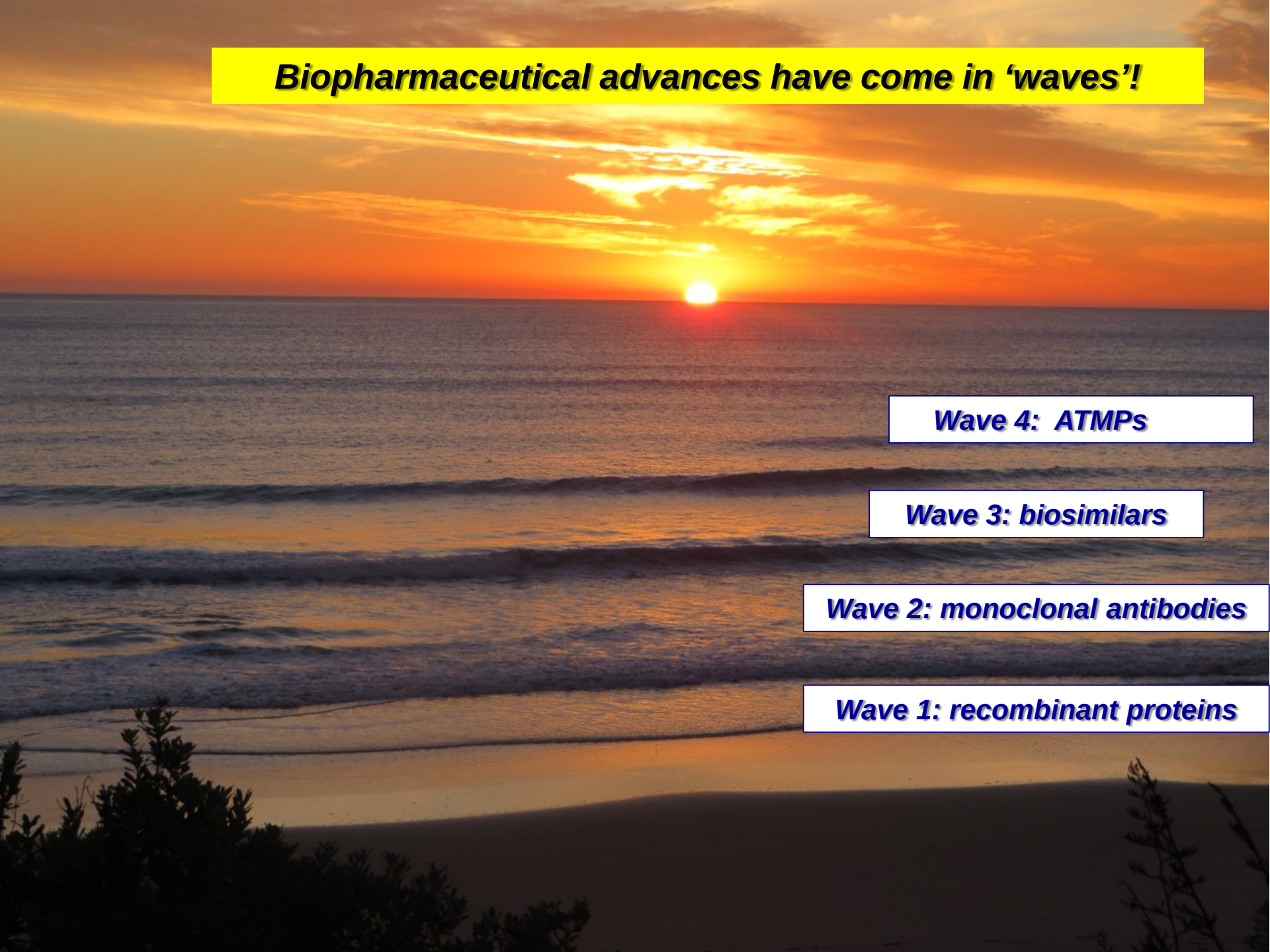
Catalent BIOLOGICS

~$1 billion

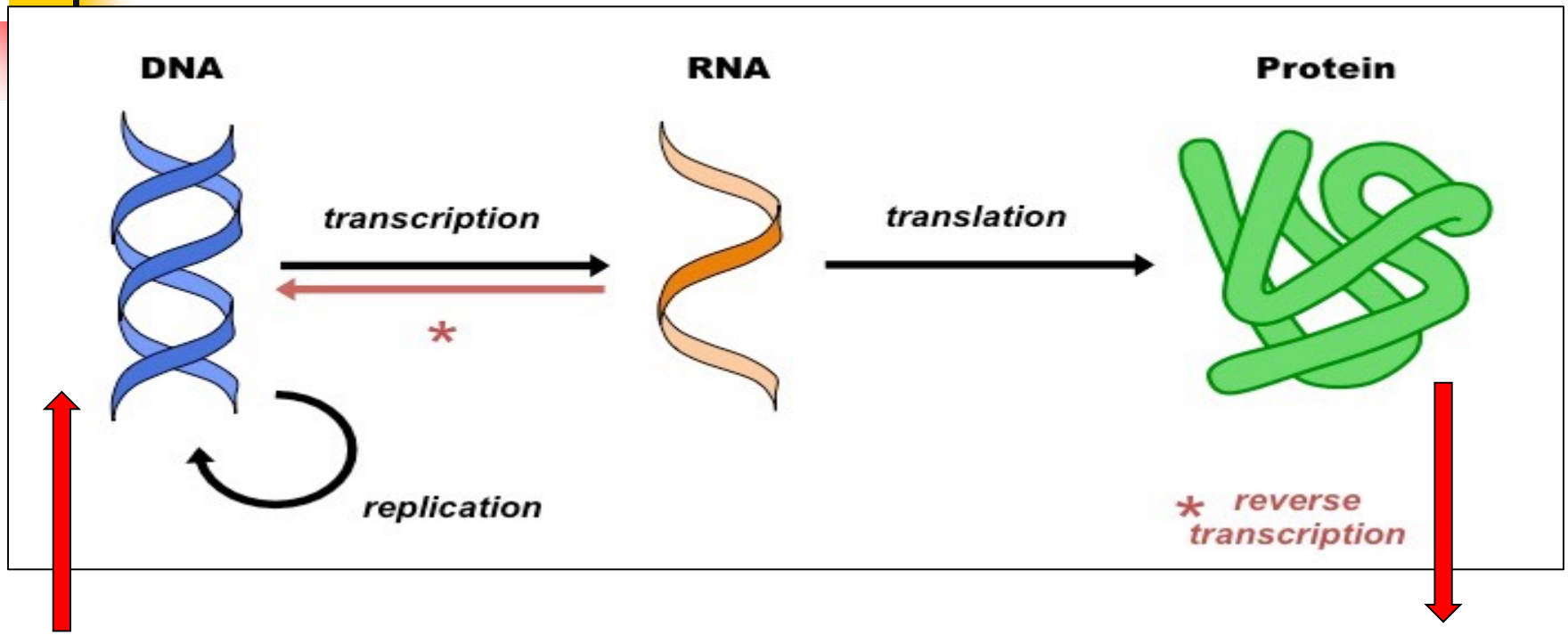
Practical Application of Phase-Appropriate GMPs & Quality to Clinical Development of ATMPs

1. Quick Overview of ATMPs (CGTPs)

- ✓ ***Critical terminology landscape for these products***
  - ***ATMP, CAT, CGTP, OTAT, RMAT, …***
- ✓ ***Diversity of ATMPs challenge the application of GMPs and Quality***


Biopharmaceutical advances have come in 'waves'!
Wave 4: ATMPs
Wave 3: biosimilars
Wave 2: monoclonal antibodies
Wave 1: recombinant proteins

WAVES 1, 2 and 3

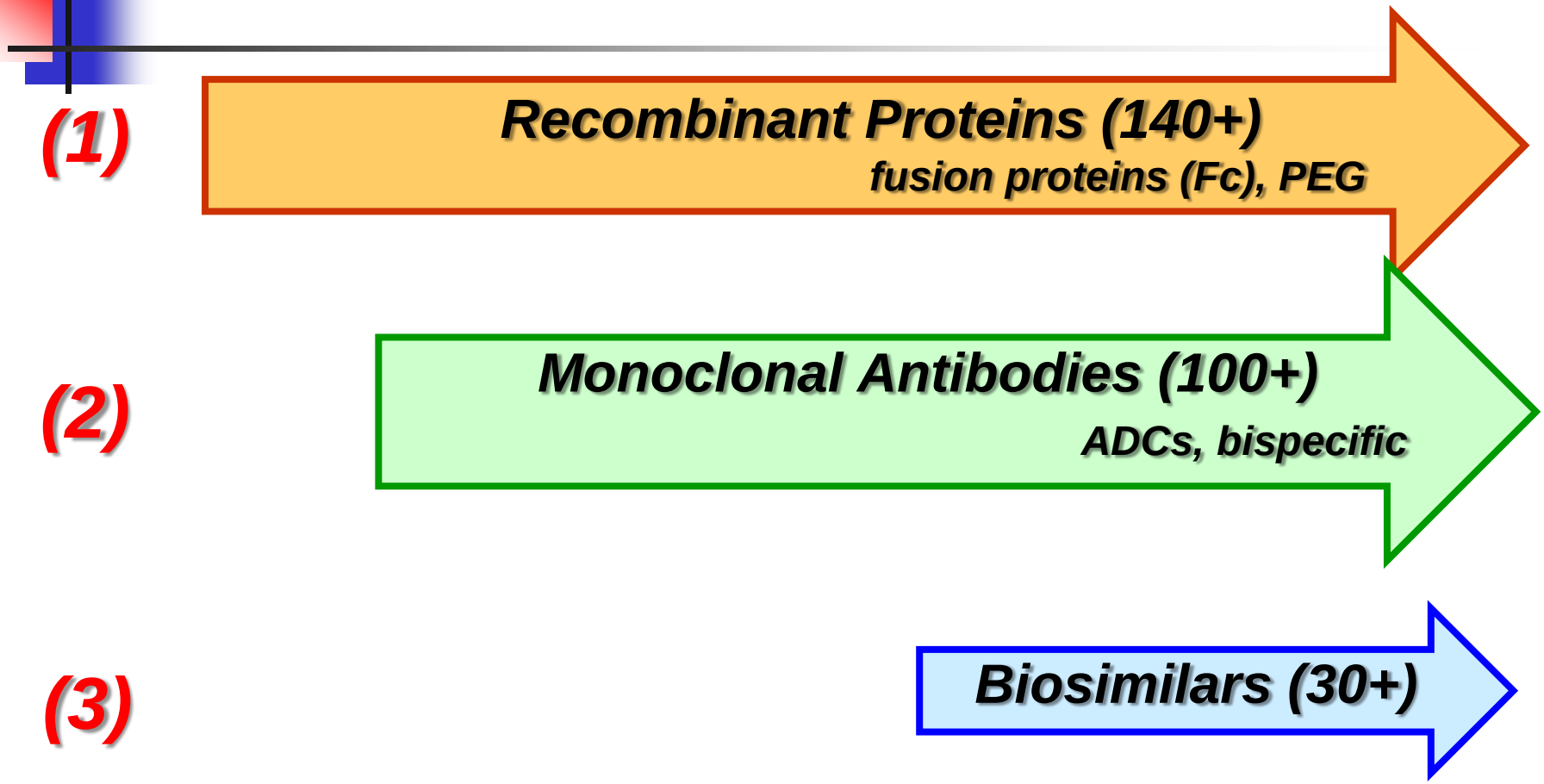


Foreign DNA inserted into a living microorganism (e.g., E. coli, CHO) that can then produce the specific protein/mAb

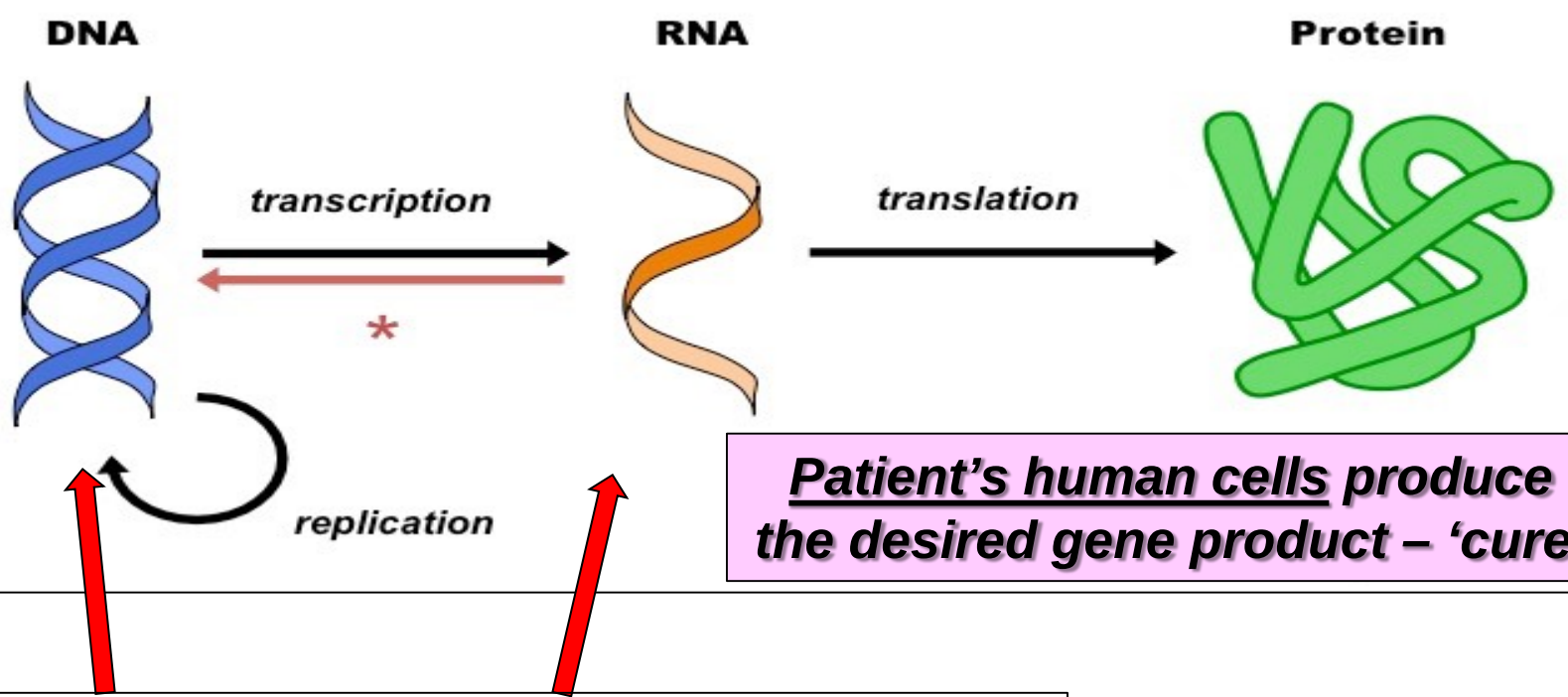
Recombinant protein/mAb isolated, purified, formulated for human administration

The biopharmaceutical industry has experienced 3 'waves' of new product types in the past 30 years

ALL non-living proteins



WAVE 4



Patient's human cells produce the desired gene product – 'cure'

Transfer of new genetic capability into or manipulation of existing genetic capability in living human cells

(ongoing debate about the amplitude of this upcoming 4th wave)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

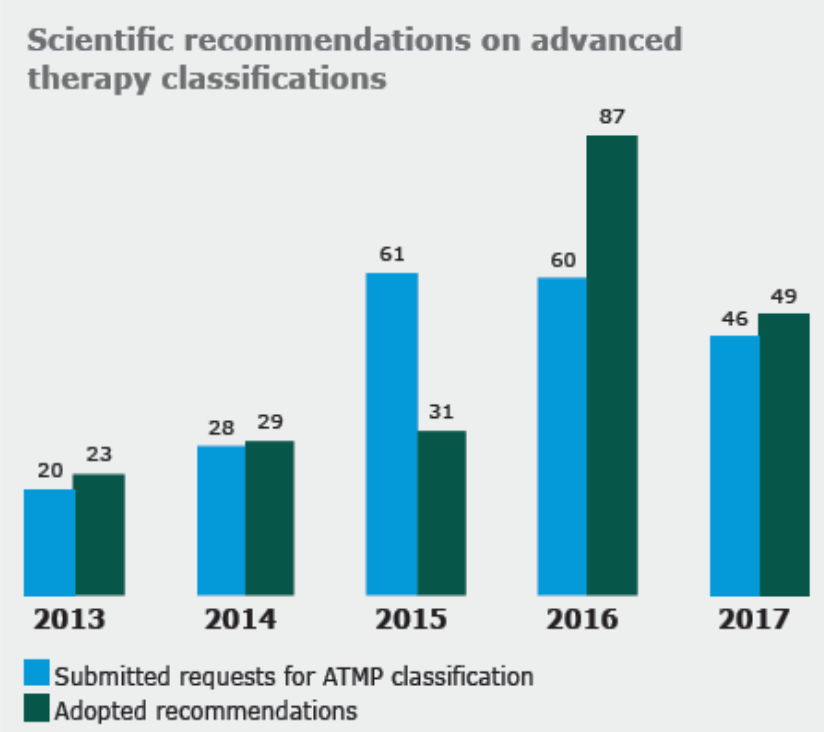
Regulatory authority consensus:

'a big wave'!

Over 200 medicines under clinical development have been designated as ATMPs

Annual Report 2017

published May 2018



A total of 49 recommendations were adopted in 2017, 43% less than in 2016. The number of requests for ATMP classification was also lower in 2017 – 46 requests compared to 60 in 2016. The 2017 figures represent the return to trend, following an increase in 2015 and 2016. This increase was due to the decision of one Member State (Poland) to recommend to all academics developing cell-based products to apply for ATMP classification (prior to them starting any clinical trial).

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

January 15, 2019

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

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

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

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

Critical ATMP Terminology Landscape

European Medicines Agency (EMA)

ADVANCED THERAPY MEDICINAL PRODUCT (ATMP)

COMMITTEE ON ADVANCED THERAPIES (CAT)

U.S. Food and Drug Administration (FDA)

ANALOGOUS BIOLOGICAL PRODUCT

CELLULAR AND GENE THERAPY PRODUCT (CGTP)

OFFICE OF TISSUES AND ADVANCED THERAPIES (OTAT)

REGENERATIVE MEDICINE ADVANCED THERAPY (RMAT) DESIGNATION

European Medicines Agency (EMA)

Advanced Therapy Medicinal Products (ATMPs)

Regulation (EC) No 1394/2007

(legal definition of ATMPs)

(member state – hospital exemption)

Committee for Advanced Therapies (CAT)

classification, review of ATMPs

ATMPs are …

(1) Gene Therapy Medicinal Products

(a) contains an active substance which contains or consists of a **recombinant nucleic acid** used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

AND

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

'vaccines against infectious diseases' - excluded

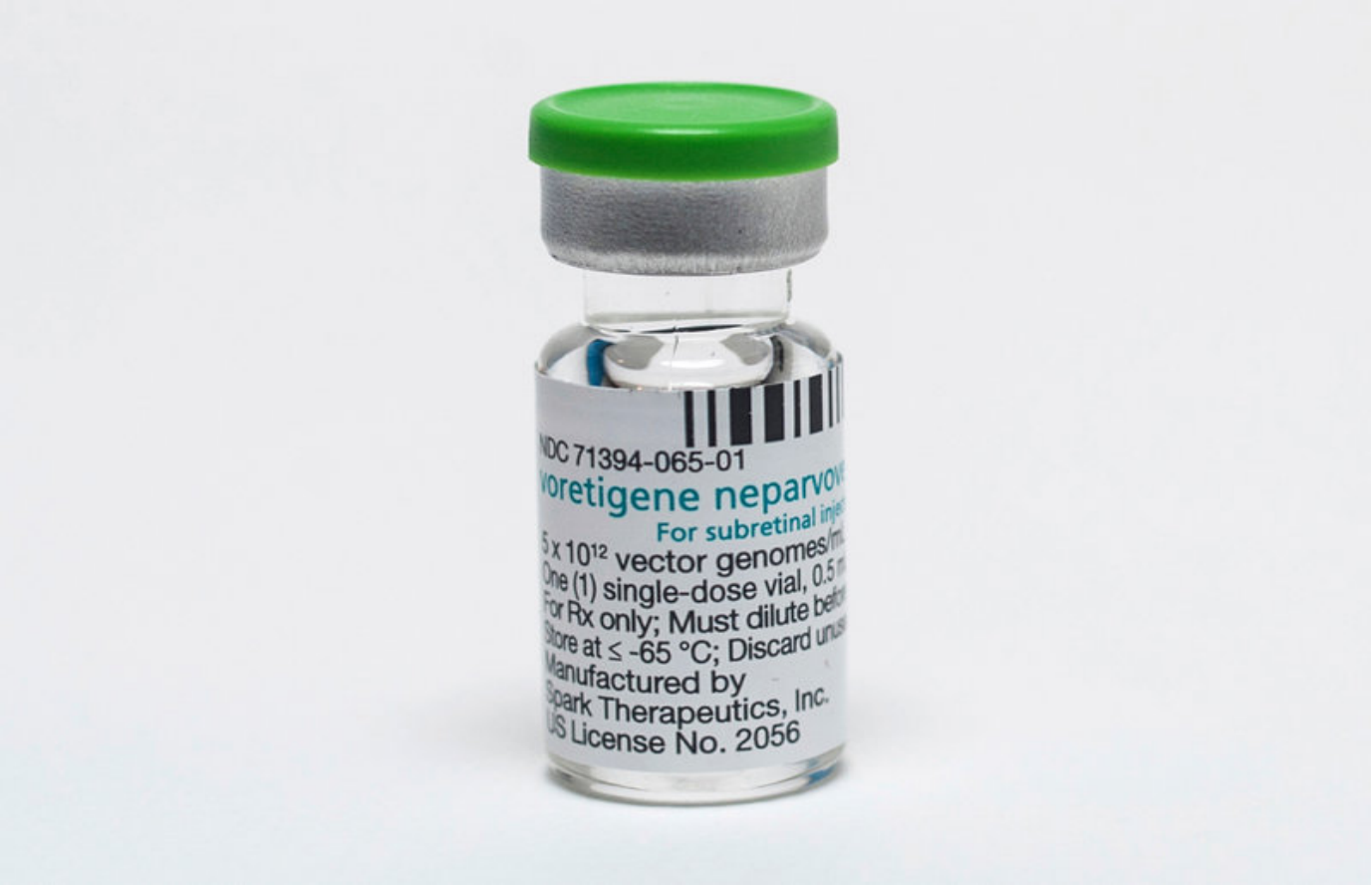
Video

Living virus (gene replacement) – in vivo

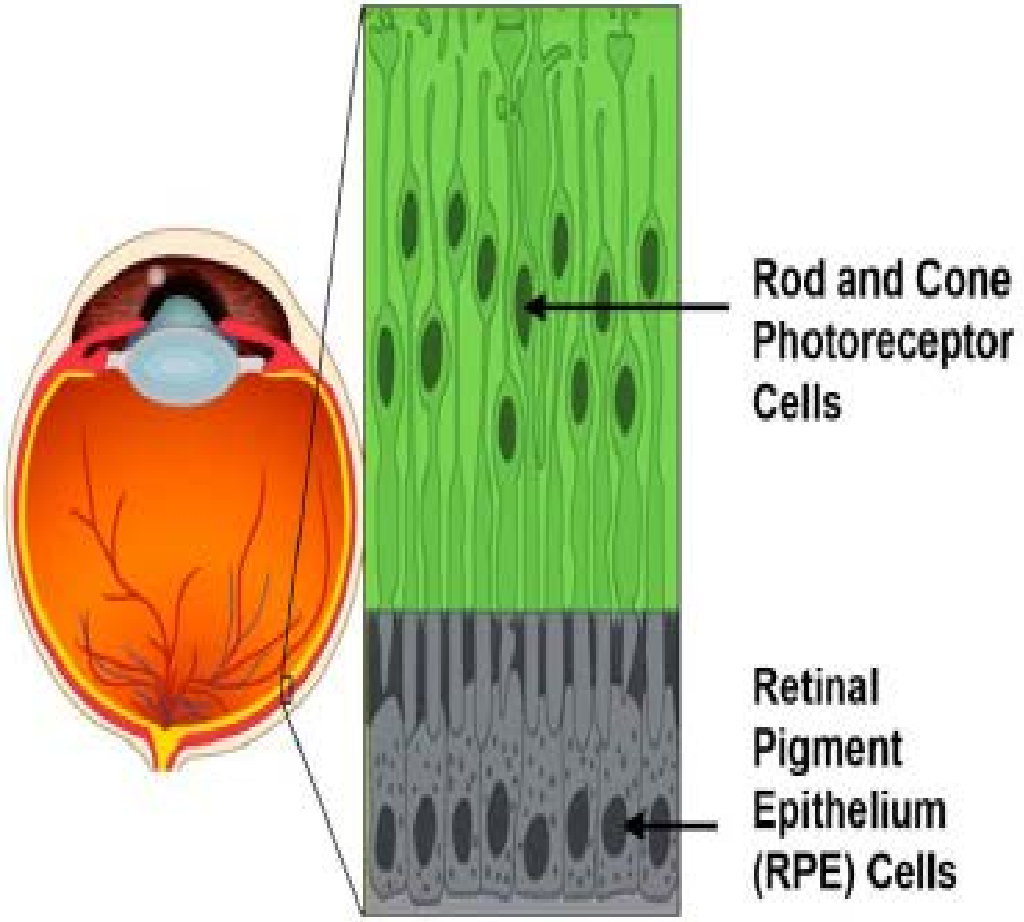
Spark Therapeutics LUXTERNA

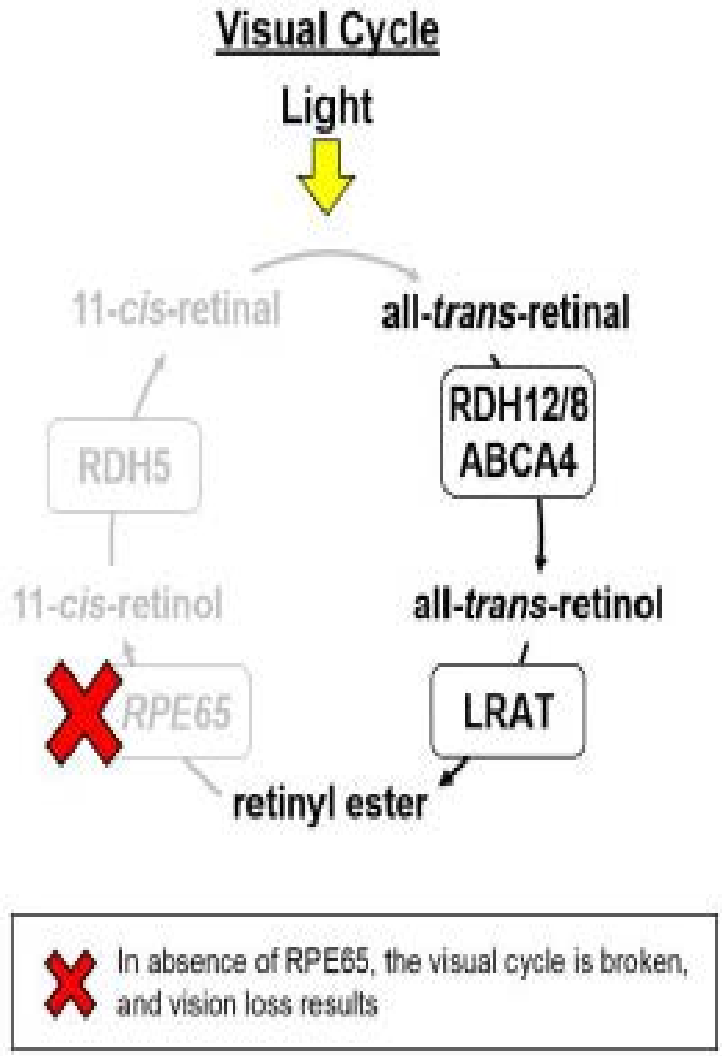
adeno-associated virus vector (with RPE65 gene)

to treat vision loss FDA/EMA approved 2017/2018



RPE65 gene produces a protein necessary in the cycle for vision





Direct injection of live virus into eye to replace defective gene

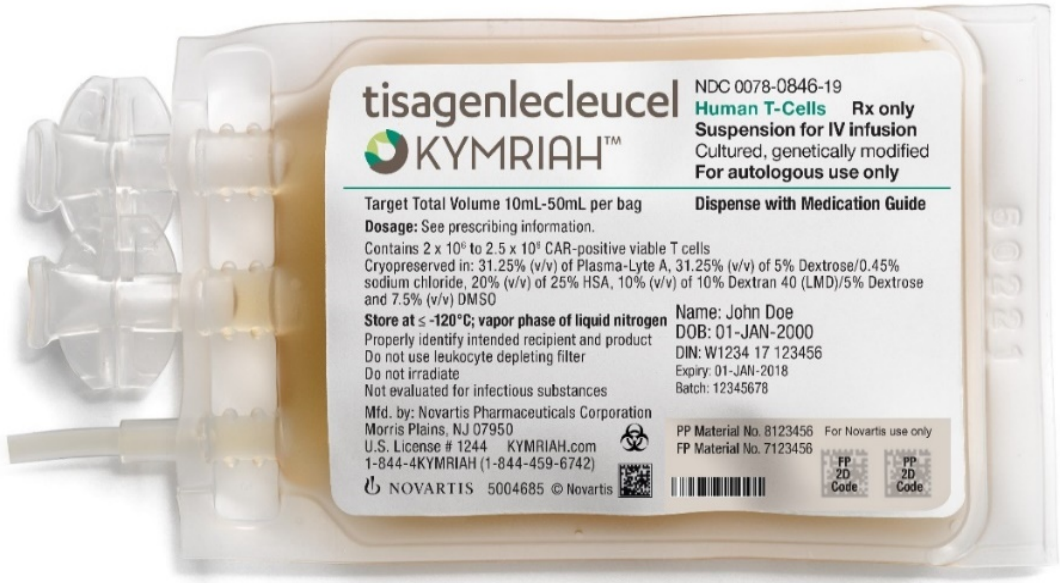
Living genetically engineered cells – ex vivo

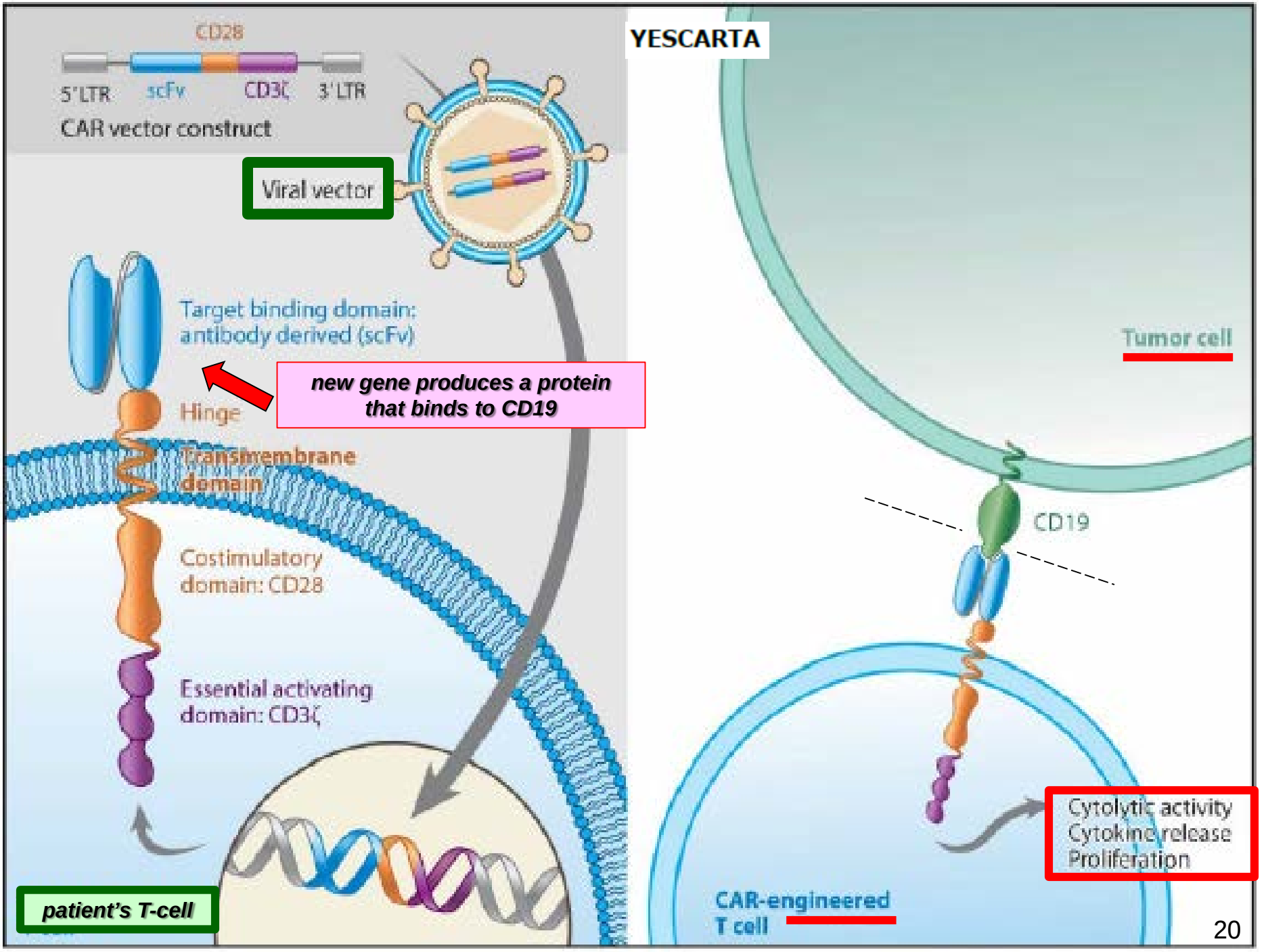
Novartis KYMRIAH

Gilead/Kite YESCARTA

Autologous genetically modified (CAR – chimeric antigen receptor) T cells to treat acute lymphoblastic leukemia (ALL)

FDA/EMA approved 2017/2018




CD28
5'LTR
scFv
CD3ζ
3'LTR
CAR vector construct
YESCARTA
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
Tumor cell
CD19
Cytolytic activity
Cytokine release
Proliferation
CAR-engineered T cell
patient's T-cell

ATMPs are …

(2) Somatic Cell Therapy Medicinal Products

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

FDA: 'more than minimal manipulation'

OR

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

FDA: 'not for homologous use'

AND

(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells

'Substantial Manipulation' is …

The cells or tissues are manipulated during the manufacturing process so that their biological characteristics, physiological functions or structural properties are modified to be relevant for their intended function e.g.,

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

'Not Substantial Manipulation' is …

- ***cutting***
- ***grinding***
- ***shaping***
- ***centrifugation***
- ***sterilization***
- ***irradiation***
- ***cell separation***
- ***concentration***
- ***freezing***
- ***cryopreservation***

ATMPs are …

(3) Tissue Engineered Products

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

OR

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

'tissues that are exclusively non-viable are excluded'

U.S. Food and Drug Administration (FDA)

Cellular and Gene Therapy Products (CGTPs)

Office of Tissues and Advanced Therapies

(OTAT, with CBER)

Public Health Service (PHS) Act 1944

(biological product legal definitions)

Regenerative Medicine Advanced Therapy

(RMAT designation)

Public Health Service (PHS) Act 1944
(last revision 2009)

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

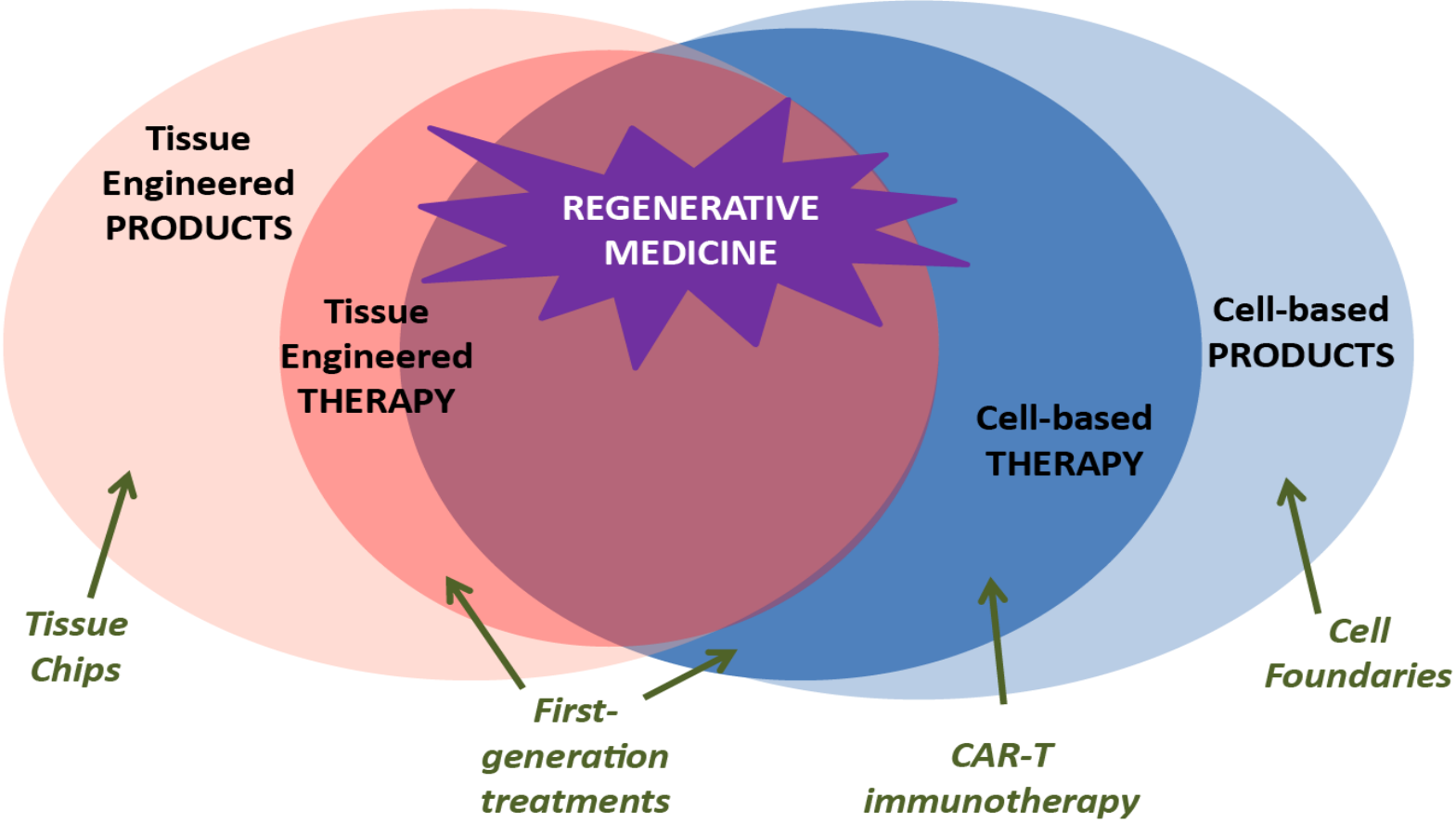
Gene-based (if from a biological origin) and cell-based medicines are under the category of 'analogous products'

chemically synthesized DNA or RNA products are chemical drugs – Alnylam's Onpattro [small-interfering (si) ds RNA, lipid]

Regenerative Medicine Advanced Therapy (RMAT)

"a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies/products"

(what's in, what's out – still under debate)



Regenerative Medicine Advanced Therapy (RMAT) Designation

	Breakthrough Therapy Designation	Regenerative Medicine Advanced Therapy Designation
Statute	Section 506(a) of the FD&C Act, as added by section 902 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)	Section 506(g) of the FD&C Act, as added by section 3033 of the 21st Century Cures Act
Qualifying criteria	A drug that is intended to treat a serious condition, **AND** preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	A drug is a regenerative medicine therapy, AND the drug is intended to treat, modify, reverse, or cure a serious condition, AND preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition
Features	• All fast track designation features, including: ▪ Actions to expedite development and review ▪ Rolling review • Intensive guidance on efficient drug development, beginning as early as Phase 1 • Organizational commitment involving senior managers	• All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints • Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements **Expedited Programs for Regenerative Medicine Therapies for Serious Conditions**
When to submit	With the IND or after and, ideally, no later than the end-of-phase 2 meeting	
FDA response	Within 60 calendar days after receipt of request	**Center for Biologics Evaluation and Research November 2017**
Designation Rescission	Designation may be rescinded later in product development if the product no longer meets the designation-specific qualifying criteria	

CONFUSED!

analogous product

ATMP

RMAT

CGTP

substantial manipulation

more than minimal manipulation

? QUESTIONS ?

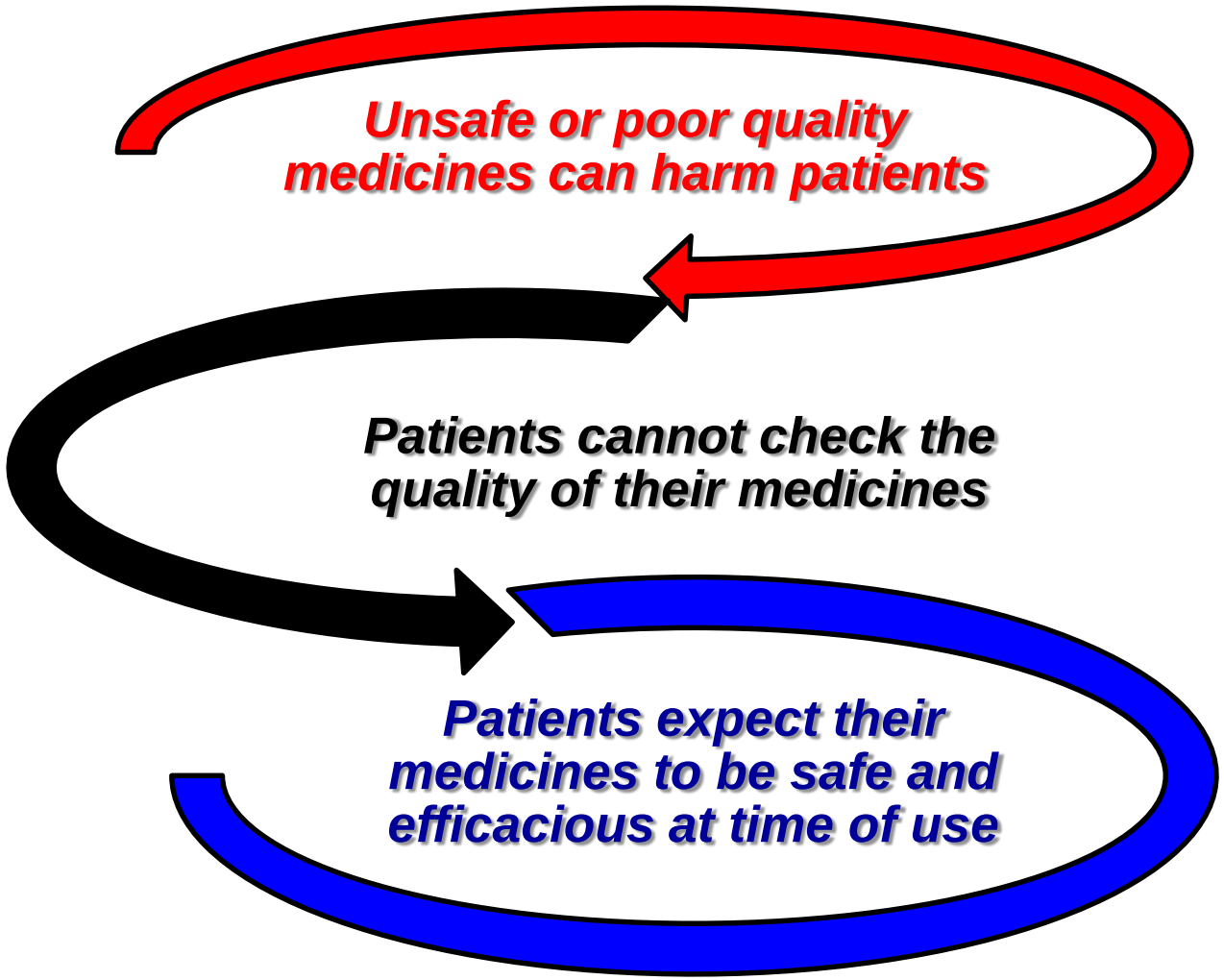
Practical Application of Phase-Appropriate GMPs & Quality to Clinical Development of ATMPs

2. ATMP GMPs and Quality Risk Consequences

- ✓ ***Necessity of a risk-based approach***
- ✓ ***Limitations of adapting from guidelines for recombinant proteins and monoclonal antibodies (mAbs)***

GMPs and Quality – necessary to protect the patient!

(facility, process, product, staff – "doing what is right")



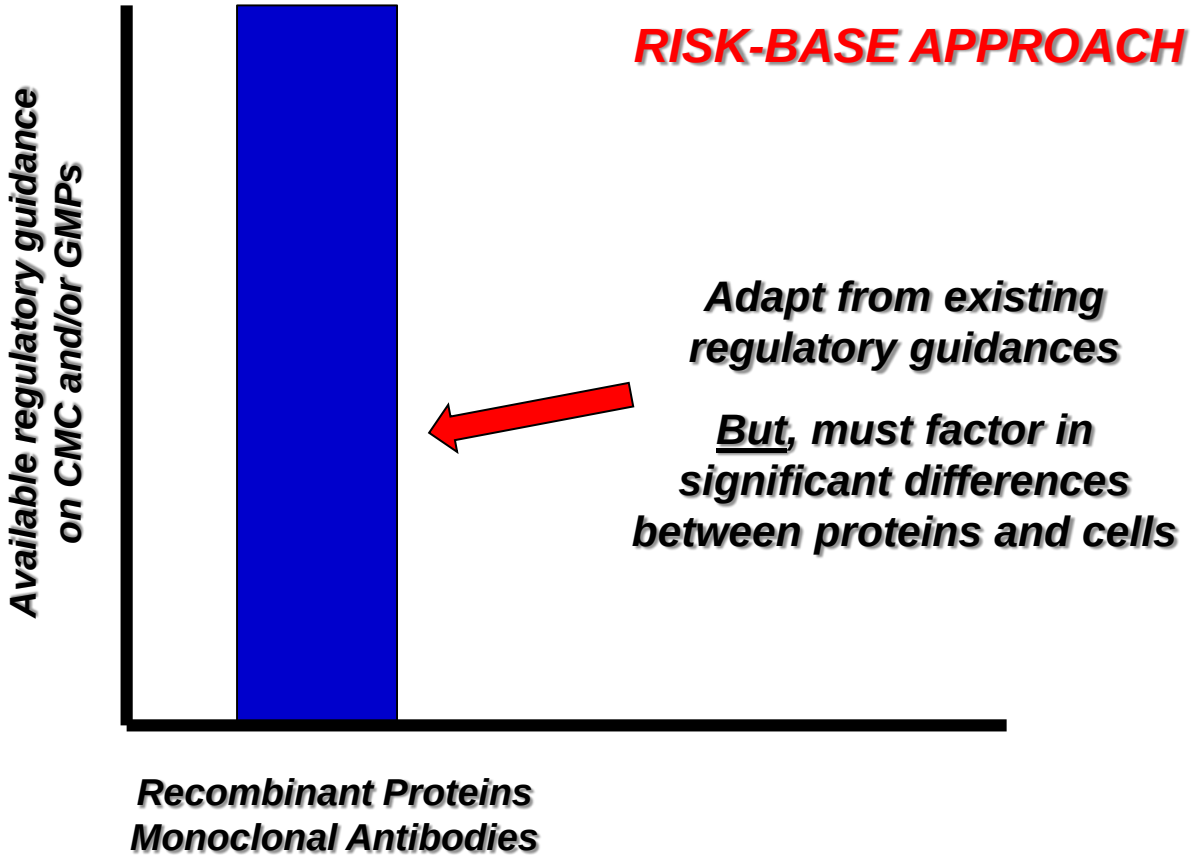
GMPs and Quality – risk-based approach

(needs to be practical and common sense)

- ***A risk-based approach focuses the process and product development on aspects that, directly or indirectly, may affect the safety and efficacy of the product***
- ***A risk-based approach does not mean doing less to ensure safety and efficacy but <u>doing the right amount at the right time</u> based on the understanding of the risks to product quality and patient safety***
- ***A risk-based approach attempts to avoid non-value-added activities and focuses efforts on critical activities***
- ***<u>Thus</u>, a risk-based development plan actually enhances safety in early clinical study phases, even when product understanding and resources may be limited***

(also referred to as 'Graded Phase-Appropriate' approach)

Availability of regulatory guidance on CMC and/or GMPs



GMPs & Quality

Difference in Risks

Comparison	Recombinant Proteins & mAbs	ATMPs (CGTPs)
Product Type	Non-living medicine (proteins)	Living medicine (virus and/or cells)

GMPs & Quality Different Risks – Due to Type of Product

- ***Viruses and cells must be kept alive! 24/7 [Not proteins]***
- ***Very high threat of adventitious agent (e.g., virus, mycoplasma, microbes) contamination due to so many manual manipulations and inability of filtration!***

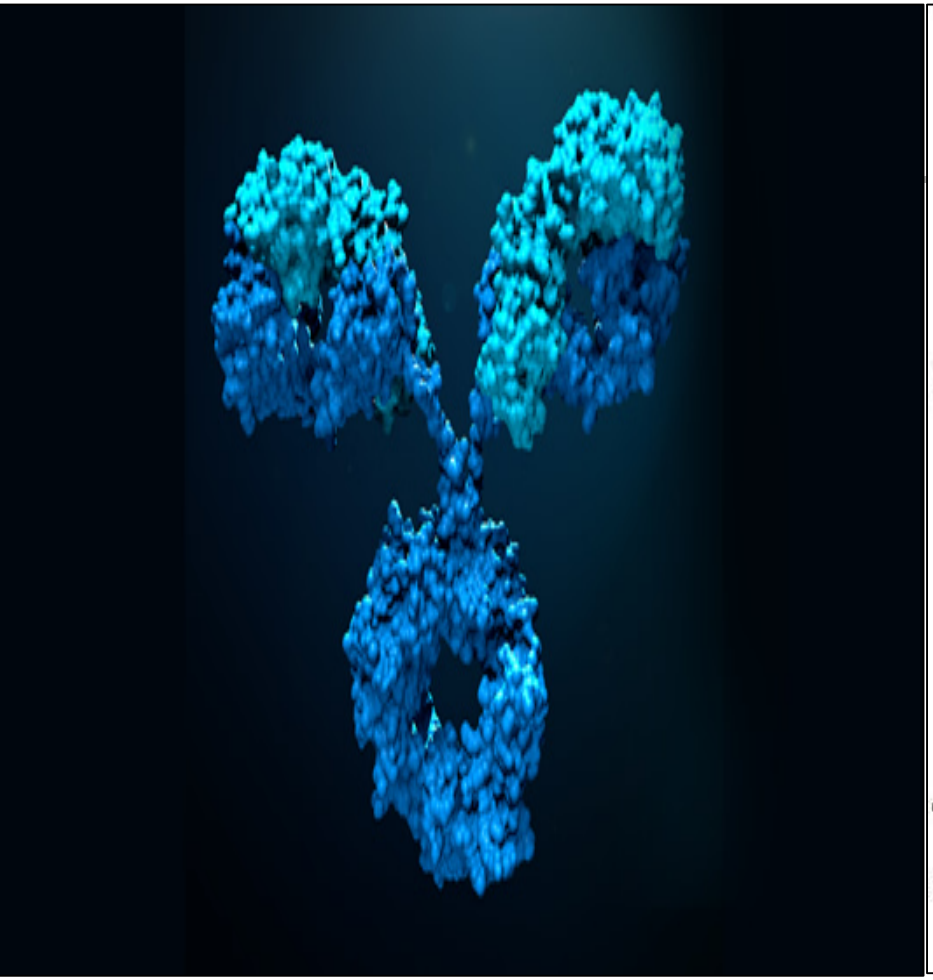
  [Protein processes are more automated, and product can be sterile filtered]

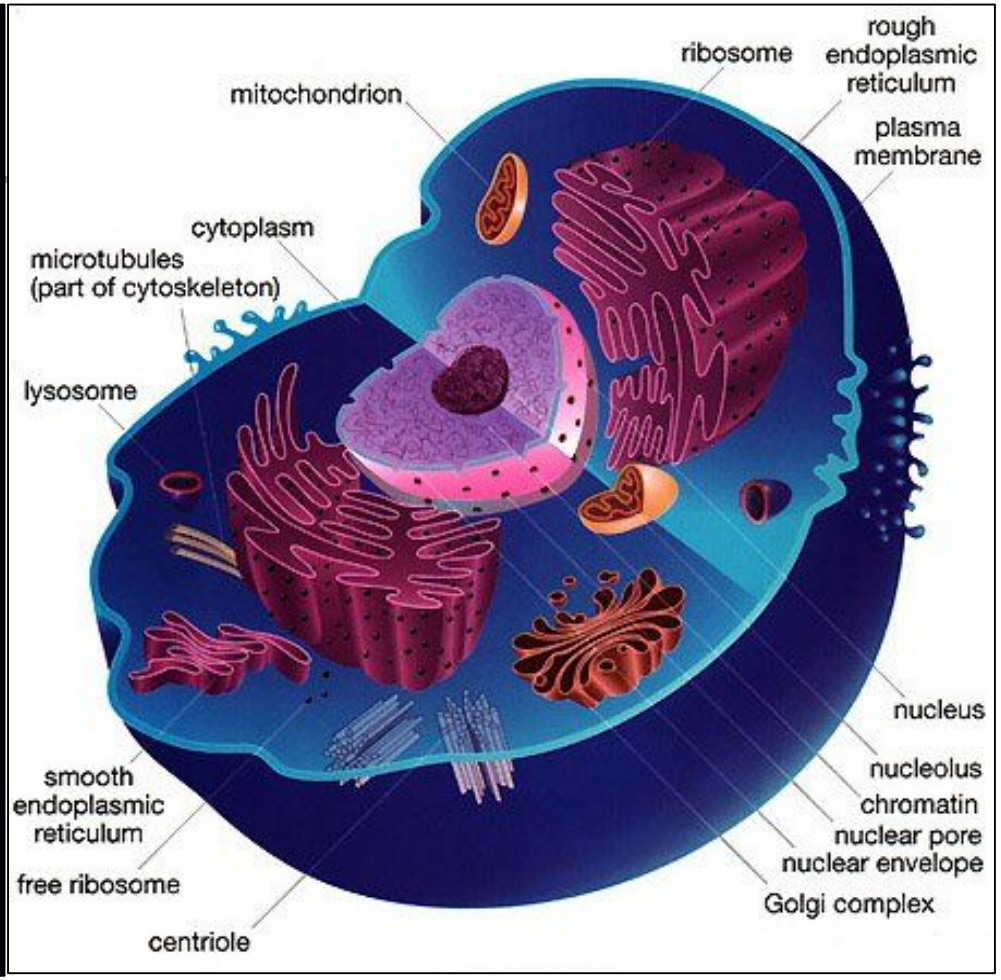
- ***"Cell therapy products have unique complexities due to the dynamic nature of living cells. For example, cells may present a variety of molecules on their membranes and express a variety of factors. These molecules and factors may be affected by the microenvironment and change over time."***

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
June 2015

While protein-based biopharmaceuticals are complex, they are no where as complex as living cells!





non-living medicine
~2 nm size
single protein
(possible 2 or 3 functional activities)

<u>living</u> medicine
~10 µm size
18K+ functionally active genes (proteins)
(not known how they interact)

GMPs & Quality

Difference in Risks

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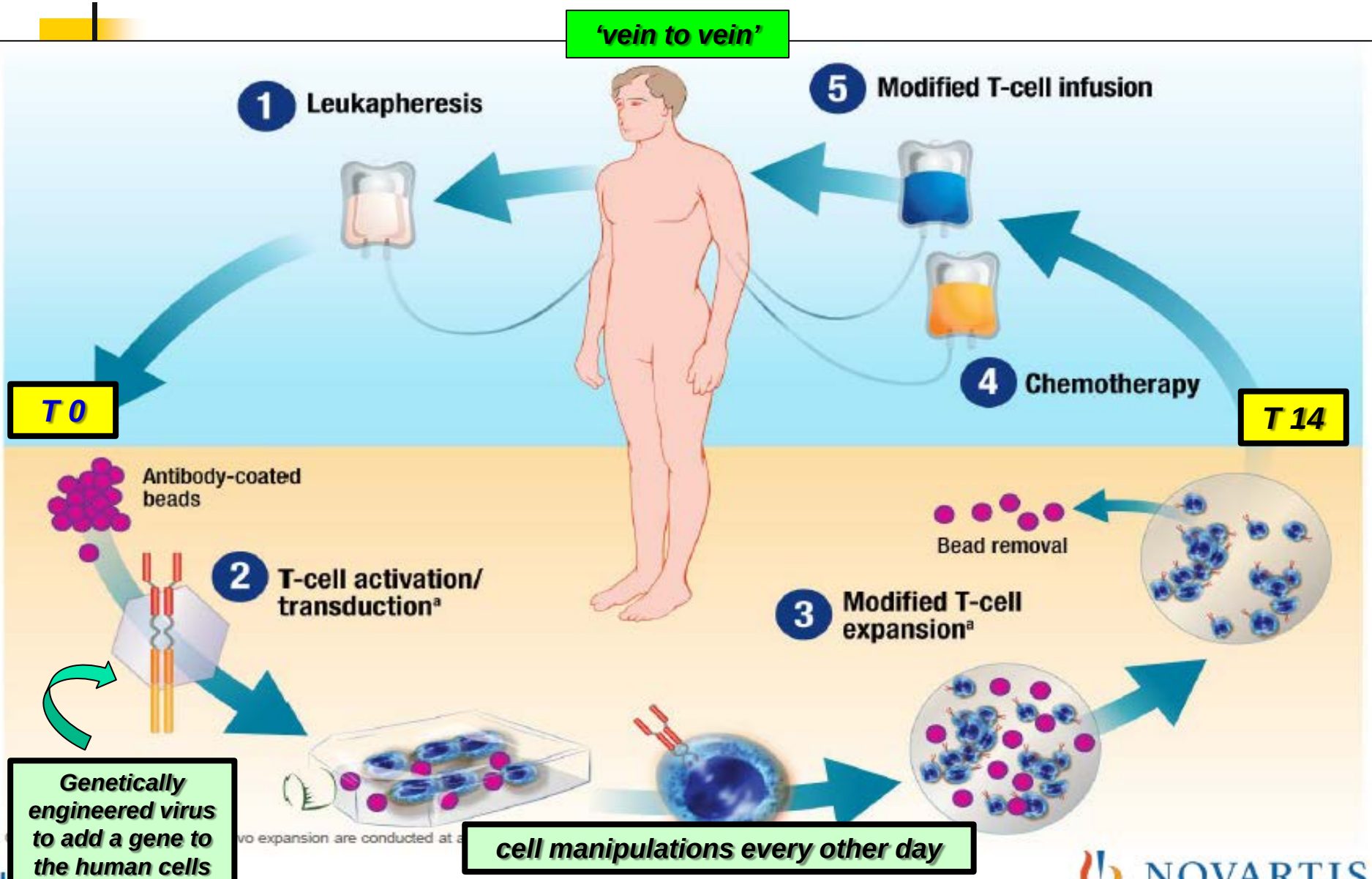
Link to Clinician and Patient	Batch independent of specific patients	Batch dependent upon clinician and patient (traceability)
Pressure on Manufacturing	None, as long as adequate inventory	Patient could die if batch not available

GMPs & Quality Different Risks – Link to Clinician/Patient

Timing, traceability and manufacturing success – ALL critical to the patient!



NOVARTIS

GMPs & Quality

Difference in Risks

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Pressure on Manufacturing	None, as long as adequate inventory	Patient could die if batch not available
Manufactured Batch Size	1 batch serves 100's or more patients	1 batch serves 1 patient
Batch Inventory	All released batches comparable	Wrong batch can kill patient

GMPs & Quality Different Risks – Specificity of Product Batch

1) ***Recombinant Proteins & Monoclonal Antibodies***
2) ***Gene Therapy DNA/RNA Plasmids, Genetically-Engineered Viruses***
3) ***Allogeneic Cells***

1 batch = 100's or more patient doses

---

4) ***Autologous Cellular Therapy (significantly manipulated)***
5) ***Autologous Gene Therapy Cell-Based Medicines***

1 batch = 1 patient dose

(challenge to control all sources of variability when each batch is a different 'product')

The new ATMP manufacturing facility has more of a 'research lab feel'

rProtein manufacture

Cell therapy manufacture

Need more protein medicine – scale up!

SAMSUNG BIOLOGICS

360,000L of biomanufacturing capacity (24 x 15,000 L)

Need more patient cell batches – scale out!

- Multiple suites and workstations with dedicated equipment
- Off the shelf, bench top equipment
- BSC for aseptic manipulations
- Modular approach
- "Scale out" opposed to "Scale up"

Kite Pharma

GMPs & Quality

Difference in Risks

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Product Characterization	Extensive analytical and bioassay tools	Limited
QC Testing	Adequate samples and test methods available	Limited samples; urgency to complete testing
QA Batch Disposition	Completed prior to batch release	Decision within 'patient window'

GMPs & Quality Different Risks – Pressure on the Quality Unit

- *Majority of QC test methods use complex technologies (flow cytometry, qPCR, cell-based bioassays)*
- *Restrictions of test samples (matrix interference, patient variability)*
- *Restrictions on test methods (limited sample volume, rapid methods)*
- *QA systems to release batch within days (not months – proteins) (CAPA, batch record closeout, CofA completion)*

GMPs & Quality

Difference in Risks

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QA Batch Disposition	Completed prior to batch release	Decision within 'patient window'
GMP Safety	Must follow GMPs, from FIH onwards	

GMPs & Quality Different Risks – Patient Safety for FIH!

Take GMPs seriously during clinical development!

National Institutes of Health (NIH) in violation of GMPs!

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

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

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

FDA Warning Letter to the NIH

GMP violations at Clinical Phases 1 and 2

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

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

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

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

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

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

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

National Cancer Institute (NCI) facility for gene therapy products also later found to be in violation of GMPs during the NIH review

Tuesday, April 19, 2016

Statement on Review of NIH Sterile Production Facilities

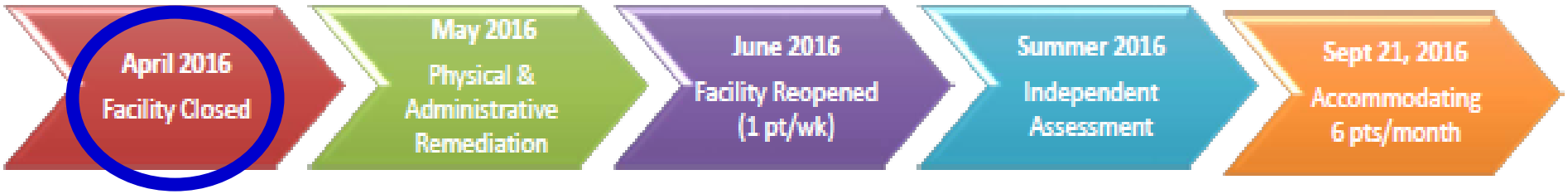
In light of serious problems identified in the NIH Clinical Center Pharmaceutical Development Section last year, NIH launched a multifaceted effort to ensure that processes for patient safety and quality of care at the hospital are of the highest standards. Accordingly, NIH hired two companies specializing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

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

National Cancer Institute (NCI) facility shut down update (2017)!

NCI Surgery Branch Cell Processing Laboratory (Located in CRC 3 West)

- **Role:** Investigational cell and gene therapy products
- **Updated Status:**
  - Construction/renovations to remediate the space, as well as administrative efforts (e.g., SOPs, equipment) completed
  - Reopened with restricted manufacturing with moderate facility control
    - Continual monitoring and reports are being provided



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Division of Environmental Protection/ORF

March 27, 2018

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

SCOPE OF THE PROJECT:

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

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

GMP lesson learned!

GMPs & Quality for live viruses and cells are similar yet different than for protein medicines

Challenging to switch a 'technical mindset'!

sometimes can feel like sailing in 'uncharted waters'

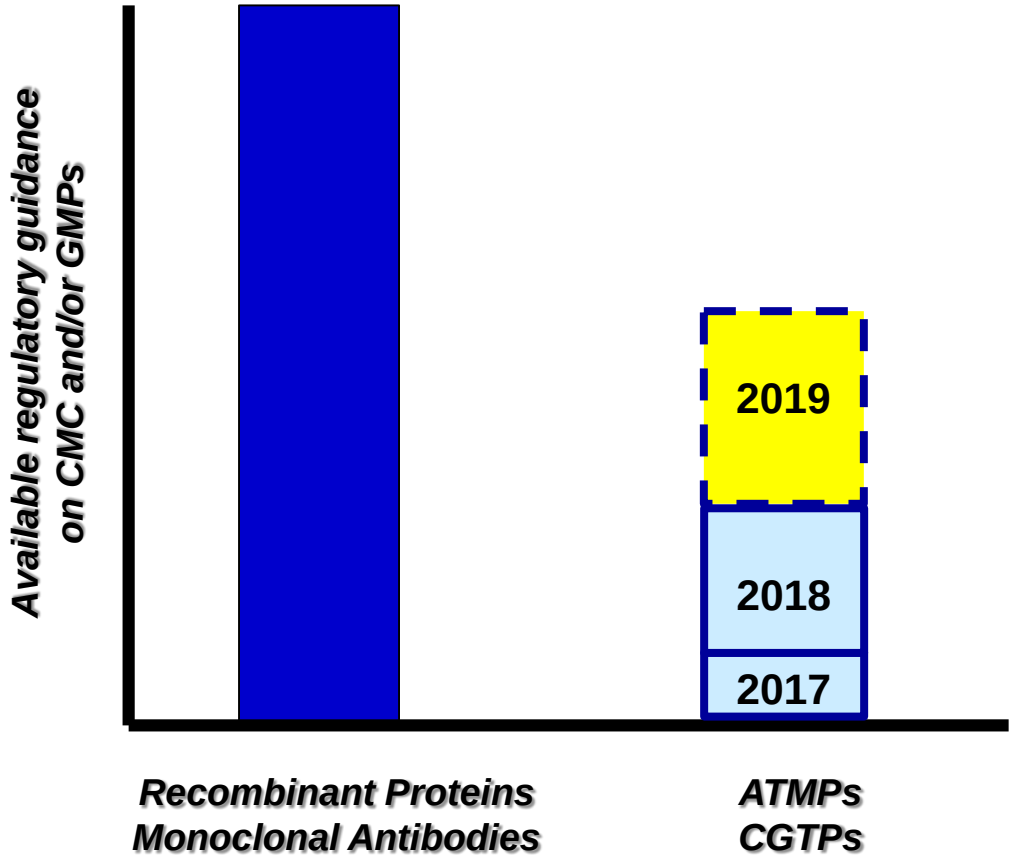
? QUESTIONS ?

Practical Application of Phase-Appropriate GMPs & Quality to Clinical Development of ATMPs

3. ATMP GMPs and Quality Specific Guidelines During Clinical Development

- ✓ *EMA/FDA guidelines for the rapidly developing ATMP field*
- ✓ *PDA guidance and industry practice*

Increasing availability of regulatory guidance on ATMP/CGTP CMC and/or GMPs



EMA GMPs and Quality Guidelines for ATMPs

Pre-2018 Guidelines

- Human Cell-Based Medicinal Products
- Development and Manufacture of Lentiviral Vectors
- Xenogeneic Cell-Based Medicinal Products
- Risk-Based Approach According to Annex I, Part IV of Directive 2001/83/EC Applied to Advance Therapy Medicinal Products
- Potency Testing of Cell Based Immunotherapy Medicinal Products for Treatment of Cancer
- Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products

❖ EC Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products

'investigational ATMPs'

EUROPEAN COMMISSION

Brussels, 22.11.2017
C(2017) 7694 final

2018 – 2019 Guidelines

- ***Quality, Non-Clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials***
- ***Quality, Non-Clinical and Clinical Aspects of Gene Therapy Medicinal Products***
- ***Quality, Non-Clinical and Clinical Aspects of Medicinal Products Containing Genetically Modified Cells***

- ***Q&A on Comparability for ATMPs (coming soon)***

FDA GMPs and Quality Guidances for Industry for CGTPs

Pre-2018 Guidances

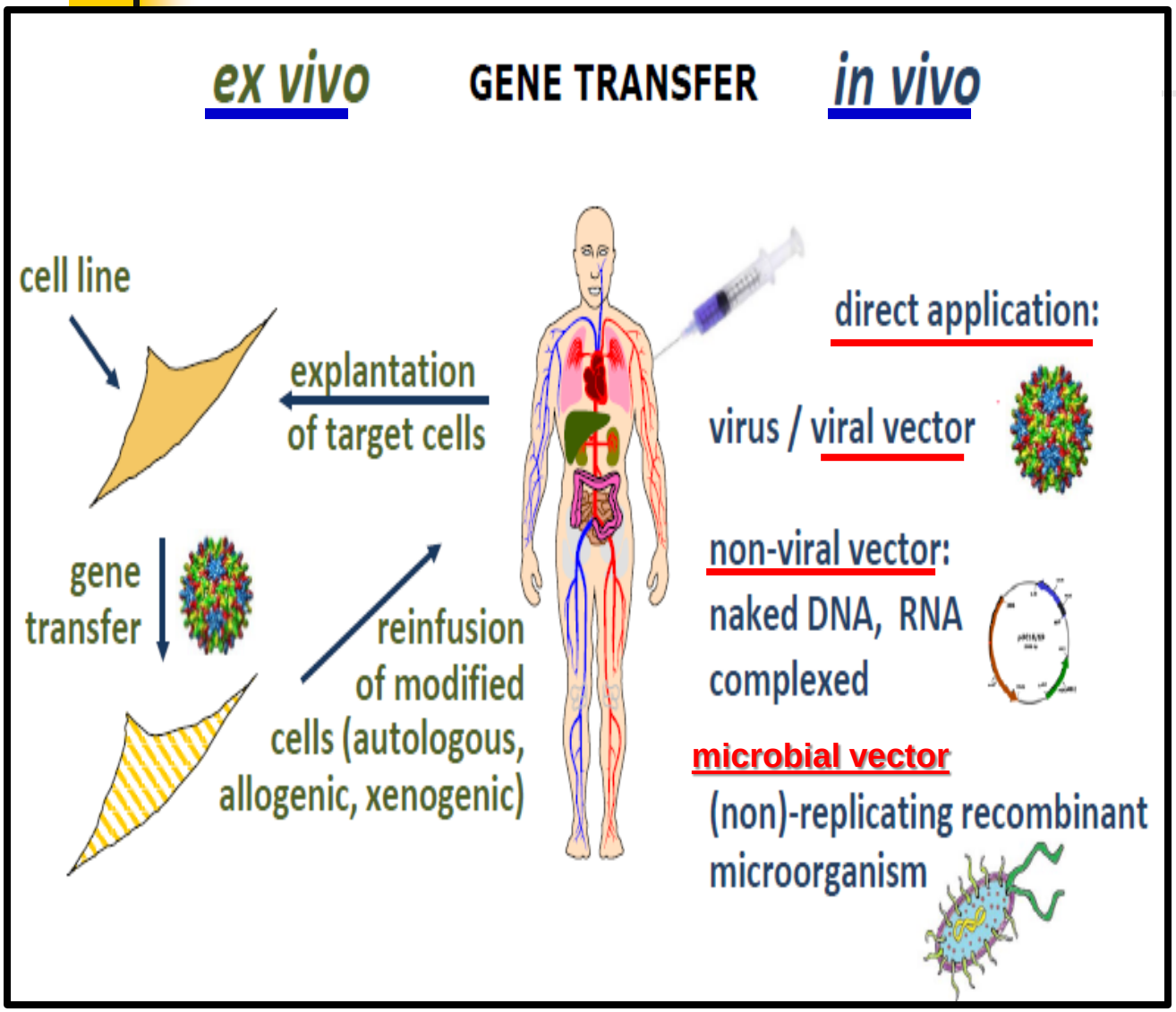
- ***Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (IND)***
- ***Recommendations for Microbial Vectors Used for Gene Therapy***
- ***Potency Tests for Cellular and Gene Therapy Products***
- ***Determining the Need For and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products***

2018 - 2019 Guidances

- ***Chemistry, Manufacturing & Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)***
- ***Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up***
- ***Evaluation of Devices Used with Regenerative Medicine Advanced Therapies***
- ***Expedited Programs for Regenerative Medicine Therapies for Serious Conditions***
- ***Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research***

Challenge of regulatory authorities to keep pace with the rapidly developing field of ATMPs

(numerous vectors, cell types, and cell handling approaches)



In progress

- ***allogeneic* cells ex vivo gene transfer**
- ***gene editing* ex vivo or in vivo (CRISPR, zinc finger nuclease)**

This diversity challenge is well known to regulatory authorities
(makes it difficult to be all comprehensive in any guideline)

Cell-based medicinal products are heterogeneous with regard to the origin and type of the cells and to the complexity of the product. Cells can be of human (autologous or allogeneic) or animal origin and may be self-renewing stem cells, more committed progenitor cells or terminally differentiated cells exerting a specific defined physiological function. In addition, the cells may also be genetically modified with newly established genotype/phenotype for the intended therapeutic effect. The cells may be used alone, associated with biomolecules or other chemical substances or combined with structural materials that alone might be classified as medical devices (combined advanced therapy medicinal products).

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

31 January 2019
EMA/CAT/852602/2018

Human gene therapy products are defined as all products that mediate their effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids, genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing,[2] and ex vivo genetically modified human cells. Gene therapy products meet the definition of "biological product" in section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. 262(i)) when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Food and Drug Administration
Center for Biologics Evaluation and Research
July 2018

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

Guidance in Developing a Risk-Based GMPs & Quality Strategy

3 Key Elements During Clinical Development

1) Risk-based provides flexibility – a necessity during clinical development due to ATMP diversity!

> It follows that, in laying down the GMP requirements applicable to ATMPs, it is necessary to recognise a certain level of flexibility so that the ATMP manufacturer can implement the measures that are most appropriate having regard to specific characteristics of the manufacturing process and of the product. 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).

EC Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products

Guidance in Developing a Risk-Based GMPs & Quality Strategy

3 Key Elements During Clinical Development

1) ***Risk-based provides flexibility – a necessity during clinical development due to ATMP diversity!***

2) ***Risk-based must evolve/mature during clinical development of ATMPs!***

Data requirements evolve as development progresses from exploratory to confirmatory clinical trials:

- Quality data compiled in the IMPD are expected to reflect increasing knowledge and experience during product development. At marketing authorisation it needs to be demonstrated that the medicinal product can be produced consistently and with reproducible quality. For example, acceptance criteria for tests parameters/in-process controls, even based on limited data should be set and they should be reviewed at later stages of development.

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

31 January 2019
EMA/CAT/852602/2018

Guidance in Developing a Risk-Based GMPs & Quality Strategy

3 Key Elements During Clinical Development

1) ***Risk-based provides flexibility – a necessity during clinical development due to ATMP diversity!***
2) ***Risk-based must evolve/mature during clinical development of ATMPs!***

3) ***Risk-based focuses on patient-safety!***

(identity, traceability, impurities, …)

> ***'In deciding on the appropriate measures to address the identified risks, the priority should be the safety of subjects enrolled in the trial.'***

The level of effort and documentation should be commensurate with the level of risk. The application of a risk-based approach can facilitate compliance but does not obviate the applicant's obligation to demonstrate the quality and safety of the product to enable the generation of reliable efficacy data. It likewise does not replace appropriate communications with the authorities.

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

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

31 January 2019
EMA/CAT/852602/2018

Patient Safety – 8 'basic' GMPs & Quality principles

1) *personnel are adequately trained and there is clear allocation of responsibilities*
2) *premises and equipment are suitable for the intended use and that there is appropriate maintenance thereof*
3) *adequate documentation system that ensures that appropriate specifications are laid down for materials, intermediates, bulk products and the finished product, that the production process is clearly understood, and that appropriate records are kept*
4) *manufacturing process adequate to ensure consistent production (appropriate to the relevant stage of development), quality of the product, and compliance thereof with the relevant specifications)*
5) *a quality control system which is operationally independent from production*
6) *arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation*
7) *quality defects and process deviations are identified as soon as possible, the causes investigated, and appropriate corrective and/or preventive measures are taken*
8) *adequate systems are implemented to ensure traceability of the ATMPs and of their starting and critical raw materials*

EC Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products

Linking IMPD information to patient safety

S	Active substance
S.1.	General information
S.2.	Manufacture
S.3.	Characterisation
S.4.	Control of the active substance
S.5.	Reference standards or materials
S.6.	Container closure system
S.7.	Stability
P	Investigational medicinal product
P.1.	Description and composition of the investigational medicinal product
P.2.	Pharmaceutical development
P.3.	Manufacture
P.4.	Control of excipients
P.5.	Control of the investigational medicinal product
P.6.	Reference standards or materials
P.7.	Container closure system
P.8.	Stability
A.1.	Facilities and equipment
A.2.	Adventitious agents safety evaluation

developmental genetics

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

31 January 2019
EMA/CAT/852602/2018

	Similarity/Difference	
	rProteins/mAbs	ATMPs
Developmental Genetics	Assembly of the genetically engineered cell line (gene, vector, host cell) (brief description)	CBP: manipulation for the target function GTP: Assembly of the genetically engineered vector (e.g., virus, plasmid) (detailed description)

CBP – cell-based product GTP – gene therapy product

b. Development Genetics

For all vectors, full documentation of the origin where applicable, history and biological characteristics of the parental virus or bacterium should be provided.

All the genetic elements of the GTIMP should be described including those aimed at therapy, delivery, control and production and the rationale for their inclusion should be given. For helper virus, the same level of detail should be provided.

For plasmid DNA, full sequence should be provided.

DNA elements used for selection should be justified. The presence of antibiotic resistance genes in a GTIMP finished product should be avoided given the burden of bacterial multi-resistance to antibiotics and the existence of alternatives methods for selection. If unavoidable a risk analysis should be made.

For viral vectors, you should include a description of the composition of the viral capsid and envelope structures, as appropriate, and any modifications to these structures (e.g., modifications to antibody binding sites or tropism-changing elements). We recommend that you include biophysical characteristics (e.g., molecular weight, particle size) and biochemical characteristics (e.g., glycosylation sites). You should also describe the nature of the genome of viral vectors, whether single-stranded, double-stranded, or self-complementary, DNA or RNA, and copy number of genomes per particle.

For bacterial vectors, you should include defining physical and biochemical properties, growth characteristics, genetic markers (e.g., auxotrophic or attenuating mutations, antibiotic resistance) and the location (e.g., on plasmid, episome, or chromosome) and description of any inserted foreign genes and regulatory elements. For additional details on microbial vectors, please see the FDA's Guidance for Industry "Recommendations for Microbial Vectors used for Gene Therapy," dated September 2016 (Ref. 10).

For ex vivo genetically modified cells, you should describe the expected major and minor cell populations as well as the vector that contains the transgene cassette that is transferred into the cell. For cells that have been genetically modified using genome editing, you should describe the gene(s) that are altered and how the change(s) was made (i.e., the gene editing technology used).

Why is a detailed description relevant to patient safety?

Linking IMPD information to patient safety

S Active substance
S.1. General information
S.2. Manufacture ...
S.3. Characterisation
S.4. Control of the active substance
S.5. Reference standards or materials
S.6. Container closure system
S.7. Stability
P Investigational medicinal product
P.1. Description and composition of the investigational medicinal product
P.2. Pharmaceutical development
P.3. Manufacture
P.4. Control of excipients
P.5. Control of the investigational medicinal product
P.6. Reference standards or materials
P.7. Container closure system
P.8. Stability
A.1. Facilities and equipment
A.2. Adventitious agents safety evaluation

S.2.3 Control of Materials

starting materials

raw materials

	Similarity/Difference	
	rProteins/mAbs	ATMPs
Starting Material(s)	Master/Working Cell Bank	Patient Cells Viral Vector Non-viral Vector Master Cell Bank

Viral vectors are starting materials, also when used to transduce cells and not remaining in the active substance. Information on the vector should be provided in the starting material section. The same level of information that is needed for the vector as active substance should be provided in this situation.

Genome editing tools used ex-vivo to generate genetically modified cells are by analogy also considered as starting materials.

Also, for in vitro-transcribed (m)RNAs used as active substances, the linearized template plasmid DNA should be considered as a starting material.

Complexing materials[6] for formulating the drug substance are considered as starting materials and have to be qualified for their intended purpose. The level of information to be provided will depend on nature of the complexing material and resulting DS.

[6] A substance used to form a complex with DNA which facilitates transfer of that DNA into a cell (for example: calcium phosphate, lipids or proteins.)

Why is the starting material relevant to patient safety?

Autologous Cellular and Gene Therapies

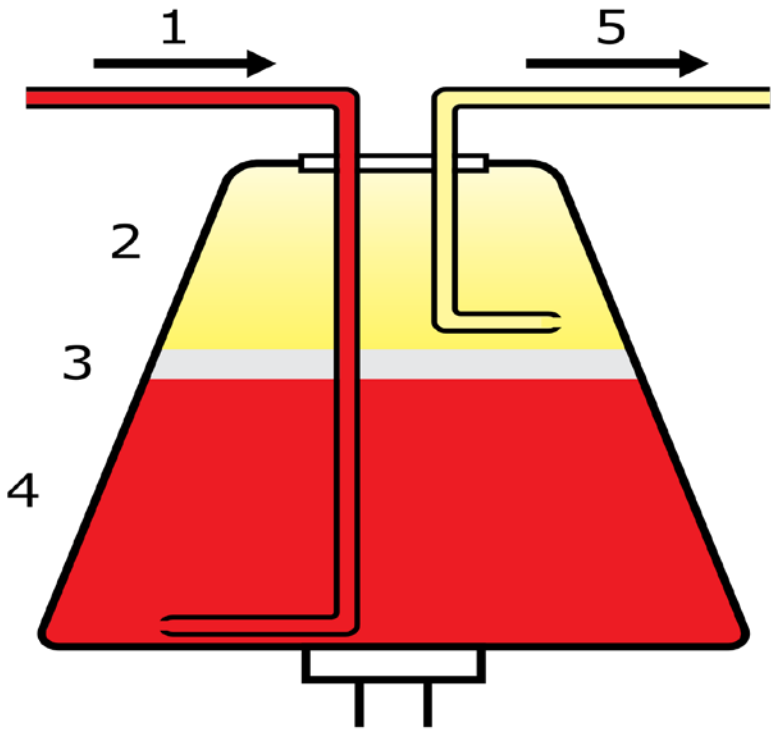
Patient cells as starting materials

- ***Every patient is different – so every patient is their own source material (autologous)***
- ***Challenge of obtaining adequate quantity of patient cells (e.g., small biopsy samples, children-sourced)***
- ***Variation of patient cell types and their concentrations across medical treatment regime***

Patient cell collection – a contributor to quality variation

case example – CAR T-cells

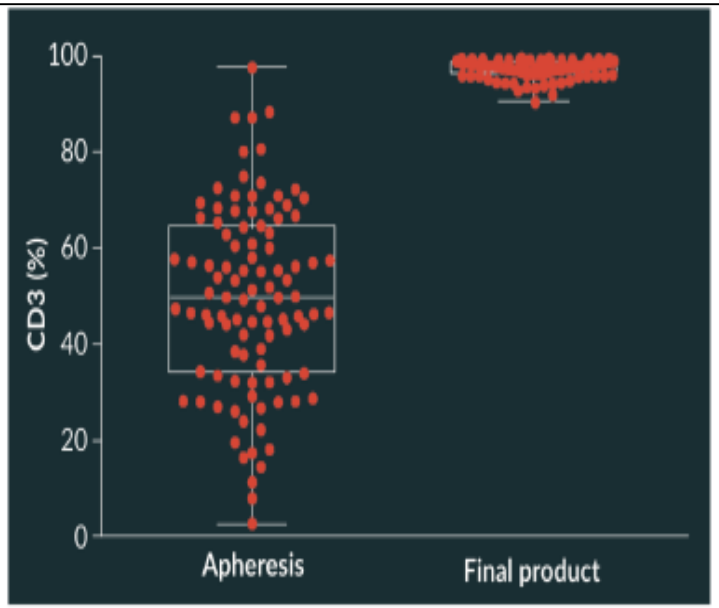
– *Variability in cell type collection (apheresis)*



1 Patient blood enters centrifuge
2 Plasma
3 Leukocytes (e.g., T cells)
4 Erythrocytes (red blood cells)
5 Selected components drawn off

Patient cell collection inconsistency can impact CQAs

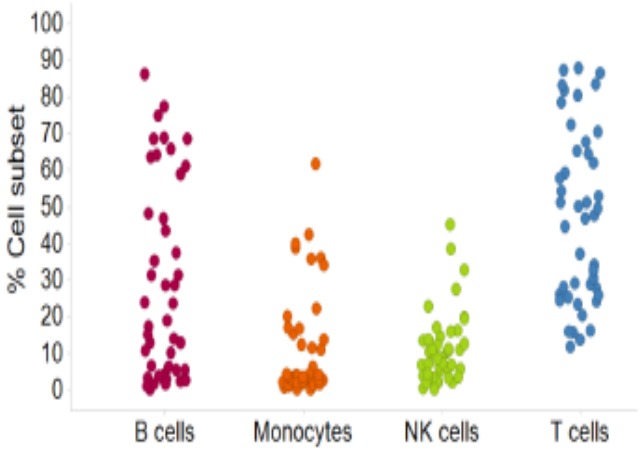
Kite's Yescarta for Lymphoma



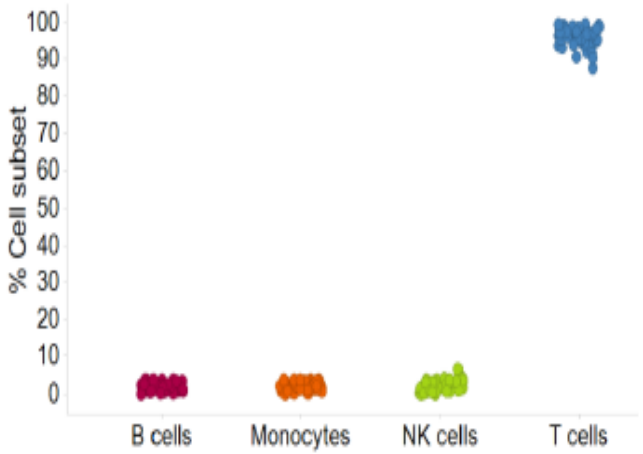
Better et al.
Cell and Gene Therapy Insights, 2018

Novartis' Kymriah for PedALL

Leukapheresis material



CTL019 final product



FDA ODAC Meeting, July 12, 2017

Minimizing heterogeneity of patient cell collection

- ***Obtained not by GMP training of hospital staff***
- ***Obtained by auditing and educating hospital staff; and then the company certifying which clinical sites are acceptable***

> For Yescarta, Kite/Gilead sends its staff to oversee and educate its supply chain centres. *"We audit the medical facilities, the apheresis and treatment centres, the nurses, the physicians which are going to be using this therapy. We have extensive training programmes as well with them."*
>
> CELL THERAPY MANUFACTURING & GENE THERAPY CONGRESS 2017

- ***Manufacturers take the extra step of further cell processing when received at their site to start with as consistent of the source material cell type as possible***

Allogeneic patient cells can end run the heterogeneity challenge

Work Problem & Discussion

What would be some of the risk-based GMP & Quality issues for these two different genetic transfer vectors (starting materials)?

Viral delivery

transduction

Generate recombinant virus via gene cloning, cell culture, virus isolation, and clone characterization.

↓

Prepare and purify high titer viral vectors.

↓

Infect cells (containing viral receptor) at appropriate multiplicity of infection (MOI).

↓

Remove virus and/or add fresh medium.

↓

Assay for gene expression or silencing.

Lipid delivery using cationic lipids

transfection

DNA, siRNA, or oligonucleotides and transfection reagent (commercially available) are diluted in separate tubes.

↓

DNA and transfection reagent combined to form complexes. Positive charge on cationic lipid binds to phosphate backbone on nucleic acid.

↓

Complexes added to cells. Positive charge on cationic lipid helps bind complex to membrane.

↓

Complexes enter the cell via endocytosis.

↓

Assay for gene expression or silencing.

	Similarity/Difference	
	rProteins/mAbs	ATMPs
Raw Materials Used in Manufacturing	Typically adequate compendial quality for raw materials Adequate purification capacity for removal of residuals	Heightened patient safety concern due to raw material quality limitations of purification (especially for cells) for removal of residuals

Raw materials are the reagents that are used during the manufacturing process but are not part of the final product. Examples include foetal bovine serum, trypsin, digestion enzymes (e.g., collagenase, DNAse), growth factors, cytokines, monoclonal antibodies, antibiotics, resins, cell-separation devices, and media and media components. Reference to quality standards (e.g. compendial monographs or manufacturer's in-house specifications) should be made. Information on the quality and control of non-compendial materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g. media components, monoclonal antibodies, enzymes) are suitable for their intended use should be provided. While raw materials should be of pharmaceutical grade, it is acknowledged that, in some cases, only materials of research grade are available. The risks of using research grade materials should be understood (including the risks to the continuity of supply when larger amounts of product are manufactured).

Why are raw materials relevant to patient safety?

non-mandatory recommendations on raw material risk assessments

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

General Chapter 5.2.12.

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

- ***Sera and serum replacements***
- ***Proteins produced by recombinant DNA technology***
- ***Proteins extracted from biological material***
- ***Vectors***

usp™

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

Ancillary Materials: raw materials that come in contact with the CGTP, but not intended to remain the in final product

Tier 1 (low risk) → → → Tier 4 (high risk)

Linking IMPD information to patient safety

S Active substance

S.1. General information

S.2. Manufacture

S.3. Characterisation

S.4. Control of the active substance

S.5. Reference standards or materials

S.6. Container closure system

S.7. Stability

P Investigational medicinal product

P.1. Description and composition of the investigational medicinal product

P.2. Pharmaceutical development

P.3. Manufacture

P.4. Control of excipients

P.5. Control of the investigational medicinal product

P.6. Reference standards or materials

P.7. Container closure system

P.8. Stability

A.1. Facilities and equipment

A.2. Adventitious agents safety evaluation

S.2.4. Control of critical steps and intermediates

P.3.4. Control of critical steps and intermediates

	Similarity/Difference	
	rProteins/mAbs	ATMPs
Aseptic Processing Manufacturing	Standard practice in the industry Ready access to 0.2 micron filtration Final product filter sterilization	Heavy reliance on single-use components Numerous manual manipulations Limitations (for cells) of final product sterilization

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. Where applicable, hold times and storage conditions for process intermediates should be justified and supported by data, as appropriate. Intermediate cell products are products that can be isolated during the process; specifications of these products should be established in order to assure the reproducibility of the process and the consistency of the final product. Tests and acceptance criteria should be described. Any storage periods during production need to be controlled (e.g. time, temperature).

Monitoring of *in vitro* cell culturing at selected stages of the production should be performed where feasible and the *in vitro* cell age (population doublings) should be controlled. The culture should be examined for any microbial contamination.

Why is the control of the manufacturing process relevant to patient safety?

Work Problem & Discussion

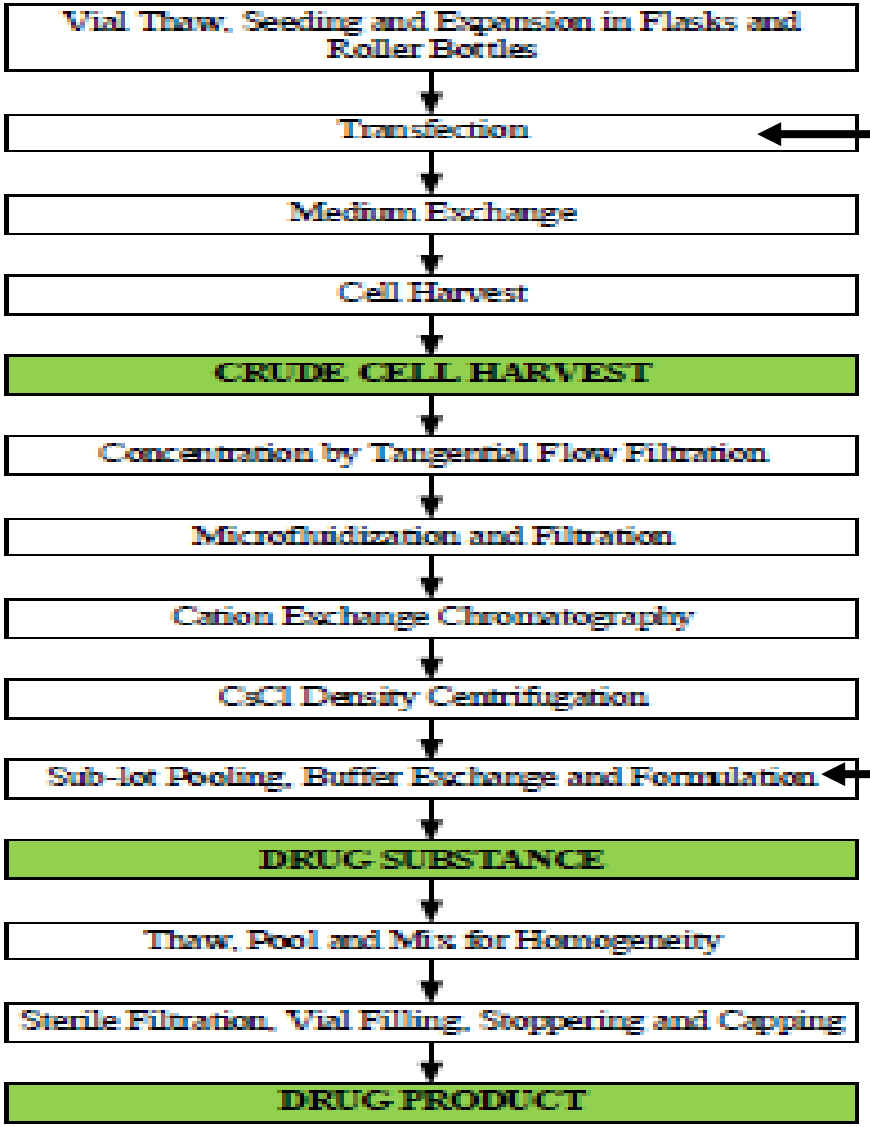
What would be some of the risk-based GMPs & Quality issues for this ex-vivo CAR T-Cell Gene Therapy Manufacturing Process

- Patients undergo leukapheresis to collect their blood mononuclear cells; these are cryopreserved and shipped to the manufacturing facility using a dedicated courier service (and stored at ≤ -120°C)
  - Each leukapheresis is assigned to a dedicated team who only work on a single product at a time (see chain of identity in Section 2.4.3)
- After thawing, cells undergo a procedure to remove cells detrimental to CAR transduction and growth (i.e. monocytes and B-lineage lymphoblasts) and to enrich for T cells
- T cells are activated ex vivo with anti-CD3/CD28 antibody-coated beads and transduced with a self-inactivating minimal lentiviral vector containing the anti-CD19 CAR transgene
- Transduced T cells are subsequently expanded ex vivo and then washed, formulated, and cryopreserved
- Full release testing is completed prior to release of the cryopreserved final product. Cells are then shipped to the clinical site.

GMPs & Quality Potential Risks of CAR T-Cell Gene Therapy Process (tumor formation, unwanted immunogenicity, treatment failure, toxicity, disease transmission)	
Risk Factor	**Address by Risk-Based GMPs & Quality**
Availability of Starting Materials (patient cells, virus vector)	
Cell Heterogeneity (unwanted cell types)	
Gene Transfer Vector Type (virus)	
Virus Recombination (formation of replication competency)	
Genetic Transfer into Patient Cells (ex vivo)	
GE Cell Expansion (growth rate, media, growth factors)	
Defective Transgene Expression (too little, too much)	
Impurities in GE Cell Product (product-related, process-related)	
Adulteration of GE Cell Product (contamination with adventitious agent)	

Work Problem & Discussion

What would be some of the risk-based GMPs & Quality issues for this Gene Replacement Therapy Manufacturing Process



transient transfection with 3 separate plasmid constructs: (1) human RPE65 expression cassette, (2) AAV2 rep and cap sequences, (3) helper virus-derived sequences required for replication of the hRPE65 expression cassette prior to packaging

formulation includes sodium chloride, sodium phosphate, and poloxamer 188

Spark THERAPEUTICS Luxturna

FDA Advisory Committee Meeting

October 12, 2017

GMPs & Quality Potential Risks of Gene Replacement Therapy Process (tumor formation, unwanted immunogenicity, treatment failure, toxicity, disease transmission)	
Risk Factor	**Address by Risk-Based GMPs & Quality**
Availability of Starting Materials (3 plasmids)	
Gene Transfer Vector Type (plasmid transfection to transfect HEK293 cells)	
GE Virus Manufacturing (growth rate)	
Virus Recombination (formation of replication competency)	
Genetic Transfer into Patient's Eye (direct injection of GE virus)	
Impurities in GE Virus Product (product-related, process-related)	
Adulteration of GE Virus Product (contamination with adventitious agent)	

Work Problem & Discussion

What would be some of the risk-based GMPs & Quality issues for a Somatic Cell Therapy Manufacturing Process

Potential Risks of Somatic Cell Therapy (tumor formation, unwanted immunogenicity, treatment failure, toxicity, disease transmission)	
Risk Factor	**Address by Risk-Based GMPs & Quality**
Cell Heterogeneity (unwanted cell types)	
Significant Cell Manipulation (enhanced bioactive protein secretion)	
Cell Expansion (media, growth factors)	
Genetic Stability (loss of bioactive protein secretion by cells due to handling or storage)	
Impurities in Product (product-related, process-related)	
Adulteration of Product (contamination with adventitious agent)	

Concept of Quality by Design (QbD) applies to ATMPs

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

31 January 2019
EMA/CAT/852602/2018

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.

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.

PDA TR81

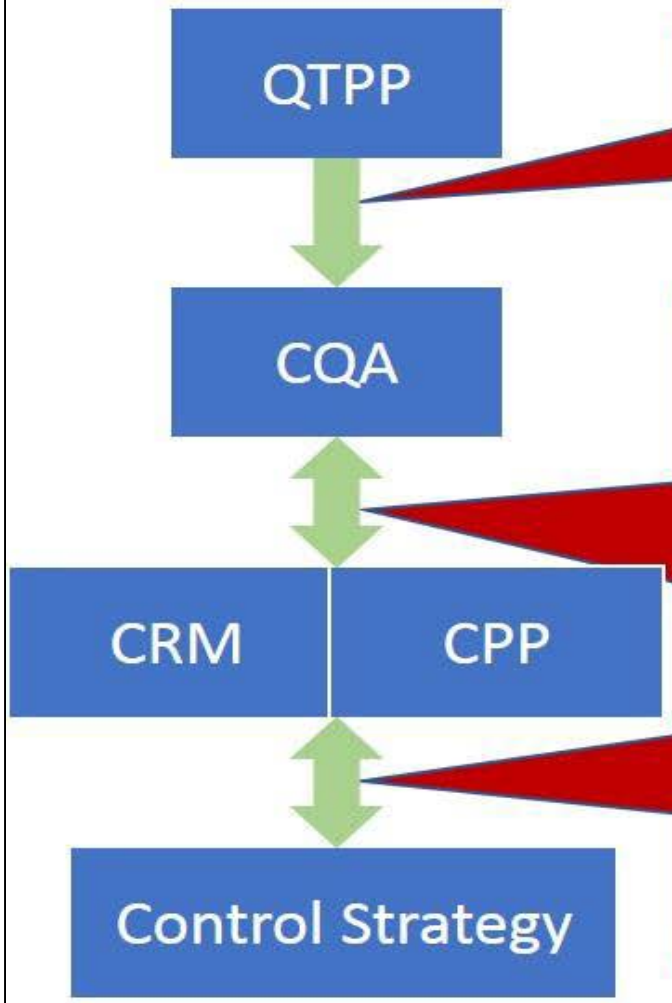
PDA Technical Report 81 (2018)

Cell-Based Therapy Control Strategy

From a manufacturing and quality perspective, ICH Quality Guideline Q8(R2) states that a manufacturing control strategy is closely linked to criticality – of quality attributes, material attributes, and process parameters – which can be identified by conducting risk assessments. Those aspects deemed critical, that is, having the highest level of risk by such assessment, must be mitigated and become the principle focus of a manufacturing control strategy.

Industry representatives from the PDA Cellular and Gene Therapy Task Force, in consultation with regulatory agency thought-leaders, set out to demonstrate how such a risk-based approach toward development of an effective manufacturing control strategy could be developed for a CGTP.

Control Strategy Development



- Various RA tools to assess criticality of QA
- Selective qualitative RA based on Severity + Uncertainty (Less cumbersome than quantitative FMEA)

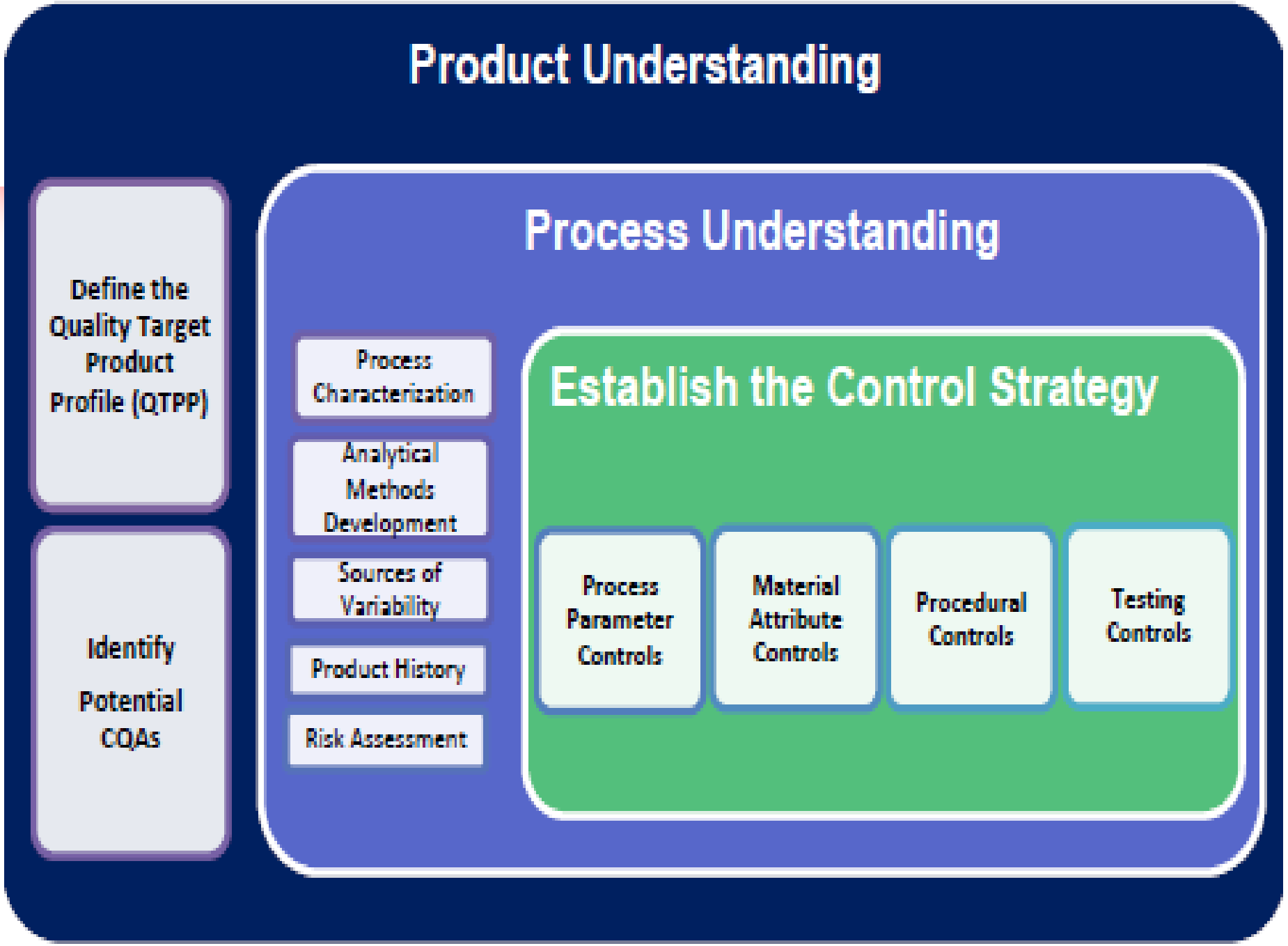
Step-by-step approach to build control strategy with incremental introduction of tools:

1. ID of PP and RM (process mapping)
2. PP + RM criticality assessment based on qualitative impact on CQA
3. PP and RM risk assessed using technical and quantitative approach (FEMA) to identify, analyze, and prioritize risks to products quality, safety, and efficacy

Outcome of RA on each CRM and CPP defines the overall control strategy:

- Development work needed to refine testing strategy
- Testing at source only
- Implementation of IPC
- Testing at release, etc.

Key: RA – *risk assessment* | QA – *quality attribute* | PP – *process parameter*
RM – *raw material* | CRM – *critical raw material* | IPC – *in-process control*


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

Linking IMPD information to patient safety

S Active substance

S.1. General information

S.2. Manufacture ...

S.3. Characterisation

S.4. Control of the active substance

S.5. Reference standards or materials

S.6. Container closure system

S.7. Stability

P Investigational medicinal product

P.1. Description and composition of the investigational medicinal product

P.2. Pharmaceutical development

P.3. Manufacture

P.4. Control of excipients

P.5. Control of the investigational medicinal product

P.6. Reference standards or materials

P.7. Container closure system

P.8. Stability

A.1. Facilities and equipment

A.2. Adventitious agents safety evaluation

S.2.6 Manufacturing Process Development

confirming product comparability after process changes

3.2.P.2.3 Manufacturing Process Development

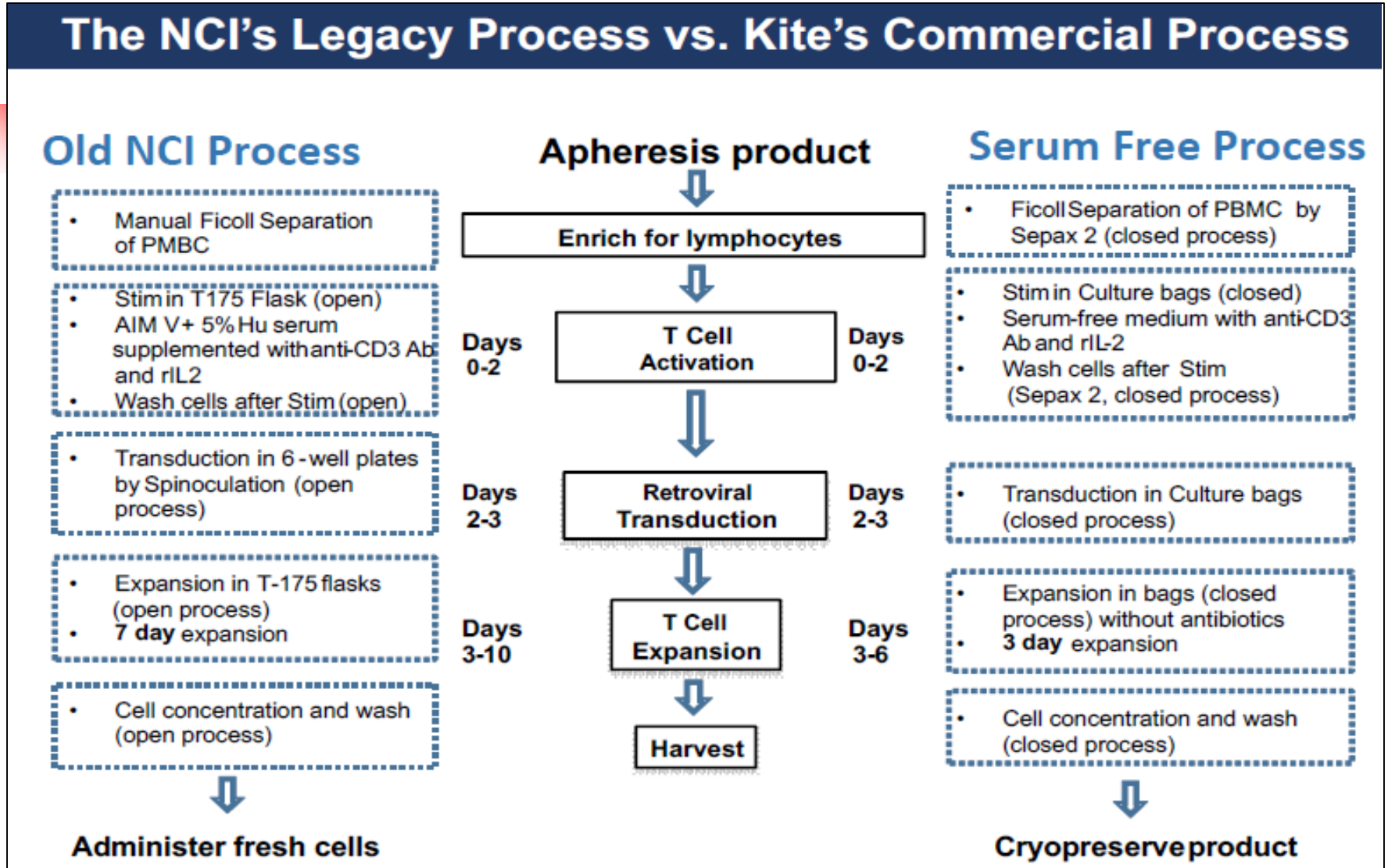
	Similarity/Difference	
	rProteins/mAbs	ATMPs
Manufacturing Process Changes	Stepwise product comparability (Q + NC +C)	Stepwise product comparability (Q + NC + C) but more challenging …

While changes to the manufacturing process commonly occur during development, the complex and dynamic nature of AMTPs presents a challenge for the evaluation of pre-versus post-change product. Orthogonal methods need to be applied in this evaluation and the potential impact on the entire product needs to be taken into consideration rather than on a single parameter.

GTIMPs:

It is recognised that in particular for GTIMPs, only a limited number of batches may be produced prior to MAA. Therefore, it is particularly important to gather sufficiently detailed manufacturing process and batch analytical data throughout the development process as these can be used as supportive information during a licence application.

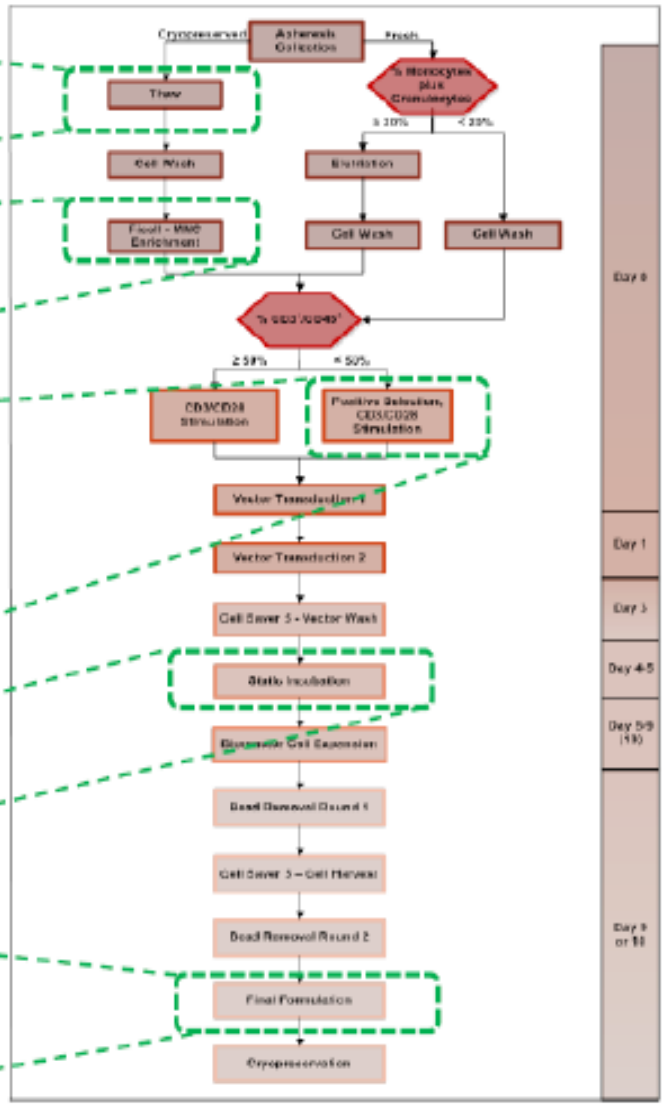
Why is product comparability relevant to patient safety?


The NCI's Legacy Process vs. Kite's Commercial Process
Old NCI Process
Manual Ficoll Separation of PMBC
Stim in T175 Flask (open)
AIM V+ 5% Hu serum supplemented with anti-CD3 Ab and rIL2
Wash cells after Stim (open)
Transduction in 6-well plates by Spinoculation (open process)
Expansion in T-175 flasks (open process)
7 day expansion
Cell concentration and wash (open process)
Administer fresh cells
Apheresis product
Enrich for lymphocytes
Days 0-2
T Cell Activation
Days 0-2
Days 2-3
Retroviral Transduction
Days 2-3
Days 3-10
T Cell Expansion
Days 3-6
Harvest
Serum Free Process
Ficoll Separation of PBMC by Sepax 2 (closed process)
Stim in Culture bags (closed)
Serum-free medium with anti-CD3 Ab and rIL-2
Wash cells after Stim (Sepax 2, closed process)
Transduction in Culture bags (closed process)
Expansion in bags (closed process) without antibiotics
3 day expansion
Cell concentration and wash (closed process)
Cryopreserve product

Novartis' Modifications of UPenn's Manufacturing Process

*Equipment Comparison to UPenn Process A**

Process A	Process B	Rational
Water bath	Plasma therm	Reduce potential contamination
Manual ficoll	Sepax ficoll	Closed and automatic system.
MaxSep; Labnet spinning rotator	DynaMag CTS; Customized rotator for bags	MaxSep discontinued; CTS meets bead manufacturer recommendation; Customized rotator for bags
Humidified incubator	Non-humidified incubator	Elimination of a water source in an ISO 7 area
Regular conical tubes	SaniSure Cap2v8	Closed system



This comparability exercise should normally follow a stepwise approach, including comparison of quality attributes of the active substance and relevant intermediates, using suitable analytical methods. Analytical methods usually include routine tests, and should be supplemented by additional characterisation tests (including orthogonal methods), as appropriate. Developing a panel of suitable assays for comparability is highly recommended from the first steps of development. As such, biological characterisation and the potency assay(s) are the most important parameters to perform comparability on quality grounds.

The analytical tools for comparability need to be chosen based on critical parameters identified throughout development.

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

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In contrast to traditional drug review, where 80 percent of the review is focused on the clinical portion of that process, and maybe 20 percent is focused on the product issues, I'd say that this general principal is almost completely inverted when it comes to cell and gene therapy.

The initial clinical efficacy is often established early, and sometimes in small series of patients.

The more challenging questions relate to product manufacturing and quality, or questions like how much you can change, or enlarge, the gene cassette that you load into a vector before the gene insert will change the conformation of the vector in ways that also fundamentally alter the entire product's safety or performance.

FDA – Speeches by FDA Officials: Remarks by Commissioner Gottlieb to the Alliance for Regenerative Medicine's Annual Board Meeting (May 22, 2018)

Common Challenges for Comparability of CGTPs

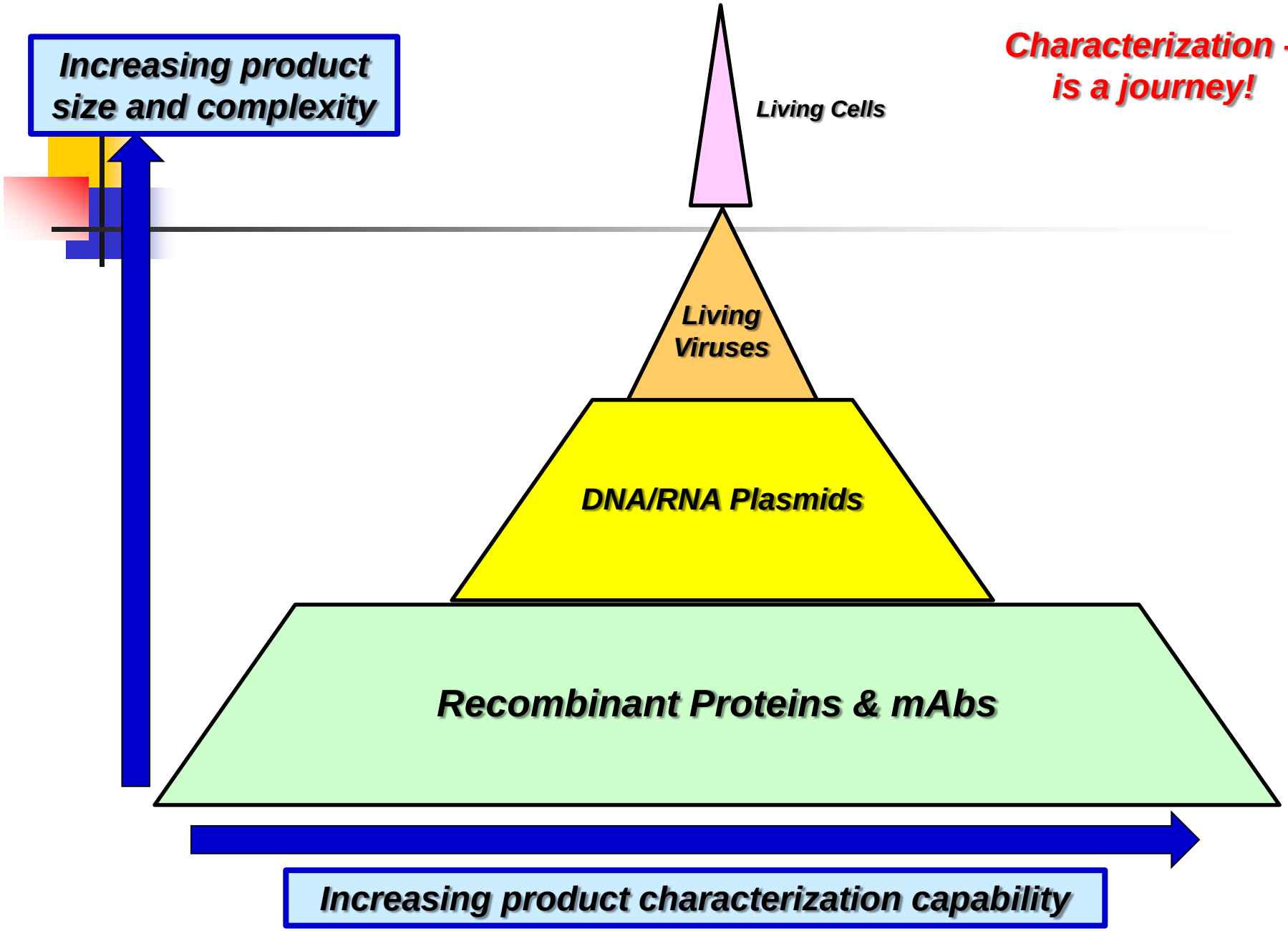
- **Limited lots** (manufacturing history):
  - Comparability studies are not statistically powered
  - Not enough retention/test samples available
- **Limited assay development** (potency, purity); assays not qualified; reference standards not established or adequately characterized.
- **Limited product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

Linking IMPD information to patient safety

S Active substance
S.1. General information
S.2. Manufacture
S.3. Characterisation
S.4. Control of the active substance
S.5. Reference standards or materials
S.6. Container closure system
S.7. Stability
P Investigational medicinal product
P.1. Description and composition of the investigational medicinal product
P.2. Pharmaceutical development
P.3. Manufacture
P.4. Control of excipients
P.5. Control of the investigational medicinal product
P.6. Reference standards or materials
P.7. Container closure system
P.8. Stability
A.1. Facilities and equipment
A.2. Adventitious agents safety evaluation

	Similarity/Difference	
	rProteins/mAbs	ATMPs
Product Characterization	Extensive test methods available	On a journey (especially for CBPs)
Process-related, Product-related Impurities	Minimize impact on patient safety	
Product Release/Stability Testing	Adequate samples Extensive release/stability test methods	Limitations of samples (autologous cells) Limitations of release/stability test methods
Specifications	'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.'	
Test Method Validation	'An appropriate degree of method qualification should be applied at each stage of clinical development'	

Why is product testing relevant to patient safety?


Increasing product size and complexity
Living Cells
Characterization – is a journey!
Living Viruses
DNA/RNA Plasmids
Recombinant Proteins & mAbs
Increasing product characterization capability

rProteins/mAbs

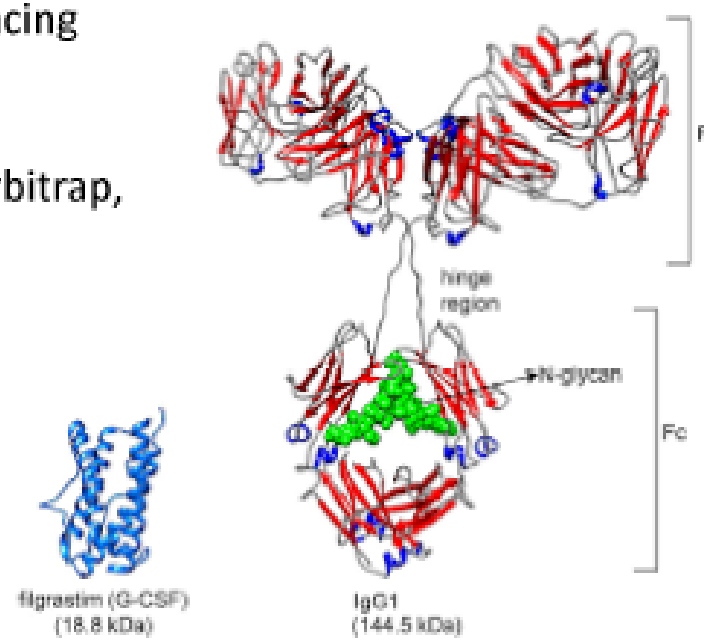
The Current Analytical Tool Box

1° Sequence/PTMs

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

HOS

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



Japelj et al Sci Reports 2016

Size/ Purity

SEC-HPLC
HIC-HPLC
RP-HPLC
CE-SDS
CGE
AUC
A4F

Future: MAM Multi-Attribute Method

Activity

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

Glycan Analysis

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

Charge

cIEF
icIEF
ICE
IEX- HPLC
CZE

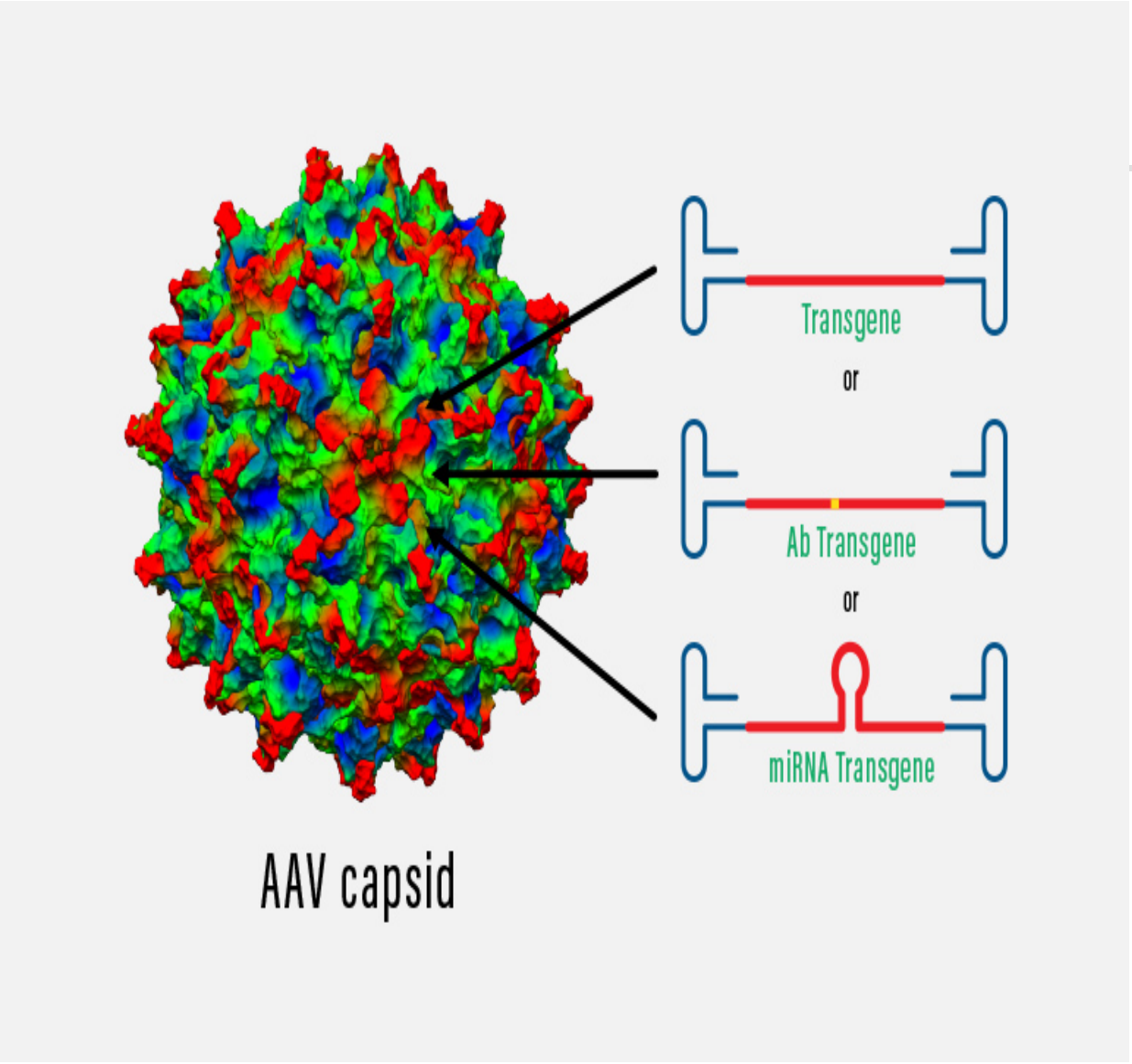
Process Related Impurities

DNA, HCP, Protein A, etc.

Safety

Bioburden
Sterility
Endotoxin
  LAL
  KT

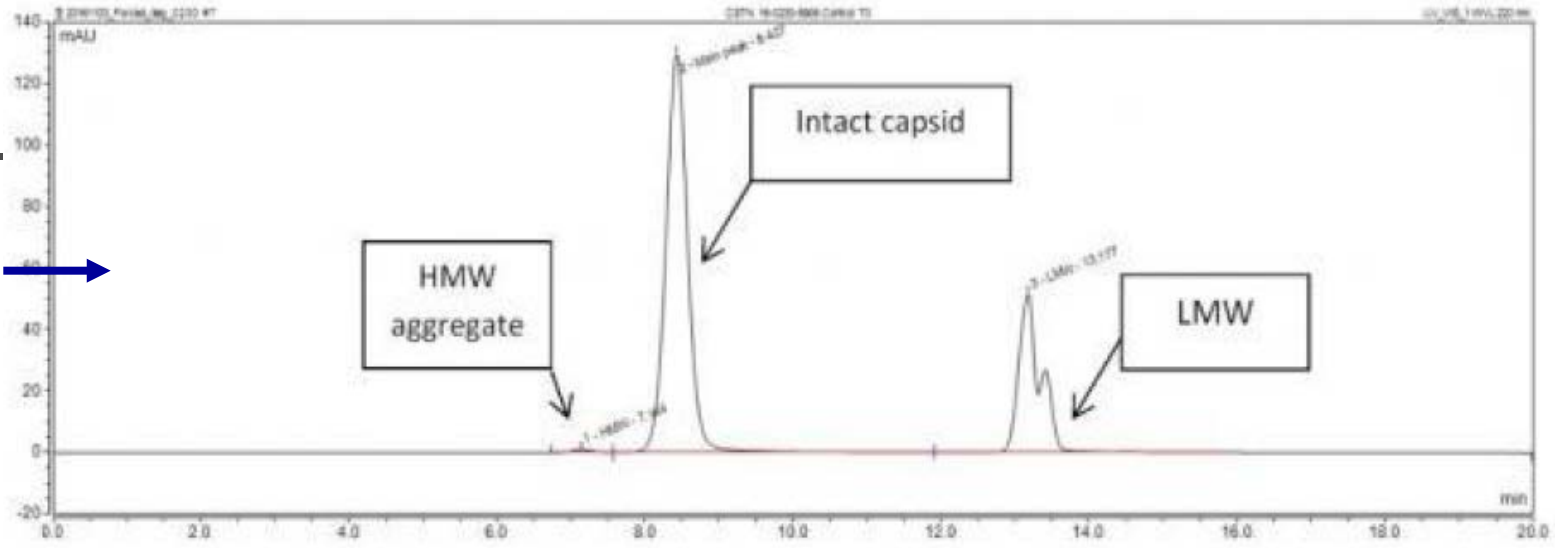
***Limited* Characterization of GE Living Virus**

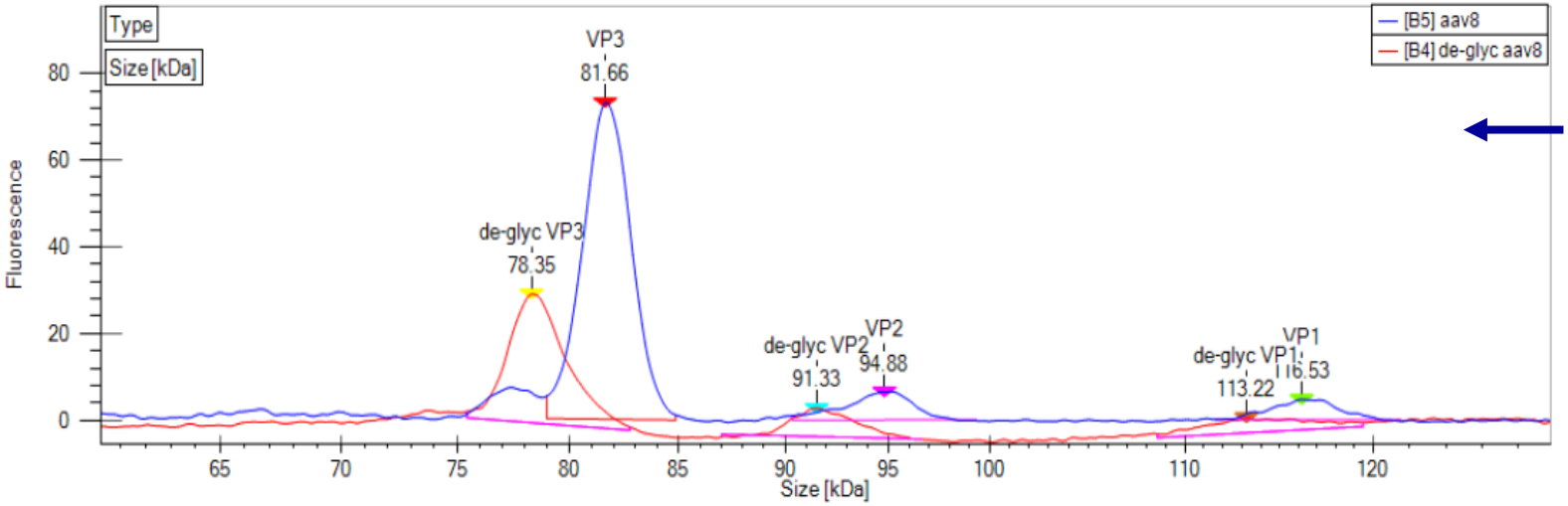


- ***Composition*** *(genome integrity and size, molecular mass, stoichiometry of capsid proteins)*
- ***Physical Properties*** *(particle size, aggregation, glycosylation state)*
- ***Primary Structure*** *(sequence confirmation, protein identification)*
- ***Higher Order Structure*** *(transmission electron microscopy, analytical ultracentrifugation for intact vs empty capsids)*
- ***Biological Activity*** *(infectious potency, ratio of full:infectious virus particles)*

Characterization test methods useful for viruses

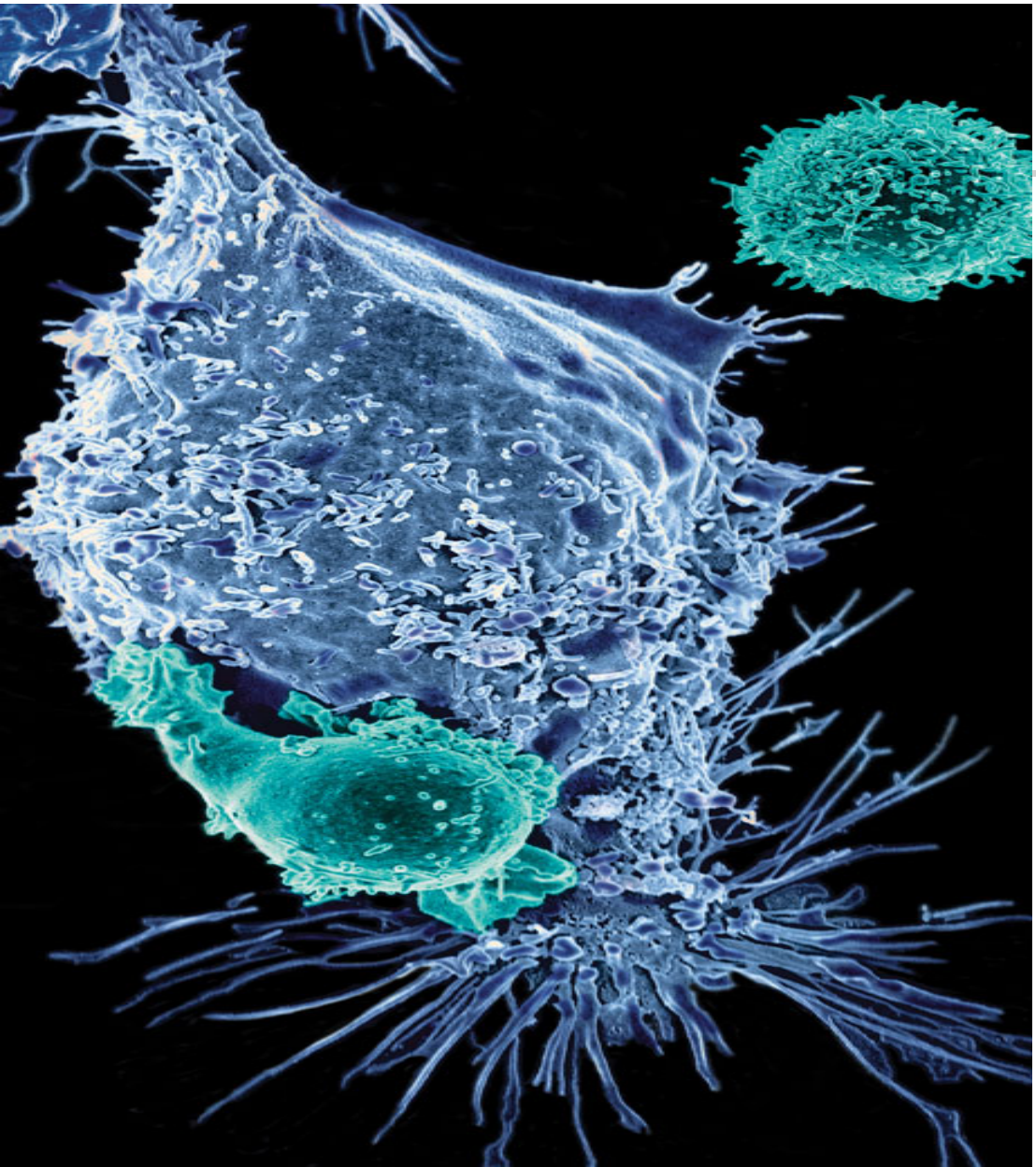
AAV viral capsid aggregation (SE-HPLC)





AAV viral capsid glycoprotein composition (CE-SDS)

Very Limited Characterization of GE Living Cell



- **Cell Morphology** (size, shape, appearance)
- **Cell Phenotype** (type and number of cell surface receptors)
- **Transduction Efficiency** (% of transduced cells, genetic stability)
- **Transgene Properties** (identity, sequence, copy number of transgene)
- **Biological Activity** (identity and activity of expressed transgene product)

Minimization of impurities essential in an ATMP risk-based approach!

During the production of an ATIMP, variable amounts of impurities, product- and process-related, may be introduced into the active substance. Any reagents known to have clinical impact in humans should be analysed in the active substance (or in individual components if otherwise not possible) and acceptance criteria should be set. The specification limits should be justified by levels detected in batches used for toxicological and/or clinical studies.

The aim should be to maximise the active components and minimise features which do not contribute, or may negatively impact on therapeutic activity/safety. The setting of purity specifications should be based on characterisation studies conducted as part of product development. Purity does not necessarily imply homogeneity, however, product consistency needs to be demonstrated.

Process related impurities (e.g. media residues, growth factors, host cell proteins, host cell DNA, column leachables) and product related impurities (e.g. cell types not linked to the therapeutic effect, cell fragments or non-viable cells, precursors, degradation products, aggregates) should be kept to the minimum or a risk assessment provided. Based on the risks identified, consideration should be given to the maximum amount for the highest clinical dose and an estimation of the clearance should be provided. In case only qualitative data are provided for certain impurities, this should be justified.

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

31 January 2019
EMA/CAT/852602/2018

Residual process-related impurities found in commercial ATMPs

(from FDA Package Inserts)

Genetically engineered viruses

Each vial of IMLYGIC may also contain residual components of VERO cells including DNA and protein and trace quantities of fetal bovine serum.

LUXTURNA may also contain residual components of HEK293 cells including DNA and protein and trace quantities of fetal bovine serum.

Genetically engineered cells

In addition to T cells, YESCARTA may contain NK and NK-T cells. The formulation contains 5% dimethylsulfoxide (DMSO) and 2.5% albumin (human).

In addition to T cells, other cell populations, including monocytes, NK cells, and B cells, may be present. The formulation contains 31.25% (v/v) of Plasma-Lyte A, 31.25% (v/v) of 5% Dextrose/0.45% sodium chloride, 10 % Dextran 40 (LMD)/5% Dextrose, 20% (v/v) of 25% Human Serum Albumin (HSA), and 7.5% (v/v) Cryoserv® dimethylsulfoxide (DMSO).

Critical importance of potency measurement for ATMPs

Generally the biological activity measurement will become the potency test for DS and DP.

From the characterisation and evaluation of the biological activities, the quality attribute(s) relevant for the potency should be identified. Potency is the quantitative measure of biological activity, which is linked to the relevant biological properties and the claimed mechanism of action. The potency assay should be developed based on the biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect).

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

Assessment of the biological properties constitutes an essential step in establishing a complete characterisation profile of a biological medicinal product. Due to their complexity, cell based immunotherapy products cannot be fully characterised like products derived by recombinant DNA techniques. Nevertheless, as for any biological medicinal product, the biological activity is an important characteristic and needs to be determined for cell based immunotherapy products.

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

FDA's viewpoint of importance of the potency assay for ATMPs

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)).

Guidance for Industry

Potency Tests for Cellular and Gene Therapy Products

Center for Biologics Evaluation and Research
January 2011

But ATMP bioassays take time to identify, develop, qualify/validate!

Don't underestimate the amount of effort and resources necessary

Determining the biological activity of cell based immunotherapy products is not easy since the active ingredient is usually composed of whole cells and the activity of these products can generally not be attributed to one specific cell characteristic. Potency assays for immunotherapy products will be based on complex immune mechanisms which are often poorly or incompletely understood and which may be complicated by multi-antigen formulations and inherent variability of the starting material.

Nevertheless, to assure a consistent functional activity of the medicinal product in the recipient, the potency of the product within justified limits should be demonstrated by a bioassay based on a defined biological effect as close as possible to the mechanism(s) of action/clinical response.

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

Risk-based approach applied to QC testing

investigational ATMPs

During clinical development a gradual approach can be applied:

- First-in-man and exploratory clinical trials: Sterility and microbial assays should be validated. In addition, other assays that are intended to ensure patient's safety should also be validated (*e.g.* when retroviral vectors are used, the analytical methods for testing for replication competent retrovirus should be validated).
- Throughout the clinical development, the suitability of analytical methods used to measure critical quality attributes (*e.g.* inactivation/removal of virus and/or other impurities of biological origin) should be established but full validation is not required. Potency assays are expected to be validated prior to pivotal clinical trials.
- Pivotal clinical trials: Validation of analytical methods for batch release and stability testing is expected.

It is acknowledged that in some cases it may not be possible to perform the release tests on the active substance or the finished product, for example due to technical reasons (*e.g.* it may not be possible to perform the release tests on the combined components of certain combined products, time restrictions (*i.e.* the product needs to be administered immediately after completion of manufacturing), or when the amount of available product is limited to the clinical dose.

In these cases, an adequate control strategy should be designed. For example, consideration can be given to the following options:

- Testing of key intermediates (instead of the finished product) or in-process controls (instead of batch release testing) if the relevance of the results from these tests to the critical quality attributes of the finished product can be demonstrated.
- Real time testing in case of short shelf-life materials/products.
- Increased reliance on process validation. When the scarcity of materials or the very short shelf-life limits the possibilities for release controls, the limitations should be compensated by a reinforced process validation (*e.g.* additional assays, such as potency testing or proliferation assays may be performed after batch release as supporting data for process validation). This may also be relevant for investigational ATMPs: while process validation is not expected for investigational medicinal products (*see* Section 10.3), it may be important when routine in-process or release testing is limited or not possible.

Case Example: Genetically-engineered T-cells release testing

KYMRIAH

Identity
- ✓ Appearance
- ✓ Vector integration

Potency
- ✓ Cytokine production
- ✓ CAR expression

Purity
- ✓ %T Cells
- ✓ Cell viability
- ✓ Transduction efficiency

Safety
- ✓ Sterility
- ✓ Endotoxin
- ✓ Mycoplasma
- ✓ RCL / vector residuals

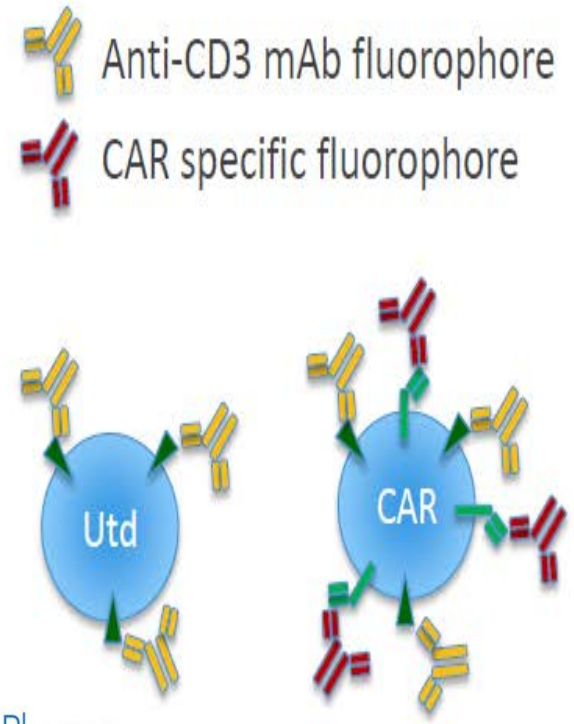
Impurities
- ✓ Residual beads
- ✓ Residual B cells / MRD
- ✓ Vector residuals

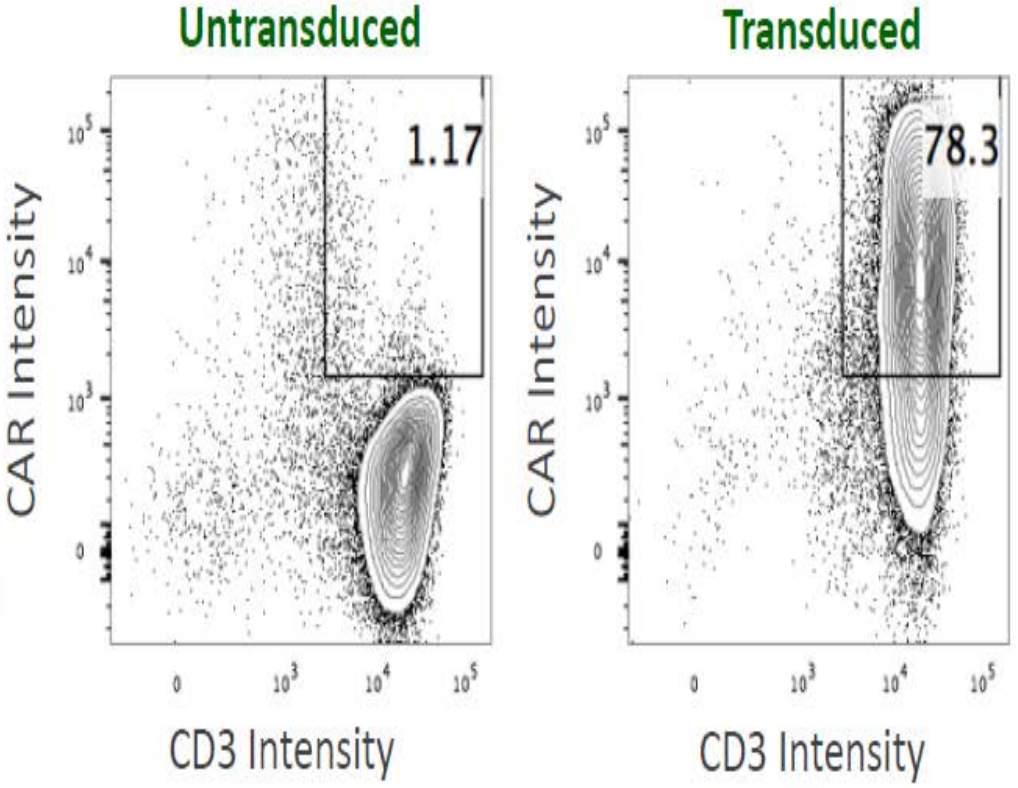
NOVARTIS

Final Product Potency: % CAR Expressing T Cells

Flow cytometry quantitates the percentage of T cells expressing the CAR.

Dose is a defined number of transduced T cells



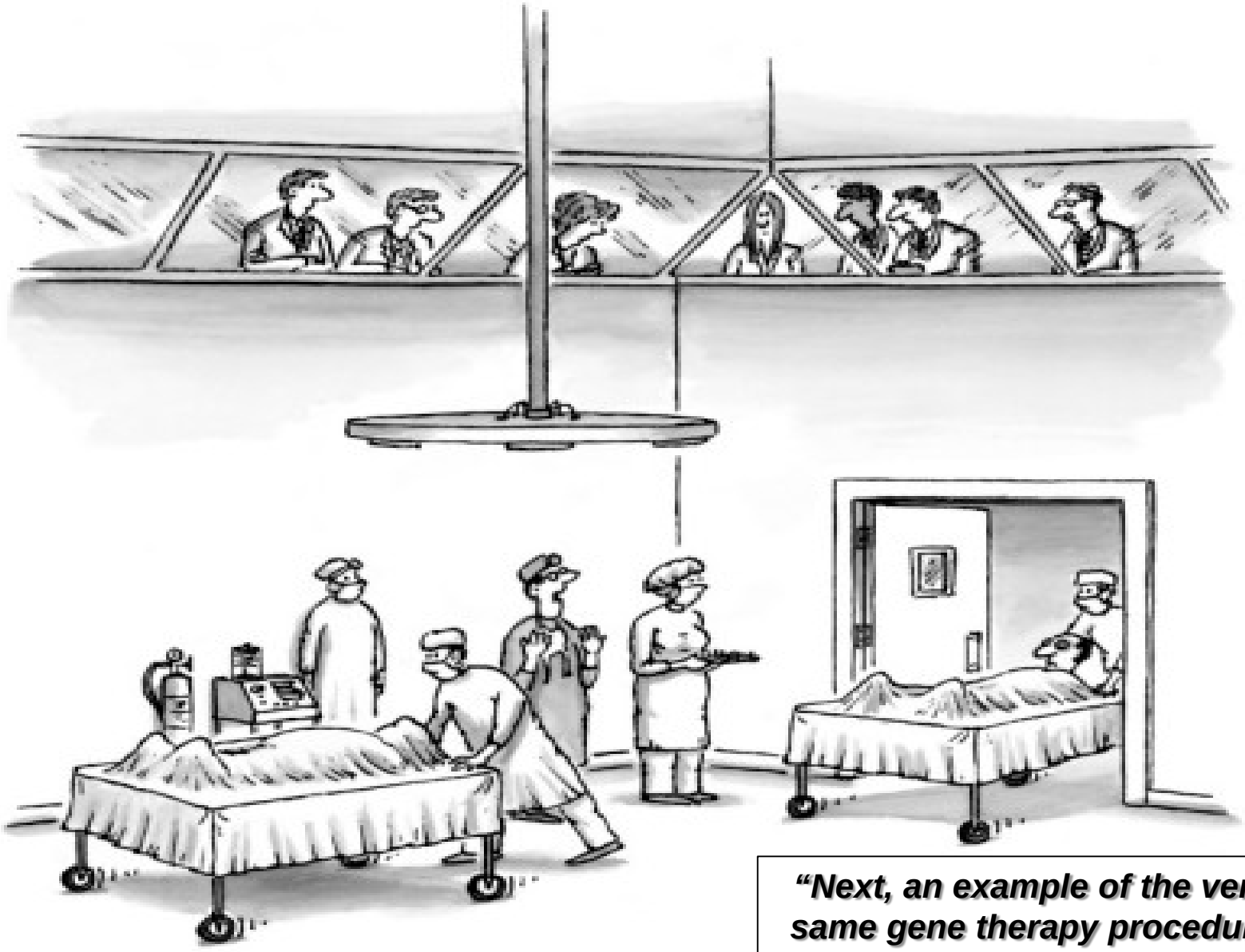


Kite Pharma
FOCUSED ON THE CURE

Illustration of evaluating a risk-base analysis (RRF) for CQA determination of a cell therapy ATMP

Attribute	Severity	Uncertainty	Result *RPN*	Rationale
Visual appearance				
Visible Foreign Particles	High	Medium	CQA	Absence of visible foreign particles is expected for all parenterals
Identity				
Expression of Chondrogenic Markers	High	Low	CQA	An autologous chondrocyte product must contain chondrocytes, which are characterized by their expression of specific chondrogenic markers
Impurities				
Fibroblastic Cells	High	Medium	CQA	Available data suggests fibroblasts may interfere with stable hyaline cartilage regeneration
Residual Trypsin	Low	Low	Non-CQA	In products manufactured to date, measured trypsin levels are 10x less than levels known to have a biological effect; as human recombinant trypsin was used, there is no risk for an immune reaction
Residual Collagenase	Low	Medium	Non-CQA	Collagenase is added to the process at levels 100x below the level known to have a biological effect

Residual Fetal Bovine Serum	High	Medium	CQA	Levels in final product known to potentially impact safety
Dead Cells	Medium	Low	CQA	Presence of dead cells monitored through cell viability
Potency				
Functional Activity	High	Low	CQA	Lack of function will inevitably result in a lack of clinical efficacy; expression of specific genes is measured as surrogate assay for function
Strength/Dose				
Total Cell Number/ Dose Unit	Medium	Low	CQA	Link between dose and efficacy needs to be established during development; in A-CeT, the dose volume is fixed, and cell concentration is an attribute that needs to be controlled
Safety				
Endotoxin	High	Low	CQA	Endotoxins (mainly lipopolysaccharides from gram negative bacteria) are highly pyrogenic substances that cause dose-dependent fever and shock
Sterility	High	Low	CQA	Sterility is a general safety requirement for all parenteral dosage forms to assure that cell products are free of microbial contamination
Mycoplasma	High	Low	CQA	Mycoplasma can cause serious contamination in cell cultures, which may affect phenotypical characteristics and normal growth of the cells; a few species can be pathogenic



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

?QUESTIONS?

Resources

Committee for Advanced Therapies (CAT)

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

Advanced therapy classification

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

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

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

FDA CBER Office of Tissues and Advanced Therapies (OTAT)

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

Case Study #2

Autologous cells subject to ex-vivo transduction and expansion prior to reintroduction

- **Open/closed manufacturing process:**
  - Aseptic cell collection by leukapheresis, transport to manufacturing facility, magnetic-bead based cell selection/expansion/viral transduction/formulation/filling/ cryopreservation, transport to patient bedside
  - Cell bags are aseptically connected between closed operation steps. Aseptic connections and disconnections are performed in ISO 5 BSC.
  - Open operations performed in ISO 5 BSC or isolator
  - Cell culture media and vector are not sterile filtered
- **Batch definition:** Single patient sourced blood cells intended for the same patient
- **Proposed APS Study Design:** Three APS modules: cell product manufacturing process, vector production and filling, preparation of cell culture media
- **FDA feedback**
  - Include antibody-coated beads during simulation of the cell selection step
  - Identify critical steps and collect samples at those steps during APS for final incubation to determine potential points of contamination
  - Change of workstation and operator between steps or shifts needs to be incorporated in APS at representative frequencies and using maximum number of operators

FDA OTAT Learn

(video courses on how FDA regulates CGTPs)

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

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

CELL & GENE THERAPY 2018: SPEAKER PRESENTATIONS

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

free downloadable presentations

FDA Perspective on Aseptic Process Simulation for Cell Therapy Product Manufacturing

Early Stage Manufacturing Considerations for Cell Therapy Products

mRNA as a Platform Technology Ideally Suited for Individualized Therapeutics

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

Comparability Is Not a Nightmare, Just Think Ahead!

PDA

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

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

Technical Report No. 81

Cell-Based Therapy Control Strategy

Cell & Gene Therapy Interest Group

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

Practical Application of Phase-Appropriate GMPs & Quality to Clinical Development of ATMPS

In Conclusion

- ***ATMPs are highly complex medicines***
- ***Regulatory authorities are becoming more comfortable (flexible) in regulating the ATMPs***
- ***You need to adapt your process and product to the appropriate GMPs and Quality principles***
- ***Patient safety must never be compromised***