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
Chair PDA Biopharmaceutical Advisory Board

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

Course Goal

To help you, the attendee, develop a practical, risk-managed, phase-appropriate compliant good manufacturing practices (GMPs) and effective Quality strategy for advanced therapy medicinal products (ATMPs),

across the clinical development lifecycle!

Clinical Development Phases

Phases 1-3 or expedited

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

Course Outline

1. ***Understanding the Basics: ATMP, HCT/P, RMAT, GMP, Quality, Phase-Appropriate Risk***

2. ***Major Differences, and the GMP and Quality Risk Consequences, Between Protein-based and Gene/Cell-based Medicines***

3. ***Regulatory Authority (EC/EMA/FDA) Expectations for ATMP GMPs and Quality – Risk-Based Approach***

4. ***Industry Practice in Applying ATMP GMPs and Quality (Including the PDA Technical Report Cell-Based Therapy Control Strategy)***

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

- *35+ 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)*
- *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 medicines*

Who are you?

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

What a difference a year has made!

(course taught last June at this conference)

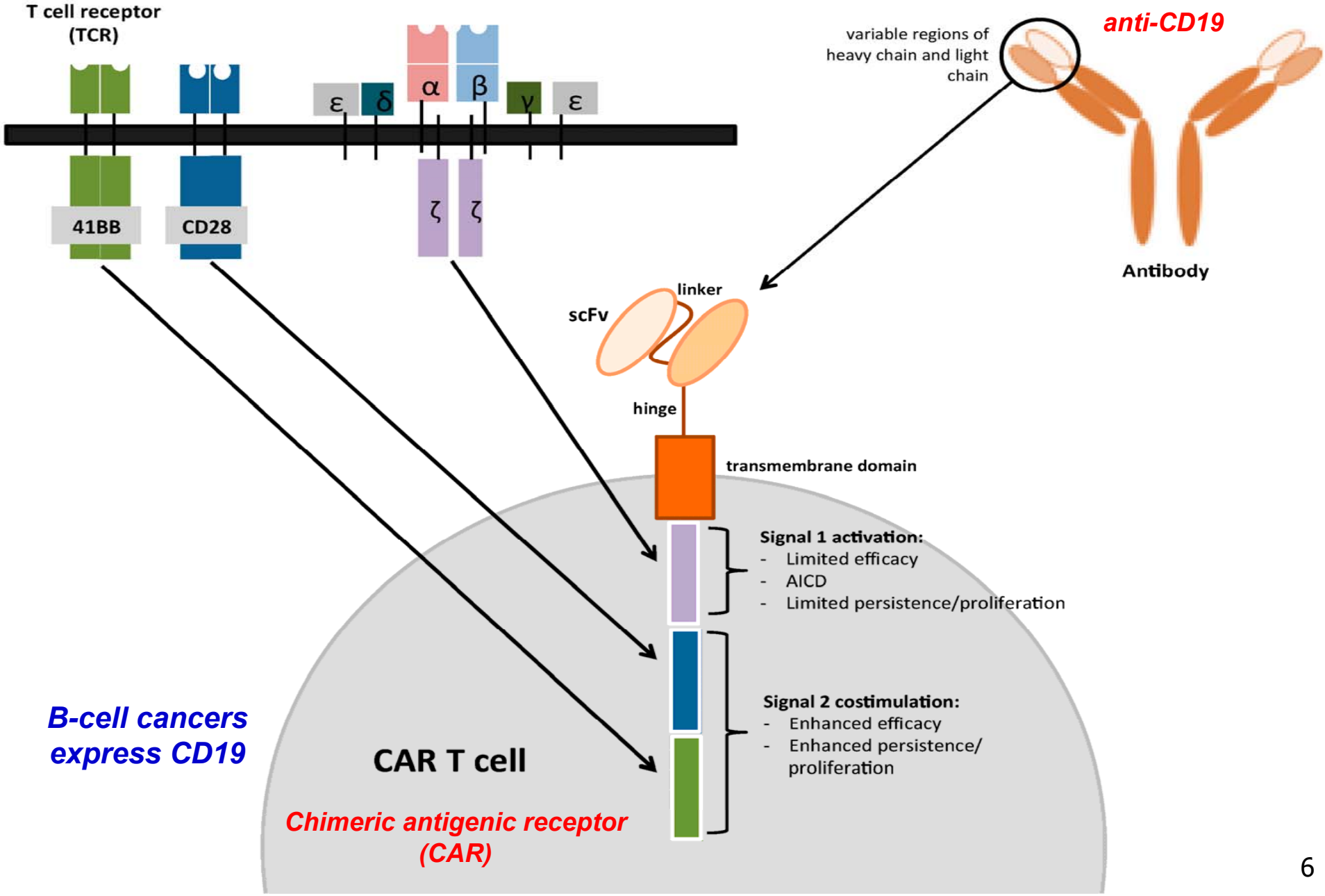
2017

➢ *Glybera (gene therapy virus)*	*withdrawn from EU*
➢ *Spherox (tissue engineered product)*	*approved EMA*
➢ *Kymriah (CAR T-cell gene therapy)*	*approved FDA*
➢ *Yescarta (CAR T-cell gene therapy)*	*approved FDA*
➢ *Luxturna (gene therapy virus)*	*approved FDA*

2018

➢ *Kymriah (CAR T-cell gene therapy)*	*MAA submitted EMA*
➢ *Yescarta (CAR T-cell gene therapy)*	*MAA submitted EMA*
➢ *Luxturna (gene therapy virus)*	*MAA submitted EMA*

A new vocabulary: CAR T cells!



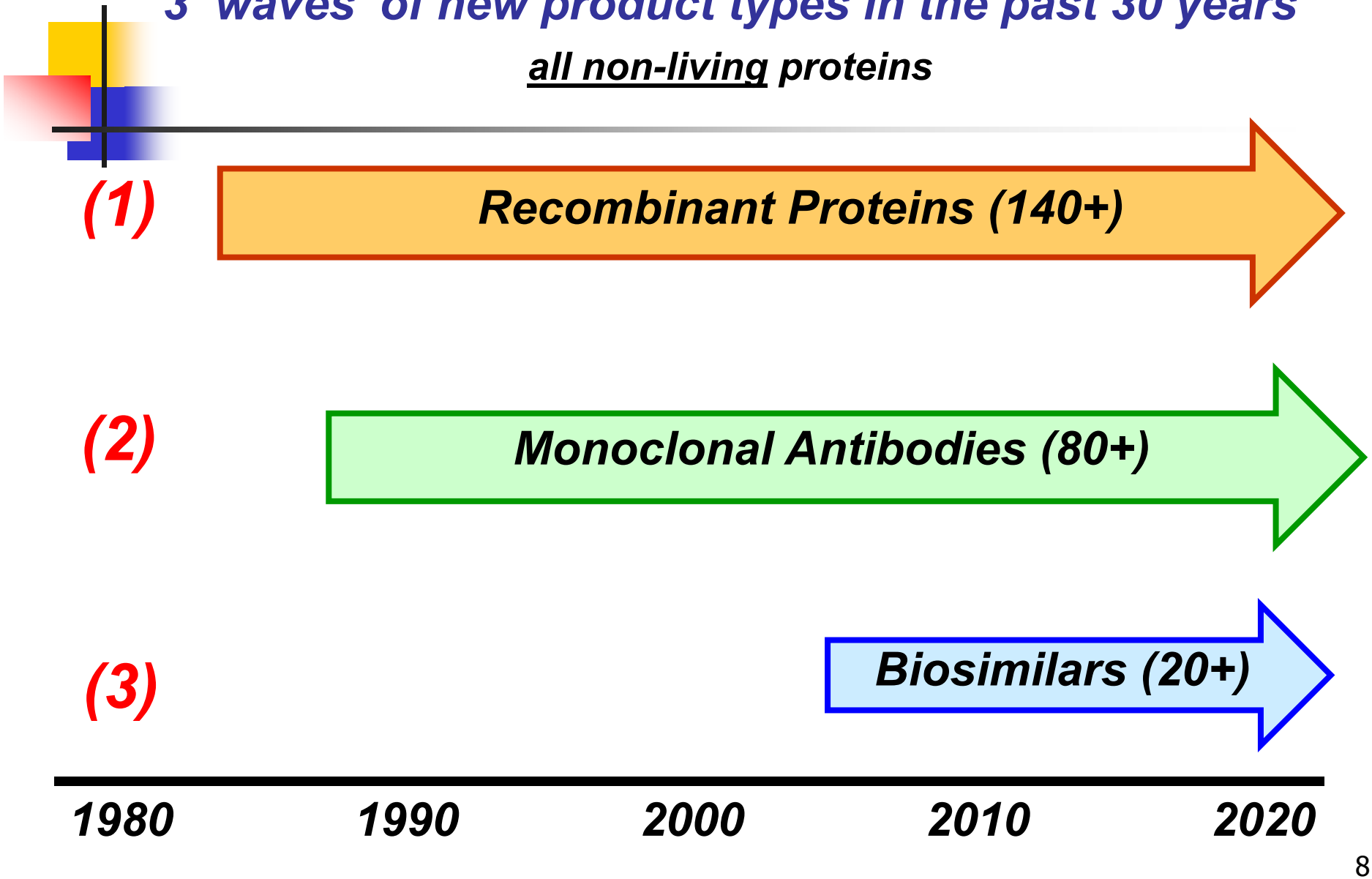
Practical Application of Phase-Appropriate GMPs & Quality to Clinical Development of ATMPs

1. Understanding the Basics

- ✓ ***Painting the terminology landscape for the products under Advanced Therapy***
  (i.e., ATMP, CGTP, HCT/P, RMAT)
- ✓ ***Introduction to the risk-based phase-appropriate GMP & Quality approach for ATMPs***

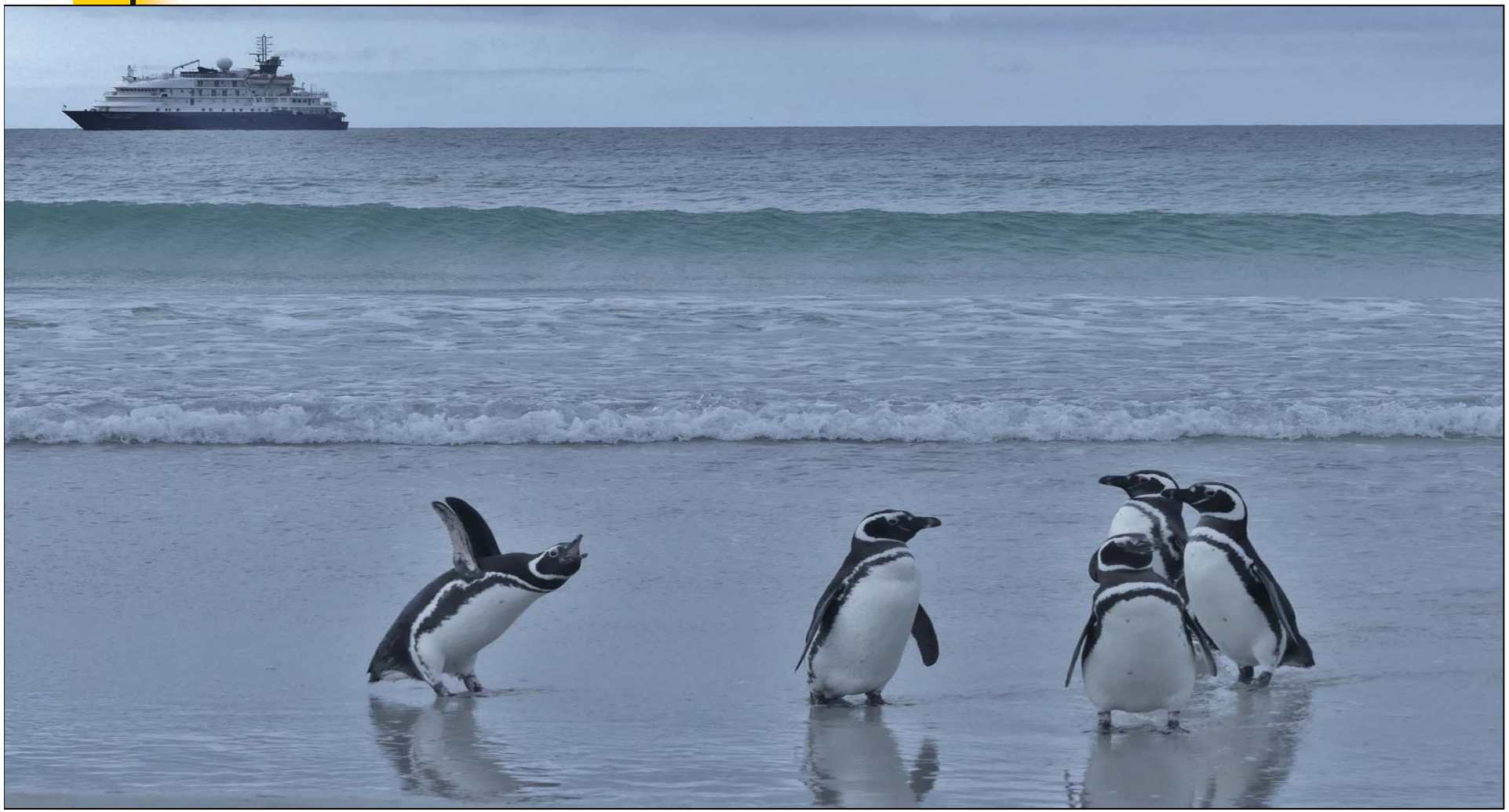
The biological industry has experienced 3 'waves' of new product types in the past 30 years

all non-living proteins



(4) The 4th biopharmaceutical wave

***living* genetically engineered viruses and cells**



(ongoing debate in the industry over whether ATMPs are the 4th wave)

Consensus is building for this next wave ….

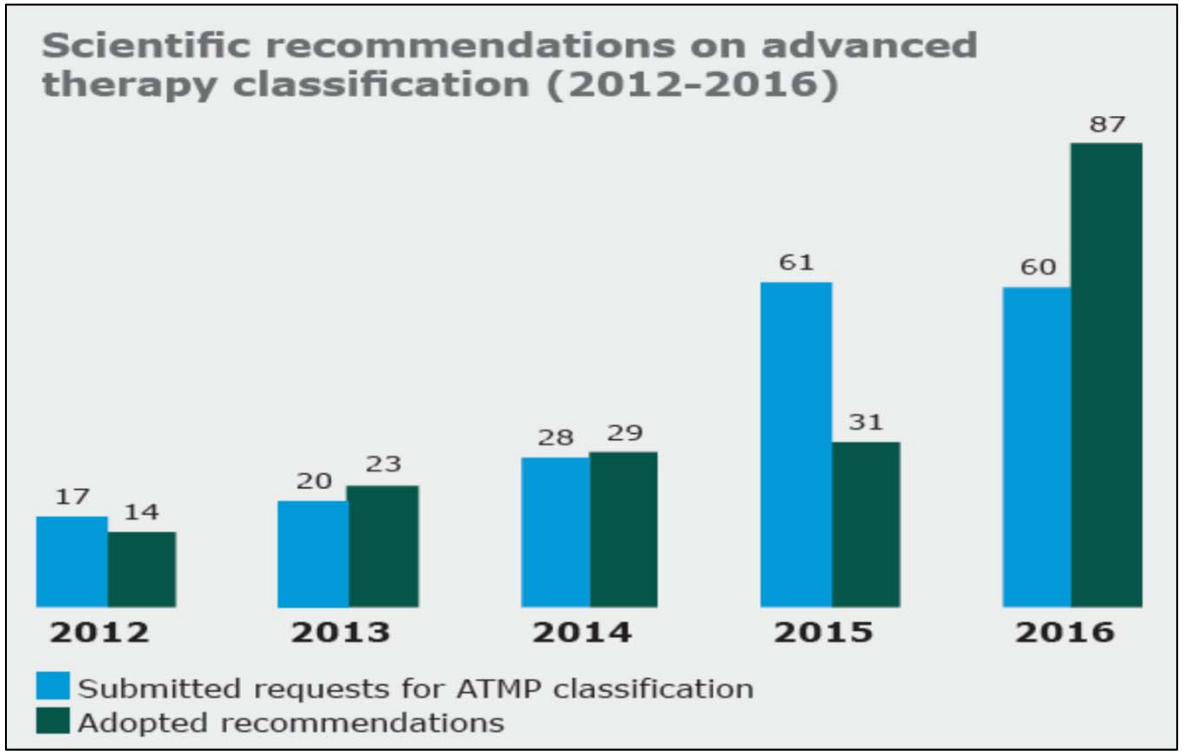
(according to EMA)

- ***Over 180 medicines under clinical development have been designated as ATMPs by the European Committee for Advanced Therapies (CAT)***

EUROPEAN MEDICINES AGENCY

Annual Report 2016

published May 2017



(according to the FDA)

- ***FDA www.ClinicalTrials.gov – 500+ active gene therapy trials listed***
- ***Over 75 chimeric antigen receptor (CAR) T-cell active INDs on file with the FDA – 2 already approved for the market (Novartis, Kite Pharma)***
- ***21st Century Cures Act of 2016 – expedited FDA review and approval for regenerative medicine advanced therapies (RMATs)***

Terminology Landscape

European Medicines Agency (EMA)

ADVANCED THERAPY MEDICINAL PRODUCT (ATMP)

GENE THERAPY PRODUCT, SOMATIC CELL THERAPY PRODUCT, TISSUE ENGINEERED PRODUCT

U.S. Food and Drug Administration (FDA)

ANALOGOUS BIOLOGICAL PRODUCT

HUMAN CELLS, TISSUES AND CELLULAR AND TISSUE-PRODUCT (HCT/P)

CELLULAR AND GENE THERAPY (CGT) PRODUCT

REGENERATIVE MEDICINE ADVANCED THERAPY (RMAT) PRODUCT

European Medicines Agency (EMA)

Advanced Therapy Medicinal Products (ATMPs)

Regulation (EC) No 1394/2007

(legal definition of ATMPs)

(Committee for Advanced Therapies, CAT, classification and review of ATMPs)

(Member state – hospital exemption)

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***

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

IN VIVO GENE THERAPY

DIRECT GENE INSERTION

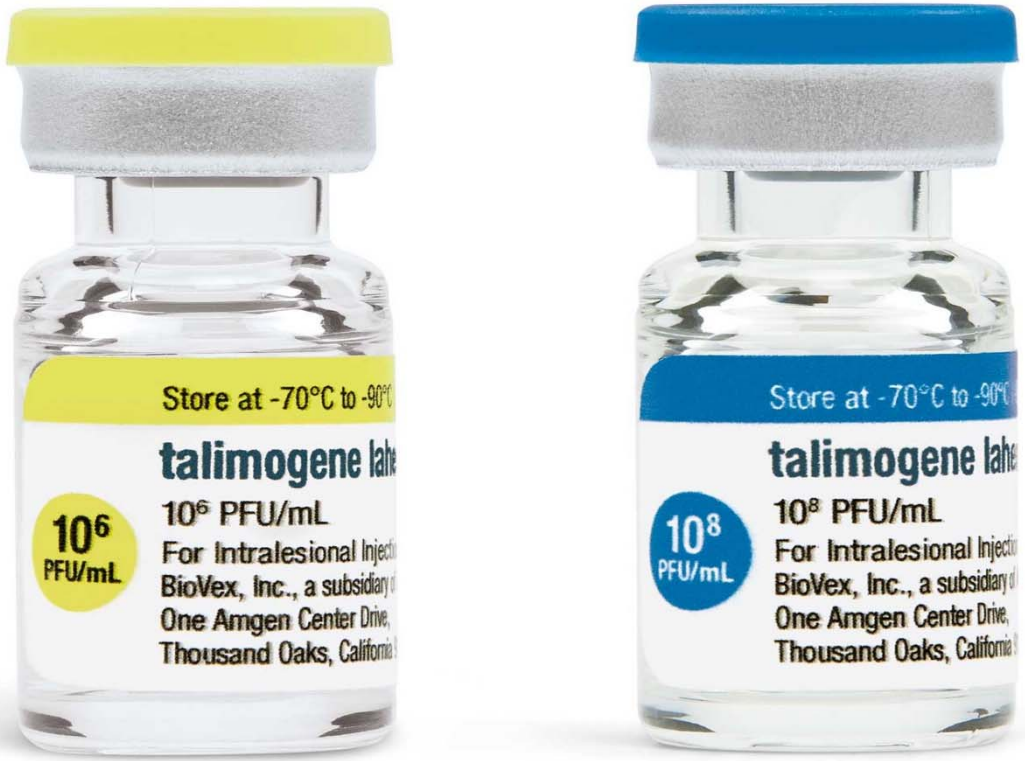
(typically by use of viruses)

UniCure YouTube

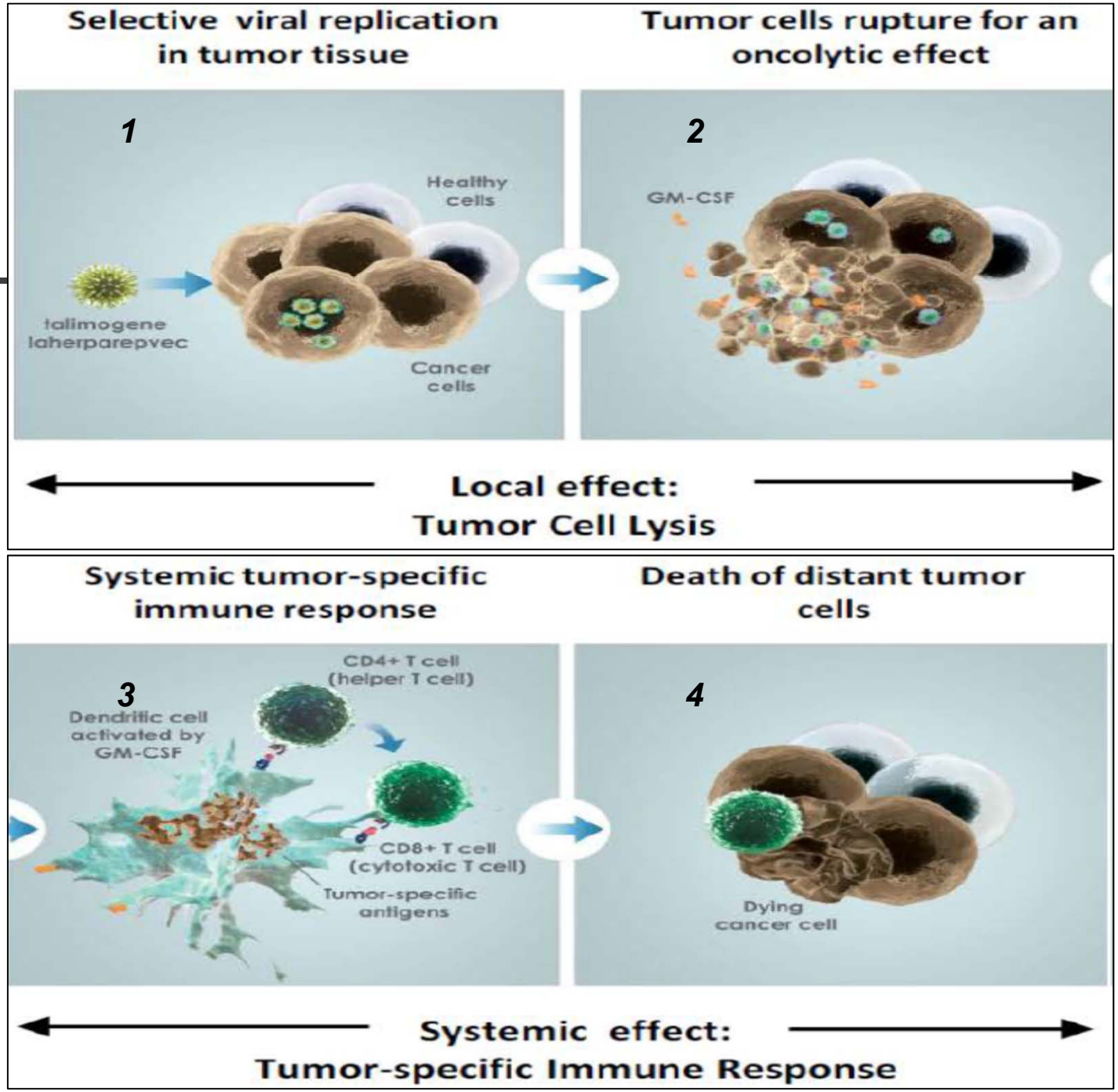
IMLYGIC (talimogene laherparepvec) is a sterile suspension for intralesional injection. IMLYGIC is a live, attenuated HSV-1 that has been genetically modified to express huGM-CSF. The parental virus for IMLYGIC was a primary isolate, which was subsequently altered using recombinant methods to result in gene deletions and insertions.

AMGEN®

FDA/EMA 2015



IMLYGIC has been genetically modified to replicate within tumors and to produce the immune stimulatory protein GM-CSF. IMLYGIC causes lysis of tumors, followed by release of tumor-derived antigens, which together with virally derived GM-CSF may promote an antitumor immune response.

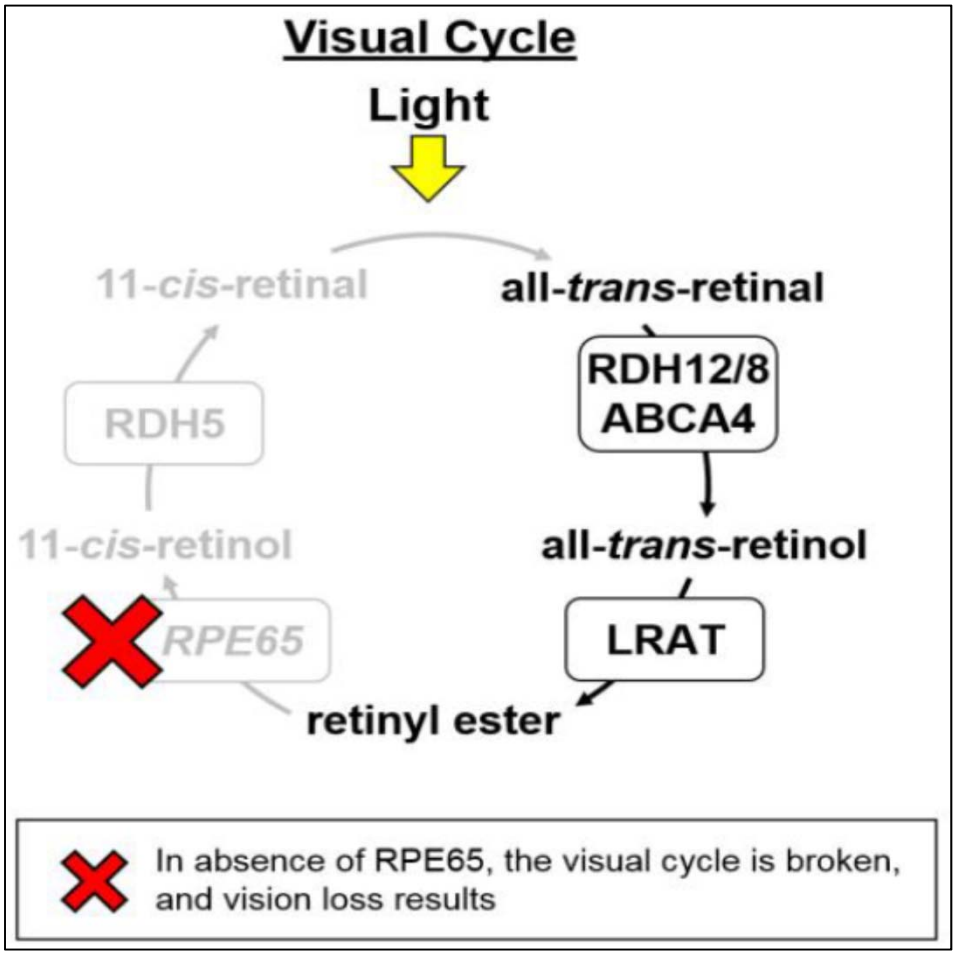

Selective viral replication in tumor tissue
Tumor cells rupture for an oncolytic effect
1
Healthy cells
talimogene laherparepvec
Cancer cells
2
GM-CSF
Local effect:
Tumor Cell Lysis
Systemic tumor-specific immune response
Death of distant tumor cells
3
CD4+ T cell (helper T cell)
Dendritic cell activated by GM-CSF
CD8+ T cell (cytotoxic T cell)
Tumor-specific antigens
4
Dying cancer cell
Systemic effect:
Tumor-specific Immune Response

Voretigene neparvovec is an AAV2 gene therapy vector with a CMV enhancer, a CβA promoter and a cDNA encoding a wild-type hRPE65 protein.

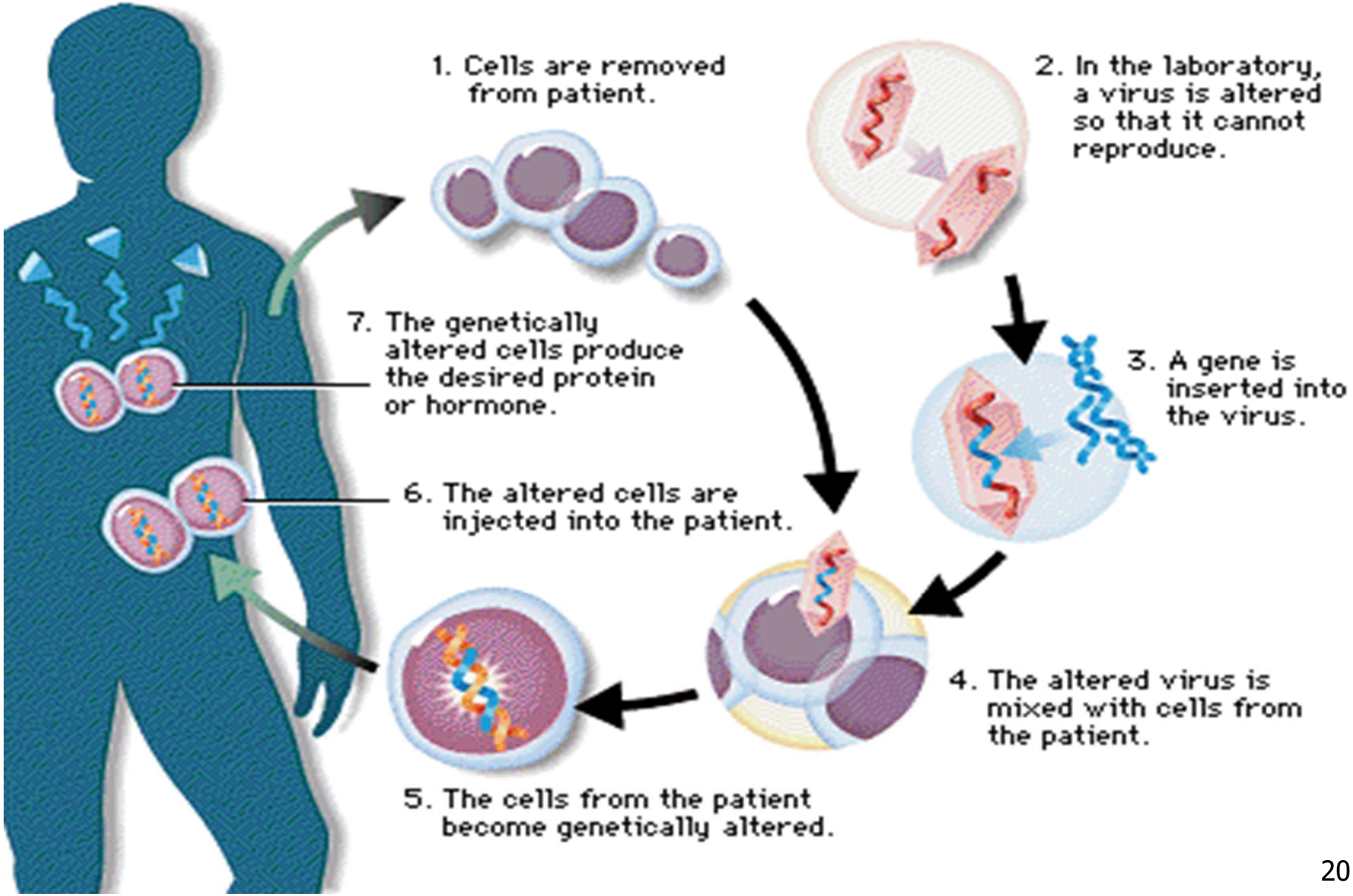
Voretigene neparvovec supplies a functional copy of a RPE65 cDNA within the RPE cells, thereby restoring the visual cycle in patients with RPE65 mutation-associated retinal dystrophy.

Spark Therapeutics, Inc
LUXTURNA™
(voretigene neparvovec)

Voretigene neparvovec employs an AAV2 vector as a delivery vehicle for an expression cassette encoding normal human RPE65



EX VIVO GENE THERAPY ⟹ GENE INSERTION VIA VIRUS TRANSDUCTION OF ISOLATED PATIENT CELLS



Novartis YouTube

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

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***
- ***Genetic modification of cells***
- ***Differentiation/activation with growth factors***
- ***Enzymatic digestion of tissue to release cells***

Reflection paper on classification of advanced therapy medicinal products

21 May 2015
EMA/CAT/285241/2010 rev.1

'Not Substantial Manipulation' is …

- *cutting*
- *grinding*
- *shaping*
- *centrifugation*
- *soaking in antibiotic or antimicrobial solutions*
- *sterilization*
- *irradiation*
- *cell separation*
- *concentration/ purification*
- *filtering*
- *lyophilization*
- *freezing*
- *cryopreservation*
- *vitrification*

MOLMED

Zalmoxis

23 June 2016
EMA/CHMP/589978/2016

SOMATIC CELL THERAPY

Suicide gene inserted into T-cells so that they can be rapidly killed should they turn and cause graph vs host disease (GvHD)

Zalmoxis therapy is intended as adjunctive therapy in patients who underwent haploidentical hematopoietic stem cell transplantation (HSCT) in order to aid immune reconstitution (IR). A hastened IR would subsequently prevent the onset of infectious diseases and thus result in a lower treatment-related or non-relapse mortality (NRM) and fewer disease relapse.

The finished product (FP) proposed for the present application is an ATMP based on somatic T-cells genetically modified to express the HSV-TK suicide gene and ΔLNGFR genes (for identification of the transduced cells). The FP has been classified by the Committee for Advanced Therapies (CAT) as an ATMP, somatic cell therapy medicinal product, as defined in Dir. 2009/120/EC amending Directive 2001/83/EC Annex I part IV (EMEA/CAT/419154/2009).

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"

Holoclar

18 December 2014
EMA/25273/2015

ocular burn injury

Holoclar is defined as autologous tissue-engineered product which consists of a transparent circular sheet of 300,000 to 1,200,000 viable autologous human corneal epithelial cells (79,000-316,000 cells/cm^2), expanded *ex vivo*, including on average 3.5% (0.4% to 10%) limbal stem cells, stem cell-derived transient amplifying and terminally differentiated cells, prepared from a limbus biopsy of the patient as starting material, and attached on a 2.2cm diameter fibrin support (manufactured from Ph. Eur. compliant human fibrin) and maintained in physiological transport medium (containing Dulbecco's modified eagle medium (DMEM), supplemented with L-glutamine). The proposed shelf life is 36 hours. The primary container is placed inside multiple layers of secondary packaging to protect the vulnerable product. The finished product presentation does not include a medical device.

(due to substantial manipulation)

ATMP also …

Regulation (EC) No 1394/2007

'Combined advanced therapy medicinal product' – an ATMP that incorporates, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC

A product which <u>may fall within the definition</u> of
– a somatic cell therapy medicinal product or a tissue engineered product, and
– a gene therapy medicinal product,
shall be considered as a gene therapy medicinal product

A product which <u>may fall within the definition</u> of
– a tissue engineered product, and
– a somatic cell therapy medicinal product,
shall be considered as a tissue engineered product

U.S. Food and Drug Administration (FDA)

Cellular and Gene Therapy Products (CGTPs)

Public Health Service (PHS) Act 1944

(biological product legal definitions)

Title 21 Code of Federal Regulations (CFR) Part 1271

(Human Cells, Tissues, and Cellular and Tissue-based Products HCT/Ps)

506(g) of the Food, Drug, & Cosmetic (FD&C) Act

(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'

CGT Products are …

(1) Gene Therapy Products

Biological products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms – direct administration or by ex vivo gene-modified cells

same definition as EMA,

except FDA considers vaccines for infectious diseases (e.g., plasmid DNA) as gene therapy

CGT Products are …

(2) Cellular Therapy Products

Biological products that mediate their effects through the pharmacological, immunological or metabolic action of somatic cells

- ***autologous (same patient)***
- ***allogeneic (different patients)***

similar definition as EMA →

EMA	FDA*
Cells subject to substantial manipulation	Cells must be more than minimally manipulated
or	and/or
Cells not intended to be used for the same essential functions in the recipient and donor	Cells not intended for homologous use (i.e., does not perform the same function in the recipient as in the donor)

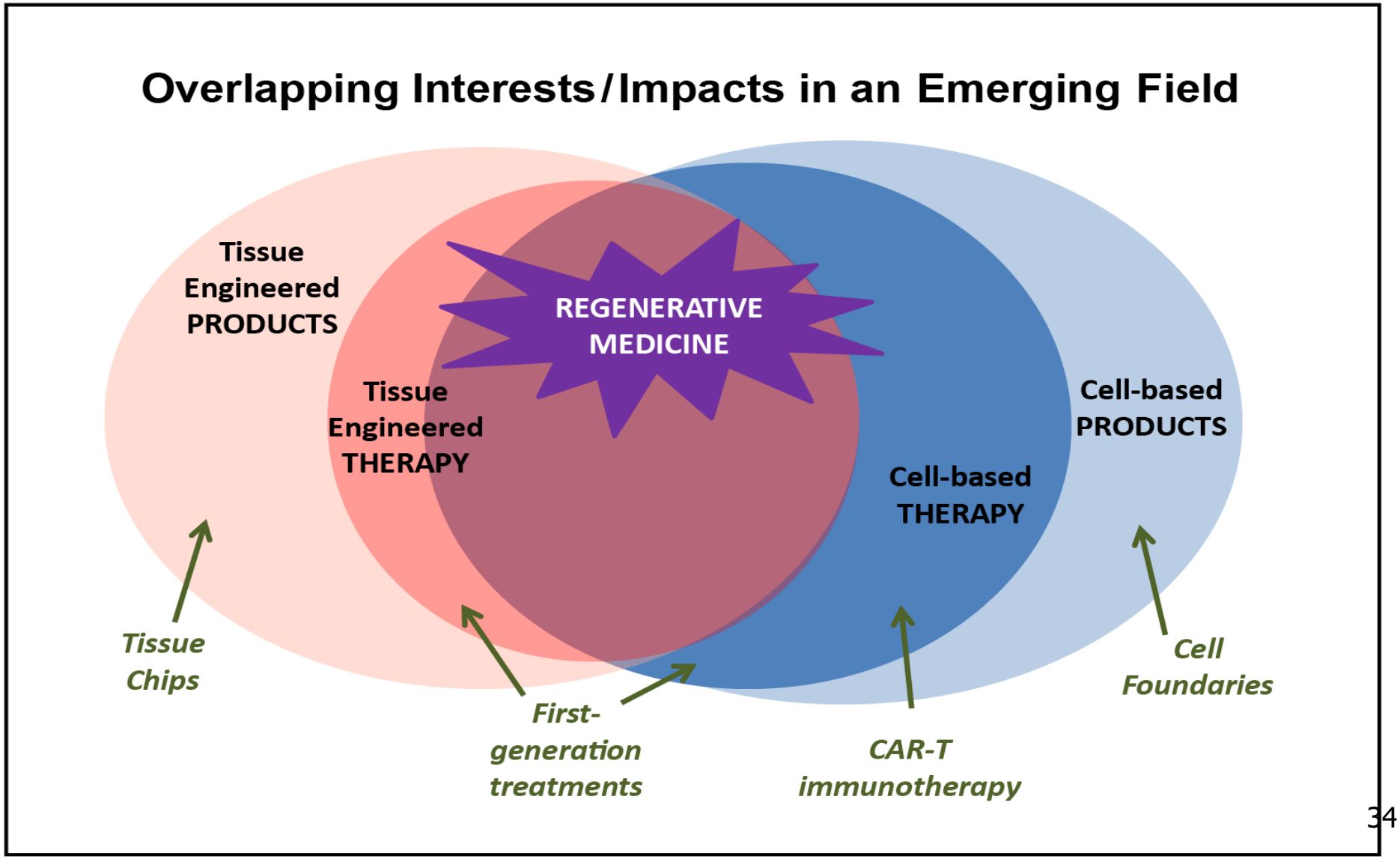
*** Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)**

- *If cells meet at least 1 of these 2 requirements, they are considered biological products under PHS Act, section 351a*
- *If cells do not meet at least 1 of these 2 requirements, they are not considered biological products – but come under section 361 (e.g., organ transplant, tissue grafting, etc.)*

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
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	
Designation Rescission	Designation may be rescinded later in product development if the product no longer meets the designation-specific qualifying criteria	

Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

Center for Biologics Evaluation and Research
November 2017

CONFUSED!

substantial manipulation

more than minimal manipulation

ATMP

analogous product

CGTP

HCT/P

RMAT

not the same essential function

not intended for homologous use

Ask EMA

Committee for Advanced Therapies (CAT)

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.

EMA ATMP website

www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0

Ask FDA

Center for Biologics Evaluation and Research (CBER)

Office of Tissues and Advanced Therapies (OTAT)

FDA OTAT website
www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/default.htm

FDA OTAT Learn
(video courses on how FDA handles CGTPs)
www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

GMPs and Quality

GMPs and Quality are the

REQUIREMENTS AND EXPECTATIONS

derived from the regulations and guidelines

pertaining to the implementation of

PRACTICES, STANDARDS AND CONTROLS

in a manufacturing and/or testing facility

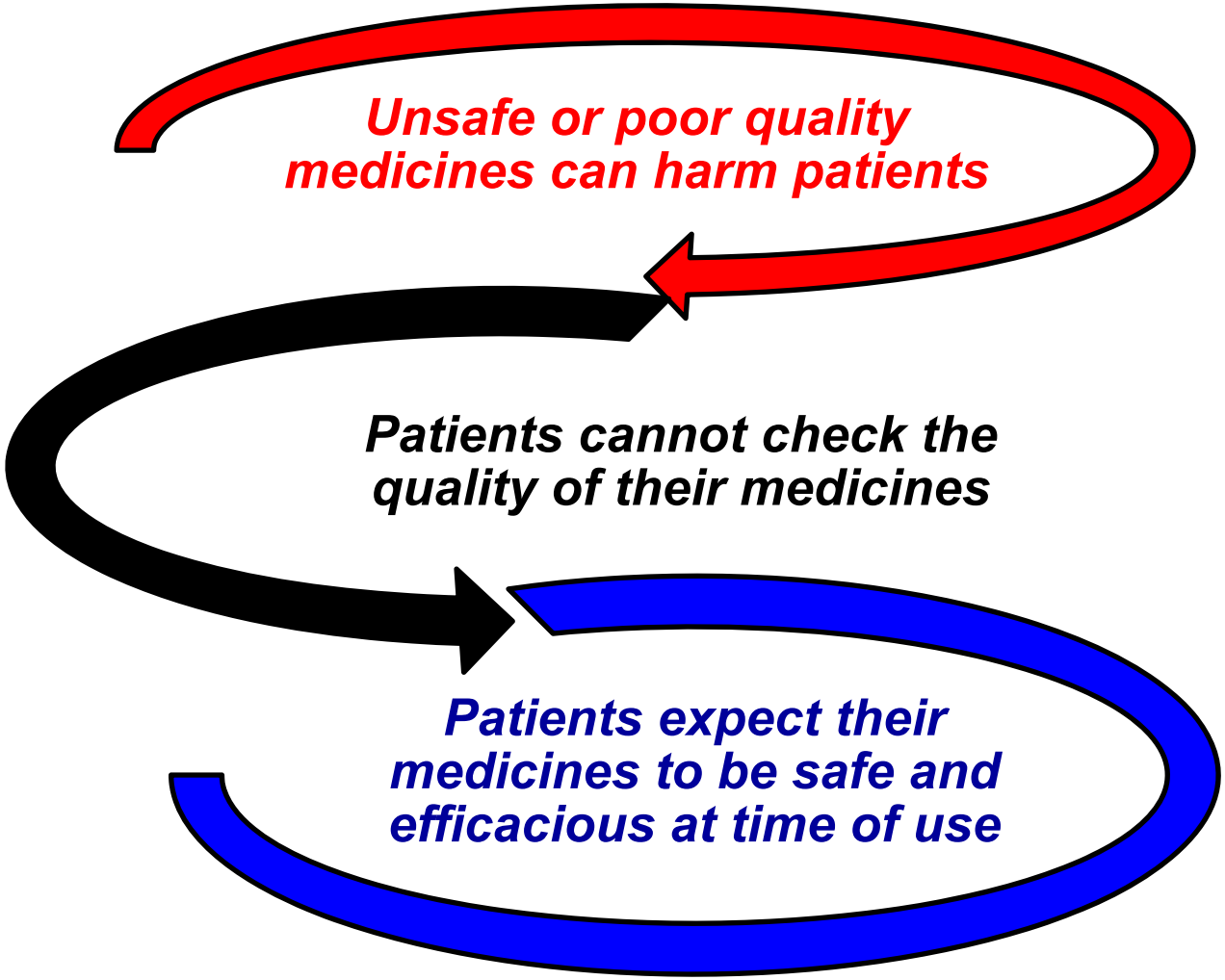
that allows for the consistent production and/or testing

of a quality product with the intended

identity, purity, safety and potency characteristics

GMPs and Quality – necessary to protect the patient!

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



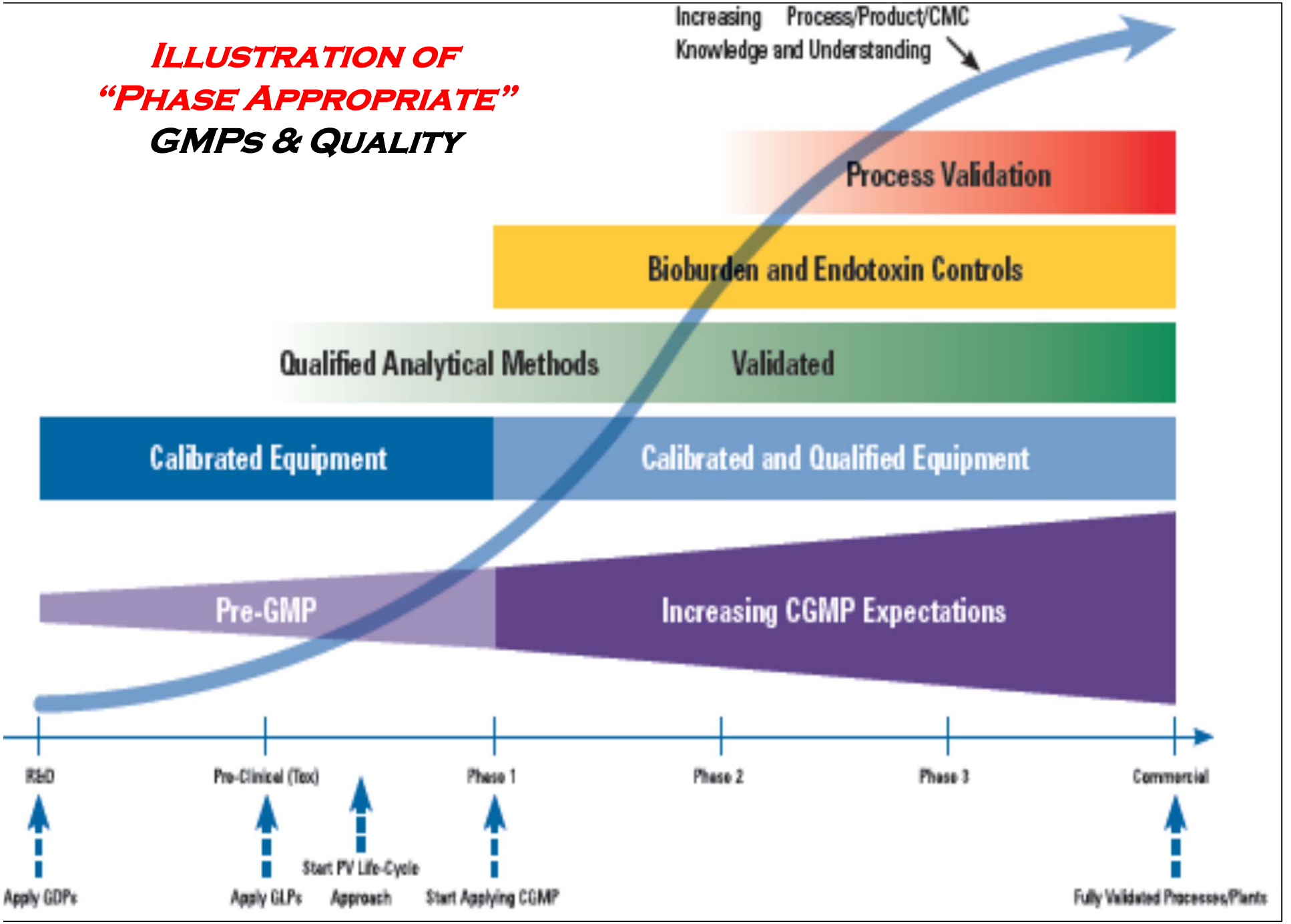
GMPs and Quality – risk-based approach

(needs to be practical and common sense)

- ***A risk-based approach focuses the 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 doing the right amount at the right time 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***
- ***Thus, a risk-based development plan actually enhances safety in early phases, even when product understanding and resources may be limited***

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

Illustration of "Phase Appropriate" GMPs & Quality



Phases 1 & 2 Clinical Trials of ATMPs

Manufacturing batch experience: limited
CMC impact on efficacy data: minimal

- ***Early stage of testing in human subjects***
- ***Small group of patients (10 - 100)***
  - ***not healthy volunteers like protein-based medicines***
- ***Assess product safety, pharmacodynamics (PD), proof of concept, dose and indication refinement***

Example
Amgen's IMLYGIC
Phases 1/2: 83 patients

Phase 3 (Pivotal) Clinical Trials of ATMPs

Manufacturing batch experience: extensive

CMC impact on efficacy data: significant

Performed with largest groups (>100's)

Designed to confirm efficacy and monitor adverse reactions (safety) during longer-term use

Demonstrate potential advantages of the new therapy over therapies already on the market

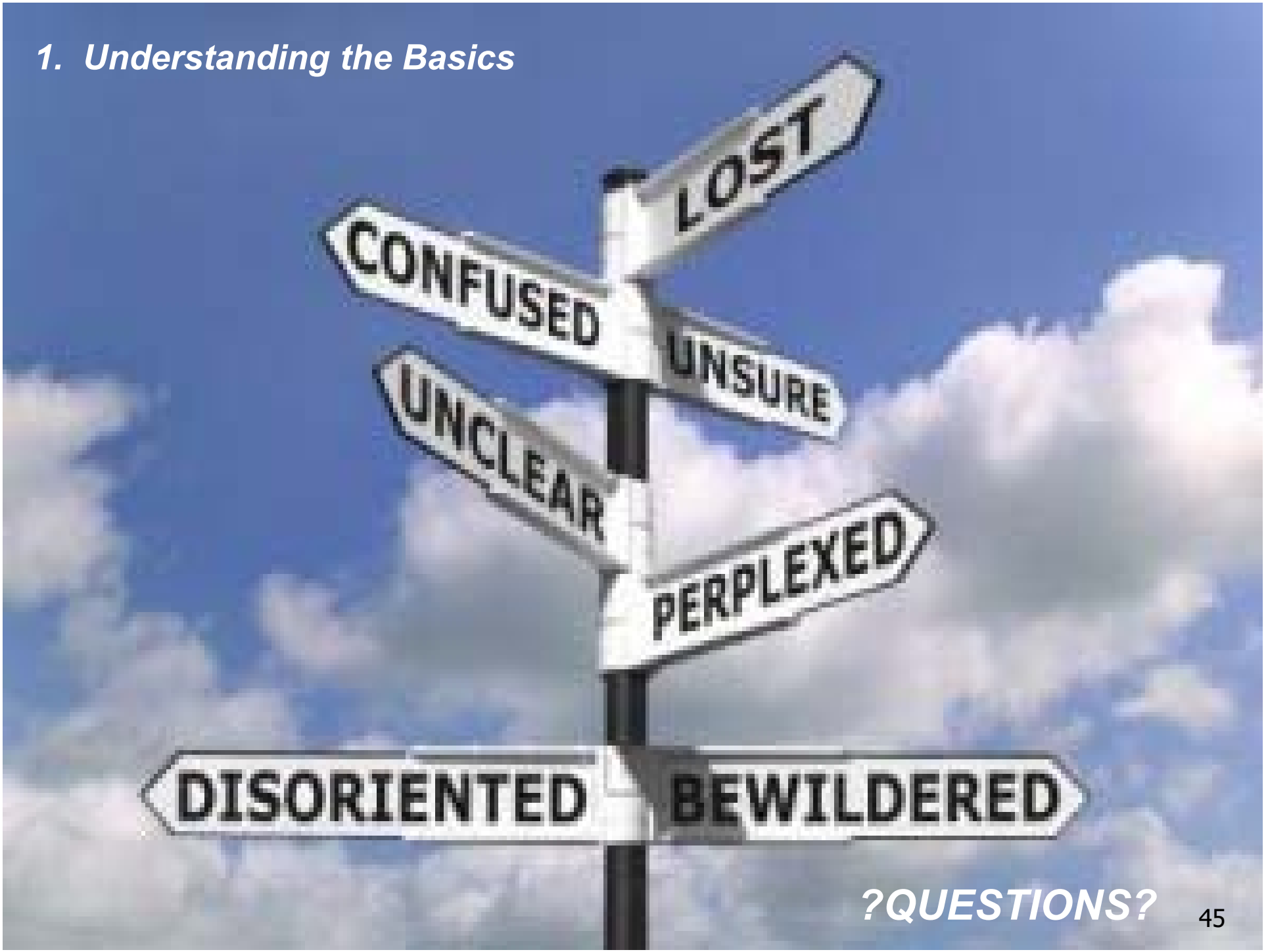
**** 64 clinical sites (USA, UK, South Africa, Canada)***

Example

Amgen's IMLYGIC

Phase 3: 436 patients*

1. Understanding the Basics



?QUESTIONS?

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

2. Major Differences, and the GMP and Quality Risk Consequences, Between Protein-based and Gene/Cell-based Medicines

- ✓ ***Living viruses/cells are <u>not</u> proteins***
- ✓ ***Risk assessment of the major differences, and impact on ATMPs during clinical development***

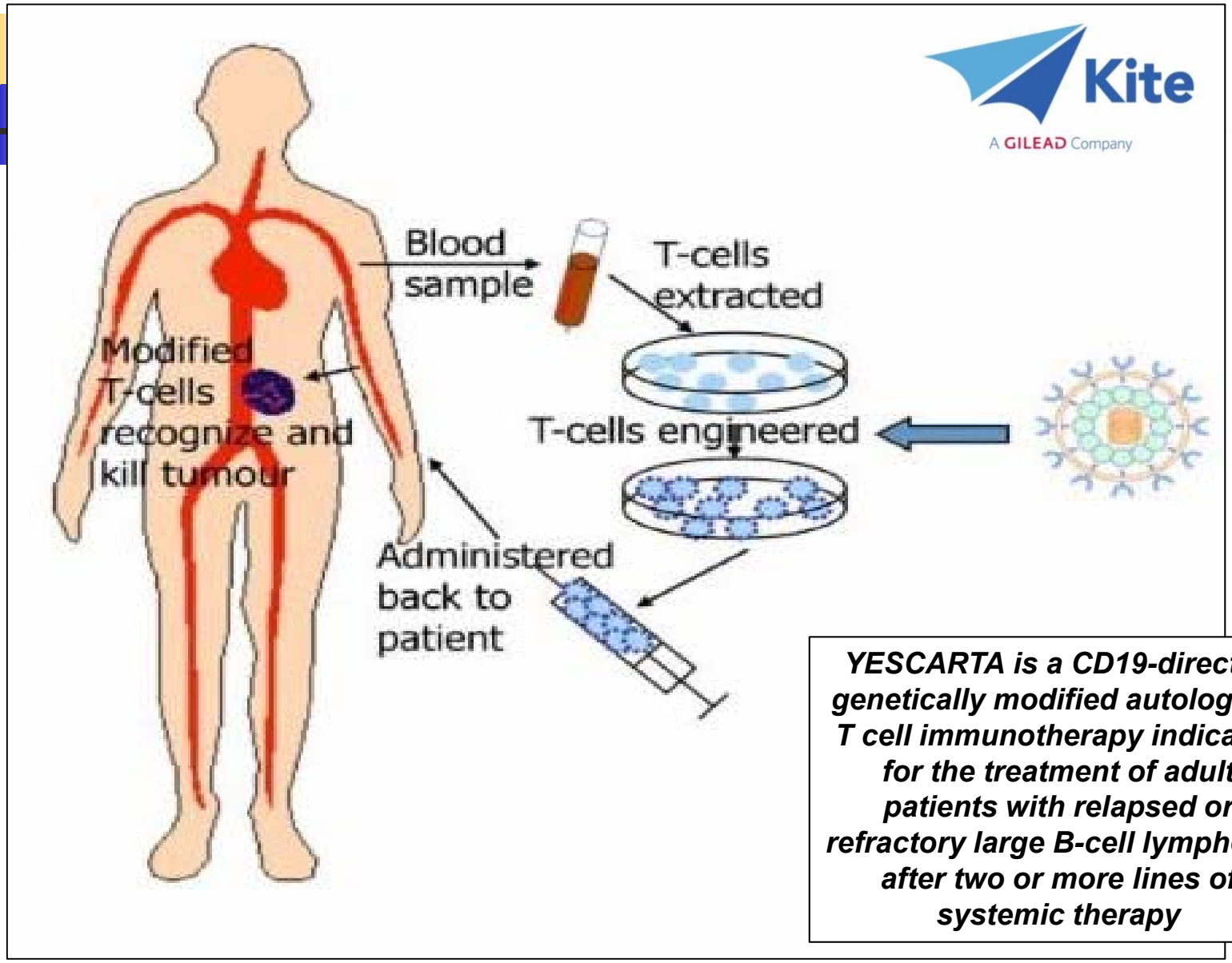
PDA TR Cell-Based Therapy Control Strategy (upcoming TR)

'Regulatory expectations for development of cell and gene therapy products (CGTP) are no different than those pertaining to traditional biologic products in this regard.

Prospective science and a risk-based approach to product development of CGTP can increase the assurance of quality in the manufacture of CGTP just as it does for other biologics.

By appropriately characterizing the risks and understanding how these risks influence or impact quality attributes of the products, a CGTP developer can effectively design a robust manufacturing control strategy and reliably ensure product quality'

A robust manufacturing process is needed for these products!



YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy

Major GMP & Quality Differences Between Biopharmaceutical Types

Comparison	Recombinant Proteins & MAbs	ATMPs (CGTPs)
Product Type	Non-living biopharmaceuticals	Living biopharmaceuticals
Link to Clinician and Patient		
Pressure on Manufacturing		
Batch Traceability		
Manufactured Batch Size		
Product Characterization		
QC Testing		
QA Batch Disposition		

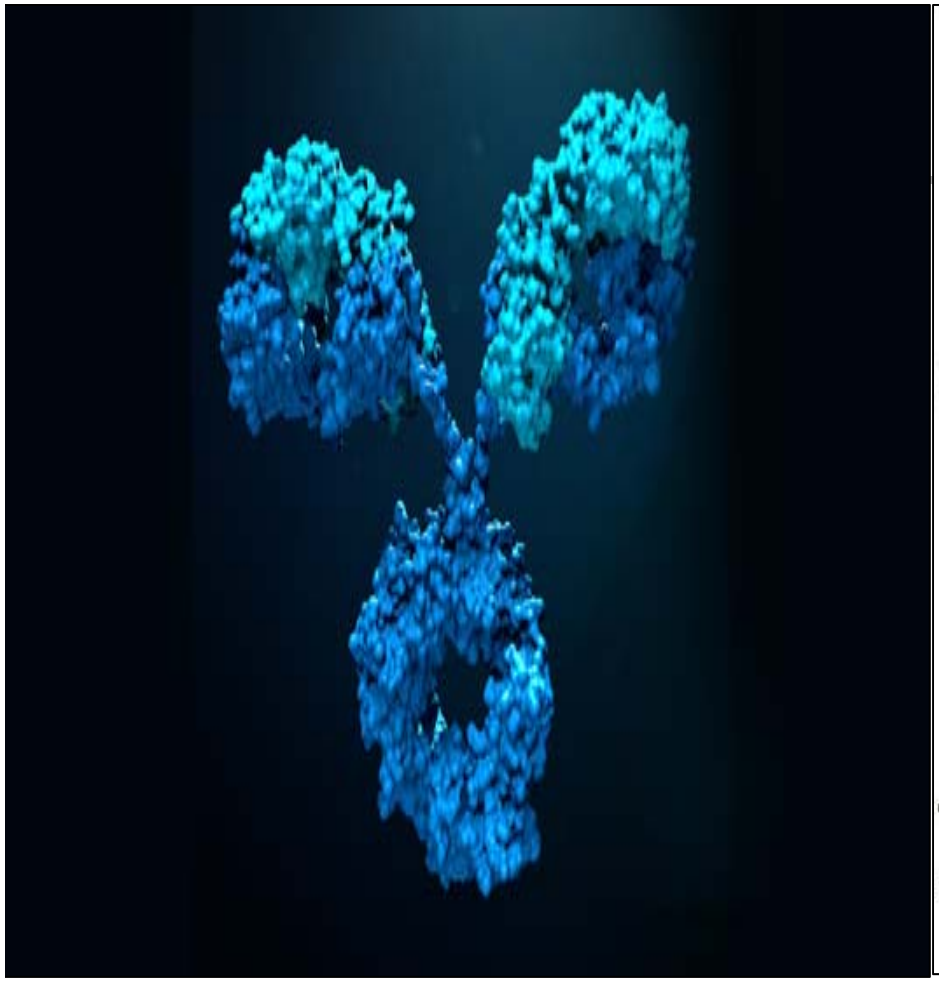
GMP & Quality Different Risks

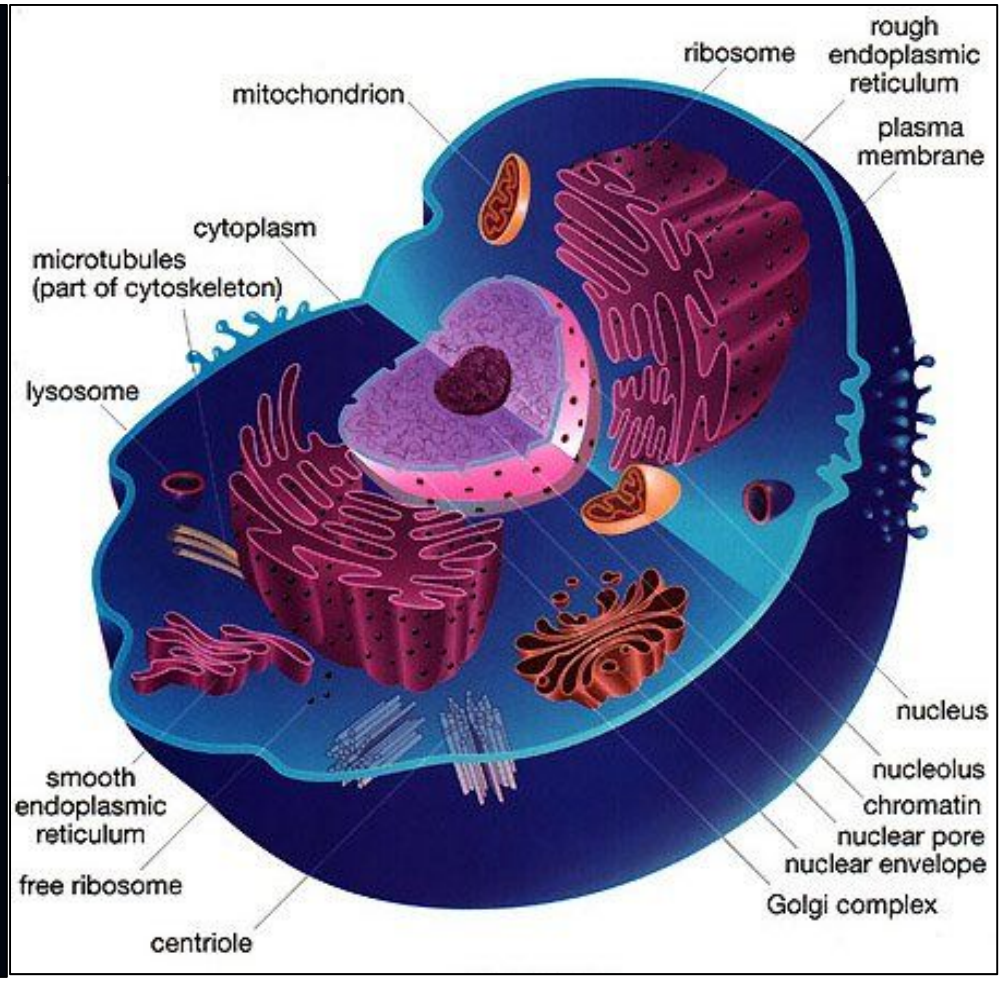
- ***Viruses and cells must be kept alive! 24/7 Not proteins***
- ***Very high threat of adventitious agent (e.g., virus, mycoplasma, microbes) contamination due to so many manual manipulations and inability of filtration! Protein processes are more closed and can be sterile filtered***
- ***"Cell therapy 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 cells!





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

living product
20 µm size
18K+ functionally active proteins

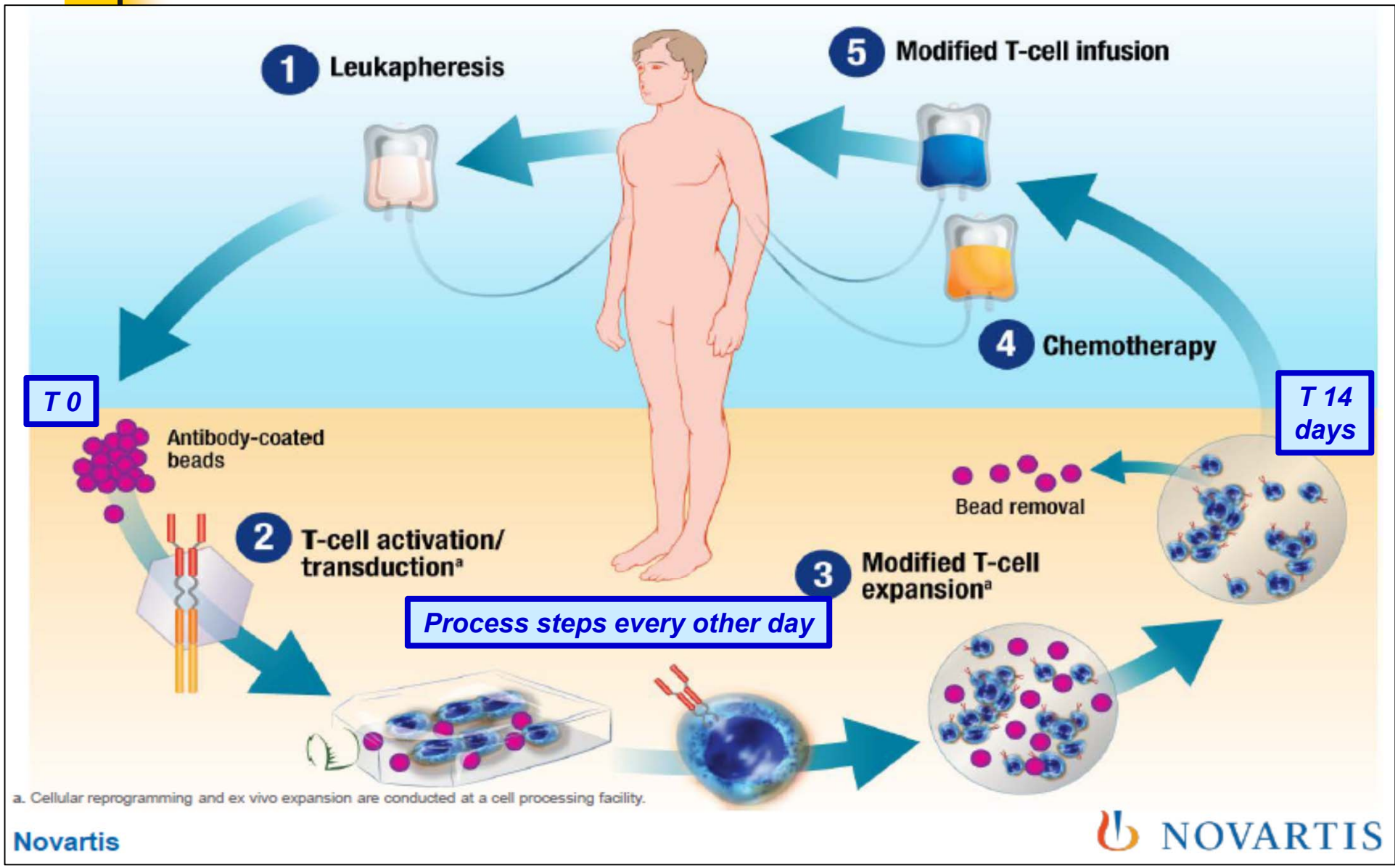
Major GMP & Quality Differences Between Biopharmaceutical Types

Comparison	Recombinant Proteins & MAbs	ATMPs (CGTPs)
Product Type	Non-living biopharmaceuticals	Living biopharmaceuticals
Link to Clinician and Patient	Batch independent of specific patients	Batch dependent upon clinician and patient
Pressure on Manufacturing	None, as long as adequate inventory	Patient could die if batch not available
Batch Traceability	All released batches comparable	Wrong batch can kill patient
Manufactured Batch Size		
Product Characterization		
QC Testing		
QA Batch Disposition		

GMP & Quality Different Risks

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

'vein to vein'



Major GMP & Quality Differences Between Biopharmaceutical Types

Comparison	Recombinant Proteins & MAbs	ATMPs (CGTPs)
Product Type	Non-living biopharmaceuticals	Living biopharmaceuticals
Link to Clinician and Patient	Batch independent of specific patients	Batch dependent upon clinician and patient
Pressure on Manufacturing	None, as long as adequate inventory	Patient could die if batch not available
Batch Traceability	All released batches comparable	Wrong batch can kill patient
Manufactured Batch Size	1 batch can serve 100's or more patients	1 batch serves 1 patient
Product Characterization	Extensive analytical and bioassay tools	Limited
QC Testing	Adequate samples and testing available	Limited sample size and testing available
QA Batch Disposition	Completed prior to batch release	All testing may not be complete prior to admin

GMP & Quality Different Risks

1) ***Recombinant Proteins & Monoclonal Antibodies***

2) ***Gene Therapy Vectors (DNA plasmids, genetically-engineered viruses)***

1 batch = 100's or more patient doses

---

3) ***Autologous Cell-Based Medicines***

4) ***Autologous Gene Therapy Cell-Based Medicines***

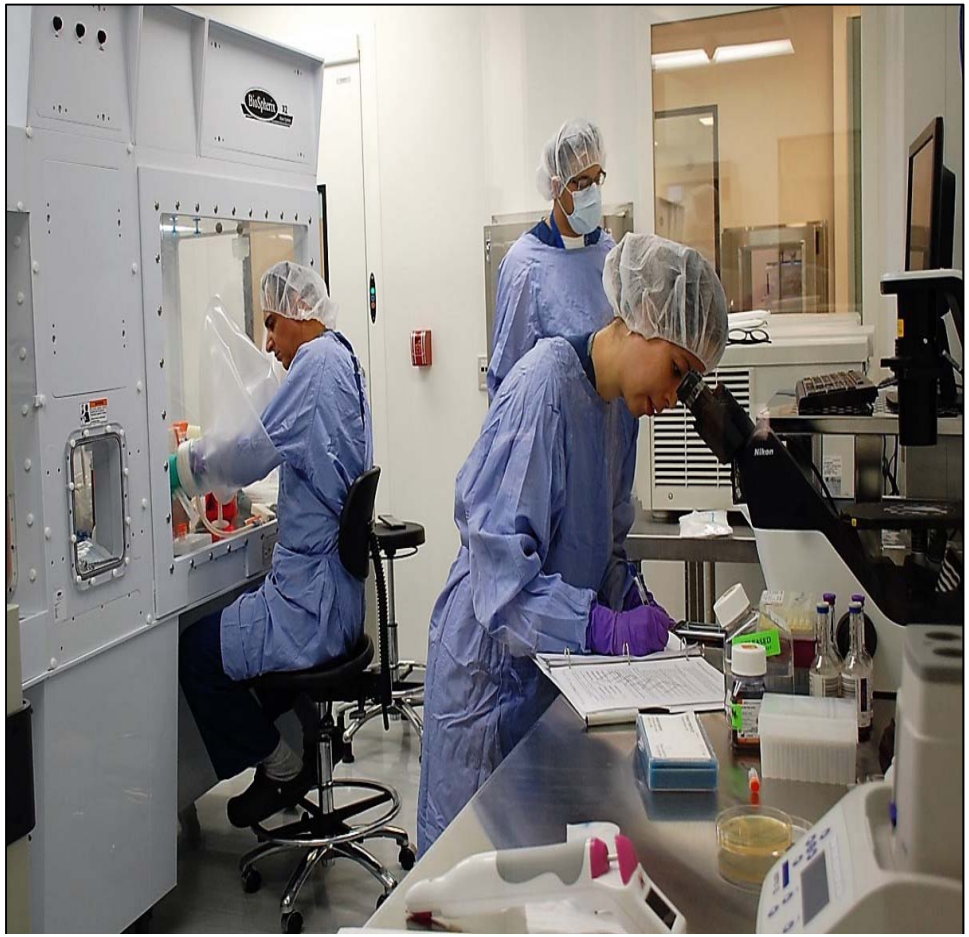
1 batch = 1 patient dose

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

The new manufacturing facility has more of a research lab feel

Protein bioreactor

Cell therapy handling



Need more protein – just scale up!

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

Major GMP & Quality Differences Between Biopharmaceutical Types

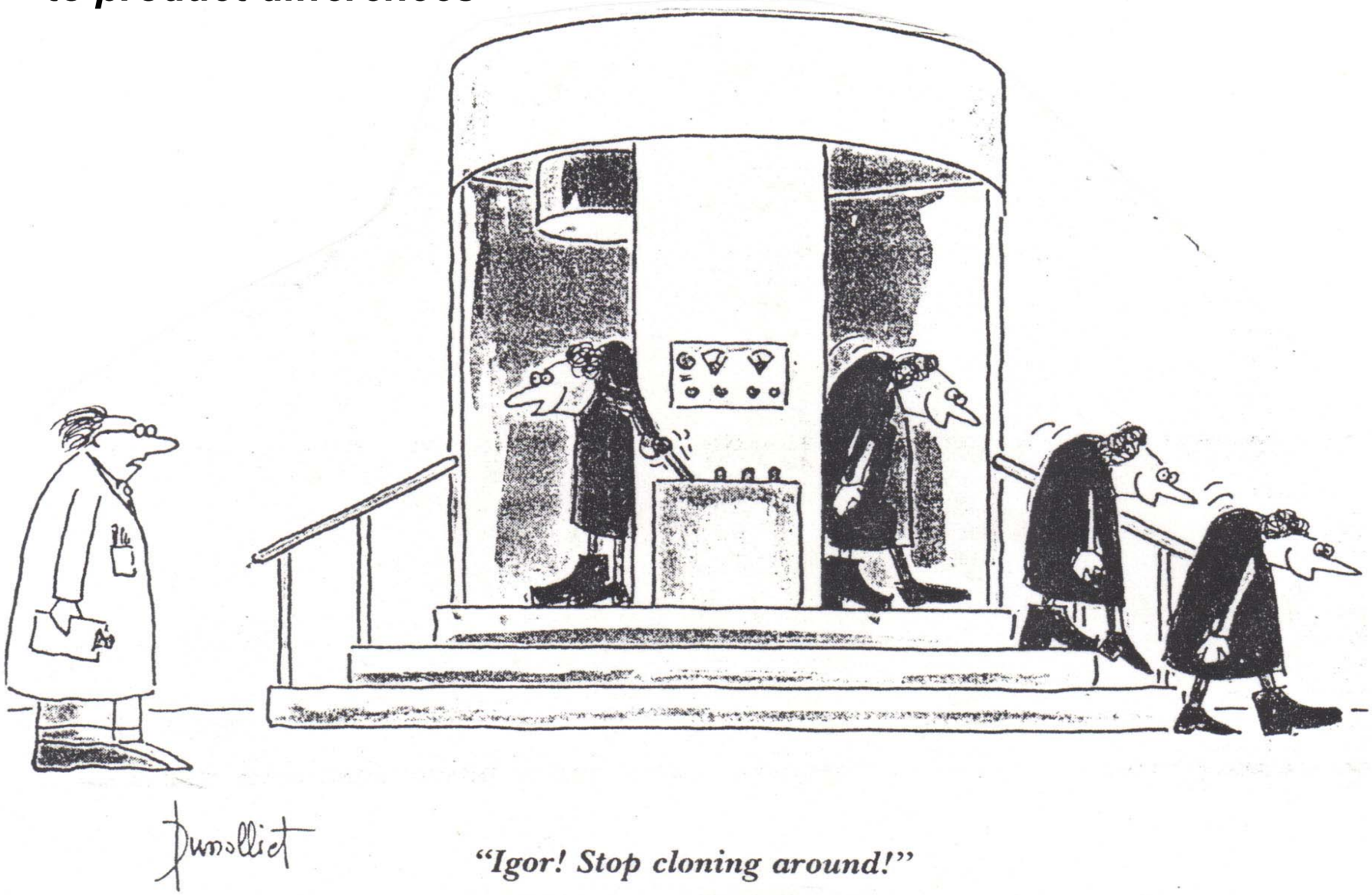
Comparison	Recombinant Proteins & MAbs	ATMPs (CGTPs)
Product Type	Non-living biopharmaceuticals	Living biopharmaceuticals
Link to Clinician and Patient	Batch independent of specific patients	Batch dependent upon clinician and patient
Pressure on Manufacturing	None, as long as adequate inventory	Patient could die if batch not available
Batch Traceability	All released batches comparable	Wrong batch can kill patient
Manufactured Batch Size	1 batch can serve 100's or 1000's of patients	1 batch serves 1 patient
Product Characterization	Extensive analytical and bioassay tools	Limited
QC Testing	Adequate samples and testing available	Limited sample size and testing available
QA Batch Disposition	Completed prior to batch release	All testing may not be complete prior to admin

GMP & Quality Different Risks

Plenty of pressure on the Quality Unit!

- *Majority of 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 required, method robustness)*
- *QA systems to release batch within hours or days (not months – proteins) (deviation management, batch record closeout, CofA completion)*

2. GMP & Quality risks due to product differences



"Igor! Stop cloning around!"

?QUESTIONS?

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

3. Regulatory Authority Expectations

- ✓ ***EC/EMA/FDA expectations for the rapidly developing Advanced Therapy field***
- ✓ ***Recommendations for a risk-based approach to ATMP GMPs and Quality***

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

SOMATIC CELL THERAPY

Somatic cells taken from patient by clinician

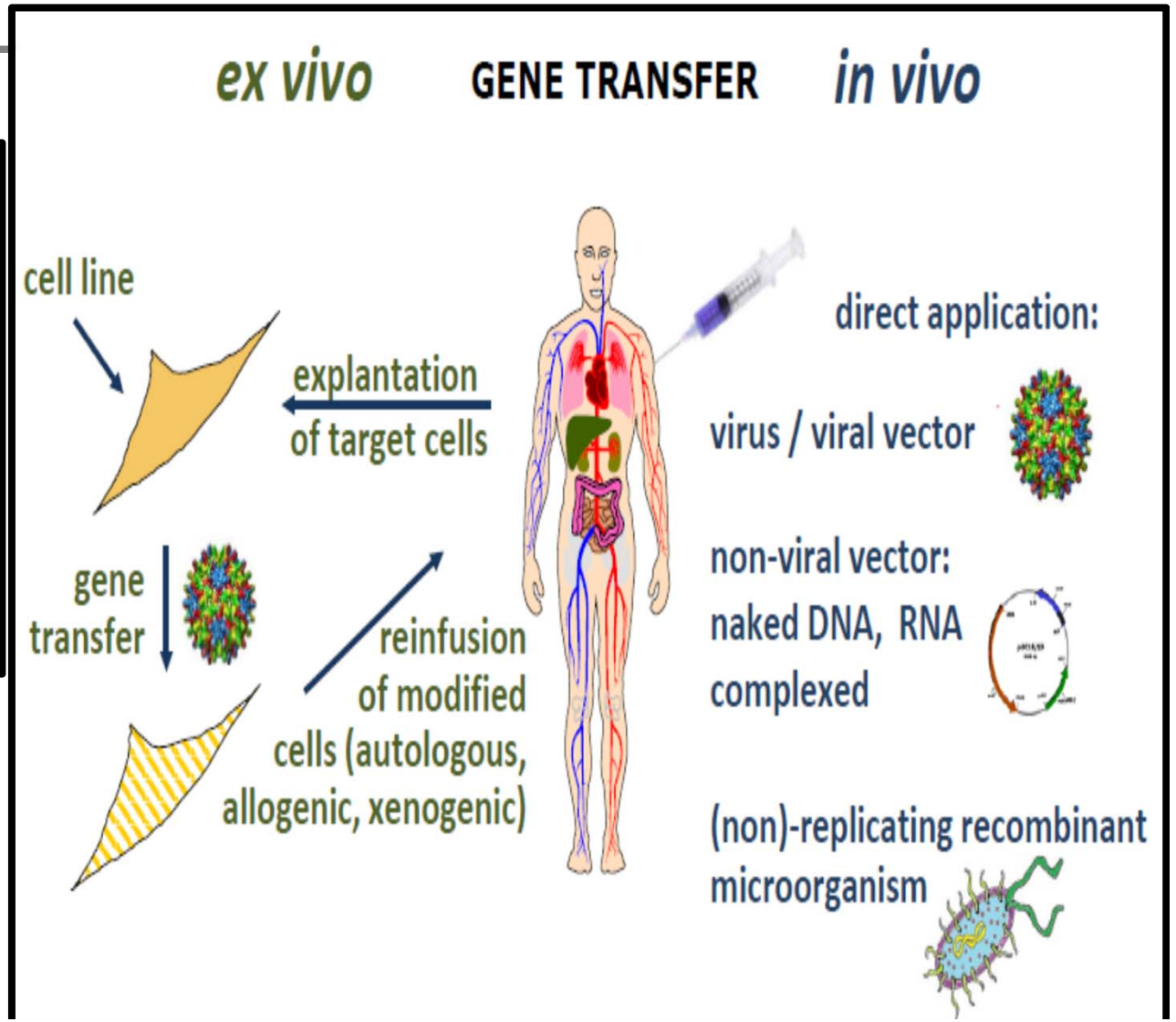
↓

'substantial manipulation' by manufacturer

↓

Cells administered back to same patient by clinician

in vivo genome editing (future)

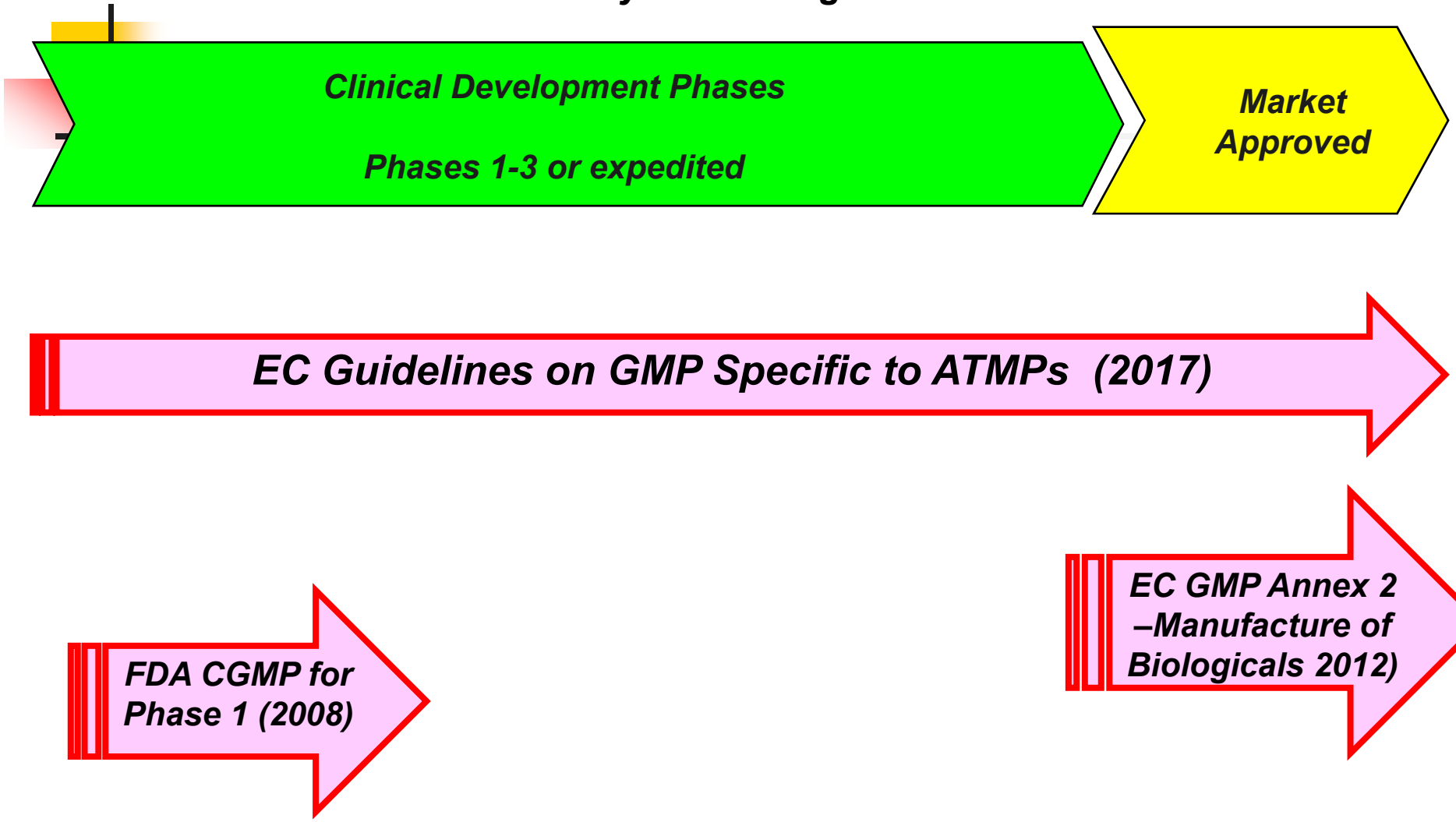


Regulatory guidance on GMPs & Quality for ATMPs

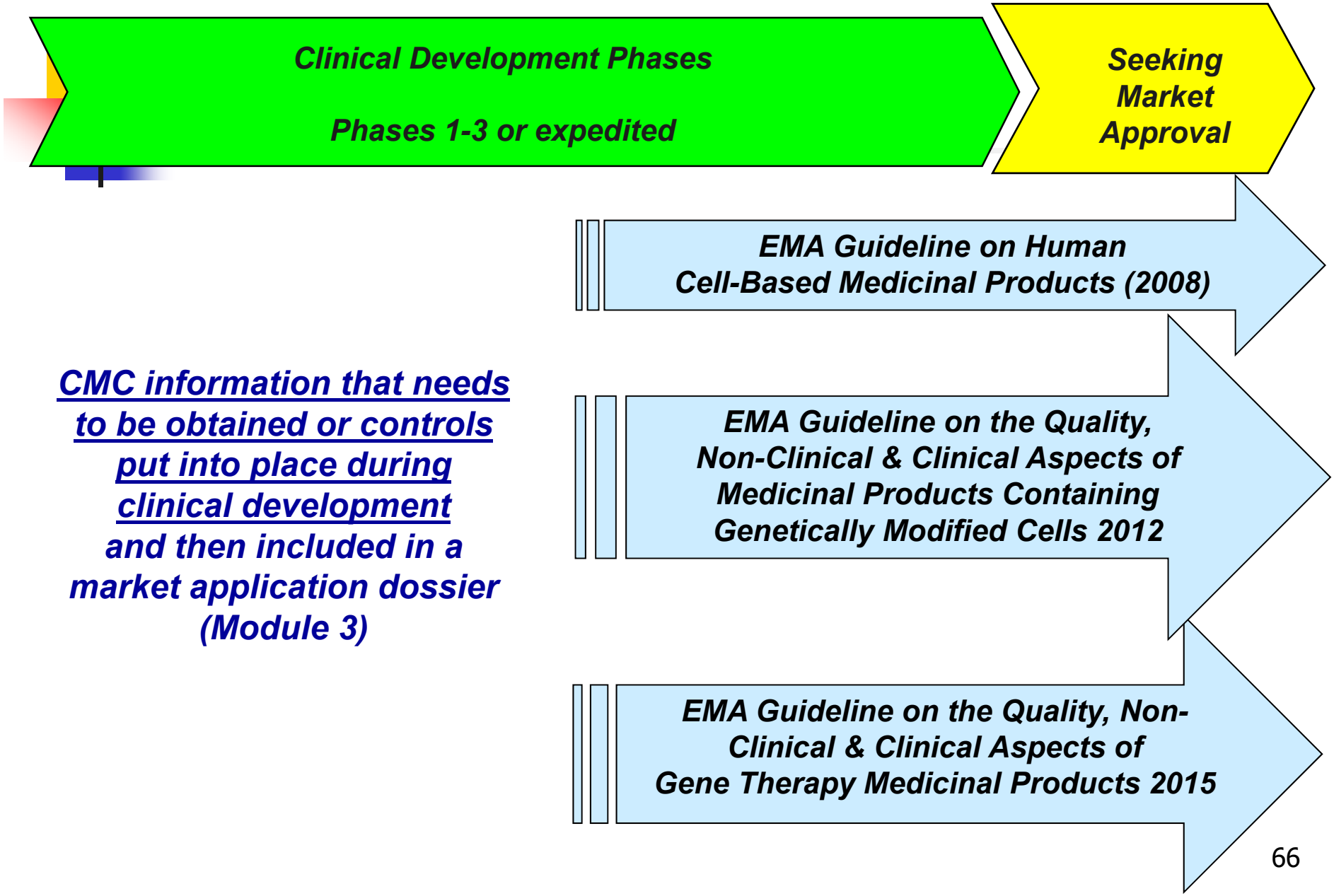
- ***'What should be done to protect the patients'***
  - ***basically adapted from GMP & Quality principles of the protein-based biopharmaceuticals***
- ***'How to accomplish this necessary patient protection across the manufacturing and quality of the many types of ATMPs'***
  - ***little by little coming out***

Regulatory Authority ATMP GMPs & Quality

currently available guidance

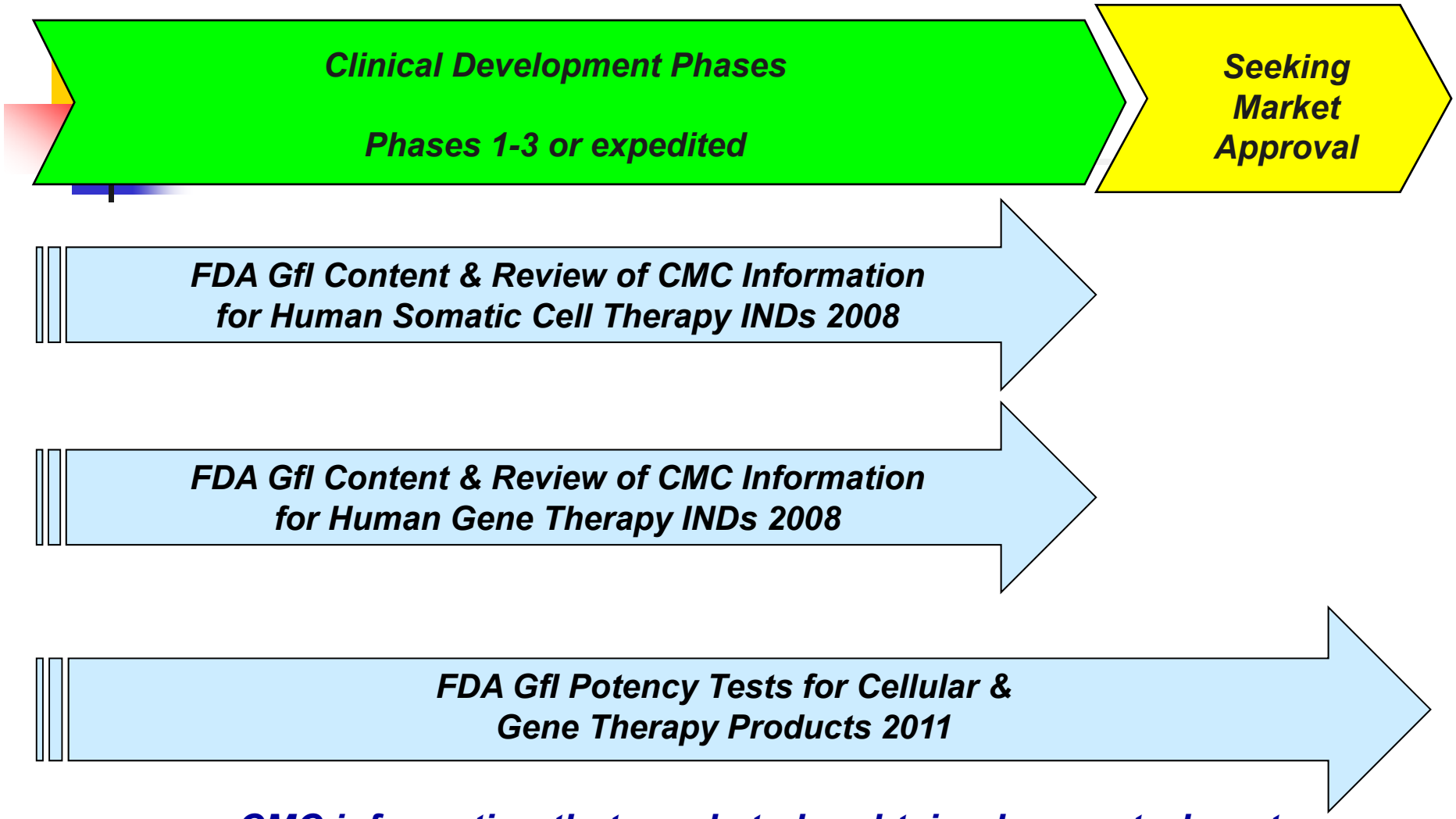


Some Other EMA Recommendations on GMPs & Quality for ATMPs



CMC information that needs to be obtained or controls put into place during clinical development and then included in a market application dossier (Module 3)

Some Other FDA Recommendations on GMPs & Quality for ATMPs



CMC information that needs to be obtained or controls put into place during clinical development and then included in a market application dossier (Module 3)

EUROPEAN
COMMISSION

Brussels, 22.11.2017
C(2017) 7694 final

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

- ***Guidance specific for ATMPs***
- ***Guidance applicable for ATMP manufacturing and testing across all clinical development phases, as well as market approved***

See Reference 1

Terminology used in the guidance

1.13. Throughout these Guidelines, the term "ATMP" should be understood as referring to both advanced therapy medicinal products that have been granted a marketing authorisation, and advanced therapy medicinal products that are being tested or used as reference in a clinical trial (*i.e.* advanced therapy investigational medicinal products). When specific provisions are only relevant for advanced therapy medicinal products that have been granted a marketing authorisation, the term "authorised ATMPs" is used. When specific provisions are only relevant for advanced therapy investigational medicinal products, the term "investigational ATMPs" is used.

General Principles of GMPs & Quality for ATMPs

(look at Reference 1 – section 1.2)

List 5 fundamental GMPs and/or Quality principles for ATMPs:

1.

2.

3.

4.

5.

Are any of these different from protein-based medicinal products?

3 reasons why a risk-based approach (RBA) is needed for ATMP GMPs & Quality

(1) Due to ATMP complexity and manufacturing constraints

ATMPs are complex products and risks may differ according to the type of product, nature/characteristics of the starting materials and level of complexity of the manufacturing process. It is also acknowledged that the finished product may entail some degree of variability due to the use of biological materials and/or complex manipulation steps (*e.g.* cultivation of cells, manipulations that alter the function of the cells, *etc.*). In addition, the manufacture and testing of autologous ATMPs (and allogeneic products in a donor-matched scenario) poses specific challenges and the strategies implemented to ensure a high level of quality must be tailored to the constraints of the manufacturing process, limited batch sizes and the inherent variability of the starting material.

(2) Due to ATMP rapid technological change and sites of mfg

ATMPs are at the forefront of scientific innovation and the field is experiencing rapid technological change that also impacts on the manufacturing processes. For instance, new manufacturing models are emerging to address the specific challenges of ATMPs (*e.g.* decentralised manufacturing for autologous products). Additionally, ATMPs are also often developed in an academic or hospital setting operating under quality systems different to those typically required for the manufacture of conventional medicinal products.

(hospital exemption)

Article 28 of Regulation 1394/2007 on Advanced Therapy Medicinal Products foresees in the implementation of a national procedure to regulate the manufacturing and use of certain non-routine produced ATMPs outside the scope of the Medicinal Product Directive 2001/23. To qualify for this so-called Hospital Exemption (HE), the ATMPs concerned should meet all the following criteria:

- Preparation on a non-routine basis
- Preparation according to specific quality standards (equivalent to those for ATMPs with a centralised marketing authorisation)
- Use within the same Member State
- Use in a hospital
- Use under the exclusive responsibility of a medical practitioner
- Comply with an individual medical prescription for a custom-made product for an individual patient

(3) Due to needed flexibility for ATMPs

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).

3 principles of a risk-based approach (RBA) for ATMP GMPs & Quality

(1) RBA is universal in ATMP application

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) RBA sometimes means doing more!

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.

(3) RBA identifies and then focuses on the major safety and quality risks to the patient

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

RBA for Investigational ATMPs

(look at Reference 1 – section 2.20-2.24)

List 5 points in the application of a RBA for investigational ATMPs:

1.

2.

3.

4.

5.

Are any of these different from protein-based medicinal products?

Illustration of RBA for Investigational ATMP GMPs & Quality

3 Personnel
4 Premises
5 Equipment
6 Documentation
7 Starting & Raw Materials
8 Seed Lot & Cell Bank
9 Production
10 Qualification & Validation
11 QP & Batch Release
12 Quality Control
13 Outsourced Activities
14 Quality Defects & Recalls
15 Environmental Controls GMOs
16 Reconstitution
17 Automated Production

(Unless specifically called out for investigational ATMPs, these GMPs apply to <u>both</u> investigational and authorized ATMPs)

Section 3 Personnel

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

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.

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.

FDA's Viewpoint of Small Organization QC Flexibility

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

Guidance for Industry

CGMP for Phase 1 Investigational Drugs

July 2008

Section 7 Starting & Raw Materials

The quality of starting and raw materials is a key factor to consider in the production of ATMPs. Particular attention should be paid to avoiding contamination and to minimizing as much as possible the variability of the starting and raw materials.

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

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

Residual impurities found in ATMPs

(from FDA Package Insert of approved products)

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).

Section 8 Seed Lot & Cell Bank

Following the establishment of cell banks and master and viral seed lots, quarantine and release procedures should be followed. Evidence of the stability and recovery of seeds and banks should be documented and records should be kept in a manner permitting trend evaluation.

In the case of investigational ATMPs, a gradual approach is acceptable. Thus, preliminary stability data (e.g. from earlier phases of development or from suitable cell models) should be available before the product is used in a clinical trial, and the stability data should be built-up with real-life data as the clinical trial progresses.

Section 9 Production

Production operations, including filling, packaging and -as applicable- cryopreservation should follow clearly defined procedures designed to ensure the quality of the product, consistent production (appropriate to the relevant stage of development), and to comply with the requirements set in the relevant manufacturing and marketing/clinical trial authorization.

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.

While investigational ATMPs should be manufactured in a facility with air quality requirements in accordance with the requirements set out in Sections 4.3.2 and 9.5, in case of investigational ATMPs in very early phase/proof of concept trials, it may be exceptionally possible to manufacture the product in an open system in a critical clean area of grade A with a background clean area of grade C if the following (cumulative) conditions are met:

(i) A risk-assessment has been performed and demonstrated that the implemented control measures are adequate to ensure manufacture of the product of appropriate quality. In addition, the control strategy should be described in the investigational medicinal product dossier.

(ii) The product is intended to treat a life threatening condition where no therapeutic alternatives exist.

(iii) The relevant competent authorities agree (agreement of both the assessors of the clinical trial and the inspectors of the site).

This has been controversial with different NCAs
(Grade A with a background clean area of grade B)

Section 10 Qualification & Validation

Manufacturing Process

The strategy to process validation should be laid down in a document ("validation protocol"). The protocol should define (and justify as appropriate) the critical process parameters, critical quality attributes and the associated acceptance criteria based on development data or documented process knowledge.

It is generally accepted that, as a minimum, three consecutive batches manufactured under routine conditions constitute a validation of the process.

The limited availability of the cells/tissues which is typical for most ATMPs requires the development of pragmatic approaches.
The approach to process validation should take into account the quantities of tissue/cells available and should focus on gaining maximum experience of the process from each batch processed. Reduced process validation should, where possible, be offset by additional in-process testing to demonstrate consistency of production:

- ***Validation with surrogate materials (use of healthy donors)***
- ***Concurrent validation approaches***
- ***Validation Strategy for closely related products (platform approach)***

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.***

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

Analytical Test Methods

All analytical methods should be validated at the stage of marketing authorization application.

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.***

FDA's Viewpoint of Analytical Method Validation

We recommend that proposed analytical procedures be based on scientific data and manufacturing experience as described below:

- Phase 1-3 – Usually based on Code of Federal Regulation (CFR) methods or alternative methods, if appropriate.
- Phase 2 – If an alternative to the CFR method is used, we recommend that the sponsor initiate validation of the alternative by Phase 3.
- Licensure – The product specification should be in place and established under a validated assay.

Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); 2008
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072587.htm

FDA's Viewpoint of Importance of the Potency Assay

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

RBA in connection with the testing strategy

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).*

The following examples may also be considered:

- ***The application of the sterility test to the finished product in accordance with the European Pharmacopoeia (Ph. Eur. 2.6.1) may not always be possible due to the scarcity of materials available, or it may not be possible to wait for the final result of the test before the product is released due to short shelf-life or medical need. In these cases, the strategy regarding sterility assurance has to be adapted. For example, the use of alternative methods for preliminary results, combined with sterility testing of media or intermediate product at subsequent (relevant) time points could be considered.***
- ***The use of validated alternative rapid microbiological methods may also be considered. For example, sole reliance on alternative microbiological methods according to Ph. Eur. 2.6.27 may be acceptable when this is justified having regard to the specific characteristics of the product and the related risks, and provided that the suitability of the method for the specific product has been demonstrated.***
- ***If the results of the sterility test of the product are not available at release, appropriate mitigation measures should be implemented, including informing the treating physician.***

- *As cells in suspension are not clear solutions, it is acceptable to replace the particulate matter test by an appearance test (e.g. colour), provided that alternative measures are put in place, such as controls of particles from materials (e.g. filtration of raw material solutions) and equipment used during manufacturing, or the verification of the ability of the manufacturing process to produce low particle products with simulated samples (without cells).*
- *It may be justified to waive the on-going stability program for products with shorter shelf-life.*

FDA's Viewpoint of GMPs at Phase 1 for ATMPs

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

Guidance for Industry

CGMP for Phase 1 Investigational Drugs

July 2008

In some cases, investigational gene and cellular therapy products may be manufactured as one batch per subject in phase 1 clinical trials (e.g., gene vector modified autologous cell products, autologous cell products). Manufacture of multiple batches will allow manufacturing and testing information to accumulate in an accelerated manner as compared to more conventional products. As manufacturing methods and assays used for testing can be novel for these products, it is important to monitor manufacturing performance to ensure product safety and quality.

When manufacturing multiple batches of the same phase 1 investigational drug, we recommend that manufacturers periodically conduct and document internal performance reviews. We recommend that this review assess whether the manufacturing process is optimal to ensure overall product quality. Based on the review, appropriate modifications and corrective actions can be taken to control procedures and manufacturing operations.

Take GMPs seriously during clinical development!

National Cancer Institute (NCI) facility shut down!

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

Filling in the GMP & Quality Gaps for ATMPs

Commitments for future guidance

EMA/CAT (planned for 2018)

- ***Revision of the guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells***
- ***Development of a guideline on quality, non-clinical and where applicable clinical requirements for applications for clinical trials for ATMPs***
- ***Development of a Questions and Answers document on comparability for ATMPs***
- ***Reflection on regulatory status and consideration of the scientific requirements of medicines based on, or produced by means of gene editing technologies***
- ***Consideration of the scientific requirements of gene therapy medicinal products based on AAVs***

Filling in the GMP & Quality Gaps for ATMPs

Commitments for future guidance

FDA (planned for 2018 release)

- ***Draft GfI: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)***
- ***Draft GFI: Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus during Product Manufacture and Patient Follow-up***

GfI – Guidance for Industry

3. Regulatory Authority Expectations

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

?QUESTIONS?

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

4. Industry Practice in Applying ATMP GMPs and Quality

- ✓ ***PDA Technical Reports (adapting TR 56; upcoming TR Cell-Based Therapy Control Strategy)***
- ✓ ***Lessons learned about the "how" from the companies moving ATMPs forward in clinical development***

Challenging to switch technical mindsets

<u>from</u> non-living protein biopharmaceutical medicines
<u>to</u> living virus/cell biopharmaceutical medicines!

like sailing in
'uncharted waters'

Easing into the ATMP space

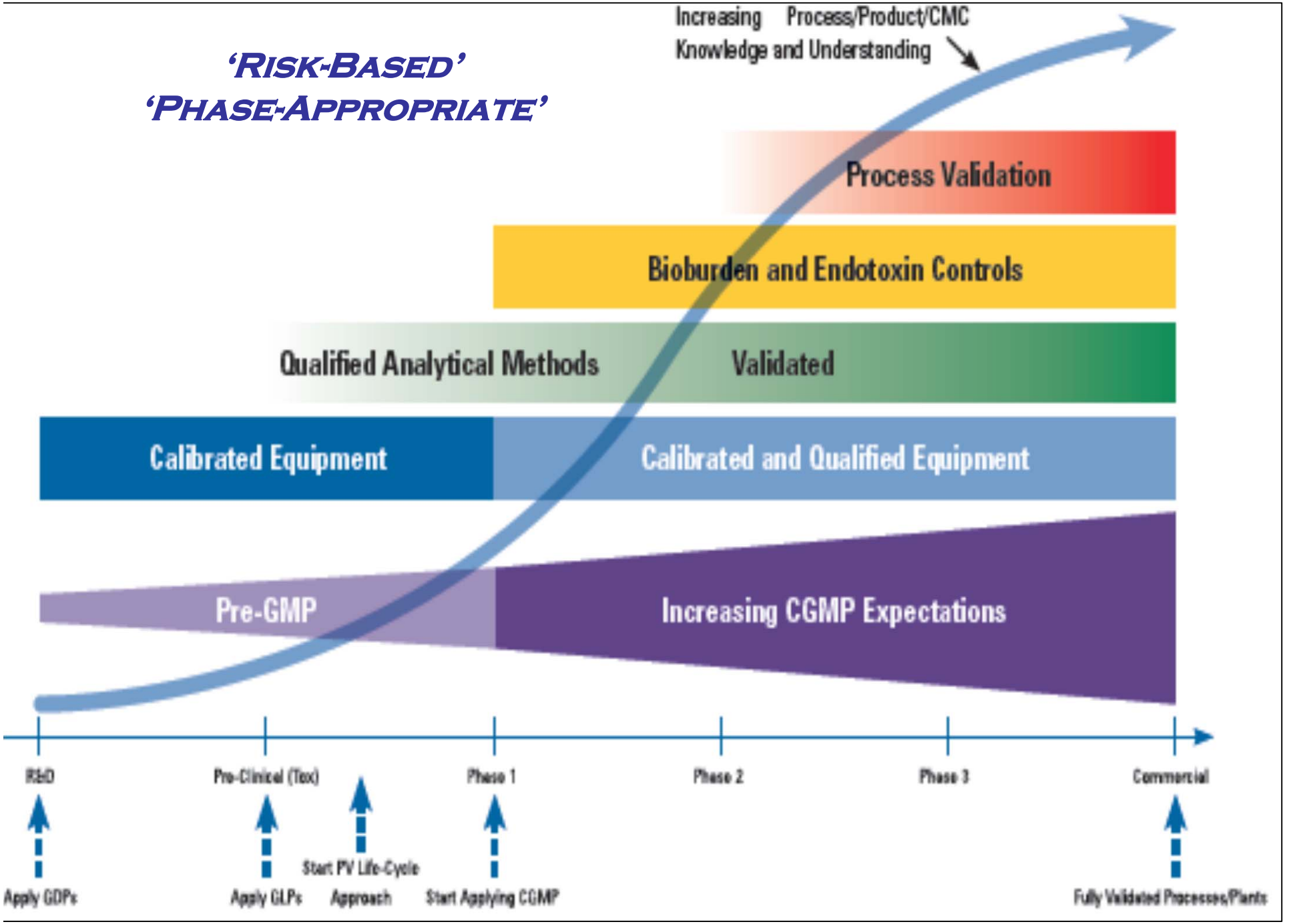
Technical Report No. 56

Application of Phase-Appropriate Quality Systems and CGMP to the Development of Therapeutic Protein Drug Substance

2016 (R1)

- ***Not a regulatory document***
- ***'Industry best practices' for protein-based APIs***
- ***GMPs & Quality 'why' practices are adaptable to ATMPs***

© 2012 Parenteral Drug Association


'Risk-Based'
'Phase-Appropriate'
Increasing Process/Product/CMC Knowledge and Understanding
Process Validation
Bioburden and Endotoxin Controls
Qualified Analytical Methods
Validated
Calibrated Equipment
Calibrated and Qualified Equipment
Pre-GMP
Increasing CGMP Expectations
R&D
Pre-Clinical (Tox)
Phase 1
Phase 2
Phase 3
Commercial
Apply GDPs
Apply GLPs
Start PV Life-Cycle Approach
Start Applying CGMP
Fully Validated Processes/Plants

Graded, phase-appropriate GMP & Quality approach

(a time to begin, and a time to increase stringency)

CGMP principles should begin to be implemented in the early investigative stages when small amounts of protein product are produced for use in human studies.

As more product batches are made to satisfy clinical testing requirements, and as product and process understanding is acquired, CGMP should be implemented with increasing stringency in order to ultimately establish readiness for commercial production.

© 2012 Parenteral Drug Association

See Reference 2

- **Quality**
- **Facilities**
- **Equipment**
- **Materials**
- **Production**
- **Laboratory**

System	R & D	Toxicity Studies	Phase 1 [b,c,d]	Phase 2 [b,c]	Phase 3 [d]
Quality[a]: • Quality management/ oversight • Personnel training • Documentation & records • Product release • Change management • Deviations/investigations • CAPA (Corrective Action Preventive Action) • Auditing • Quality agreements	Personnel have science background & are trained in routine laboratory practices but should also be made aware of GMP principles. Signed notebook records are kept of production and testing activities. If batches fail, they are studied to increase product and process knowledge. R&D activities are well documented in the notebooks, as well as in periodic development reports. There is a need to document source/ pedigree/ chain of custody of biological starting materials – cell ancestor and any animal materials used to create the initial cell line to the extent feasible (Reference Appendix 1 and in section 3.3.3 of this technical report for more information).	GLP practices are implemented as per regulations in specific global regions EU and FDA GLP Requirements cover the areas of: • Organization and Personnel • Facilities • Equipment • Facility Operation • Articles • Protocol and Conduct • Records and Reports • Disqualification There is a need to document the Tox lot and reference standard material with sufficient diligence to allow comparability to clinical/GMP lots later.	It is expected that a laboratory director with a science background is in charge of the Quality Unit (or equivalent function) and reviews all procedures and documents. Use of batch records are highly recommended but could be generic. The Bulk Drug Substance is released by QA/QP after satisfactory review of the manufacturing and analytical records and data (e.g. Completed batch record, analytical results, COA, environmental and water monitoring data, deviations and changes), as well as compliance to the investigational new drug registration (e.g., IND, IMPD). Manufacturing or testing deviations or unexpected events that do not impact product quality or patient safety should be documented, but could be appended to the executed batch records. Formal deviation and CAPA systems are recommended, albeit a simple and uncomplicated system, with the level of investigation dictated by the severity of the incident. Change management is important during development of a product and the process	Responsibilities are governed by CGMP (e.g., ICH Q7 Eudralex - Volume 4 Good Manufacturing Practice Guidelines, and its Annex 13 by phase of development for some items (e.g., as methods are fully validated or transferred, as master batch records are created). QA/QP responsibilities must not be delegated to another functional area (unless allowable by local law), but may be contracted to a qualified external service providers. QA/QP takes a more active role in directing investigations and approving findings and CAPAs. The reporting structure and hierarchy of the Quality Unit should ensure its ability to be independent from production. (From ICH Q7: There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities). Quality standards (e.g., policies, SOPs) must be reviewed and approved by QA. Even when these standards and procedures have not been formally changed, they should be subject to periodic review in order to ensure that they are still valid and up to date with actual practices. It is recommended that for each phase of clinical development, the relevant summary development reports should be completed to review process development activities and results. The reports should include an evaluation of deviations and unexpected results that are encountered during clinical production, scale up, tech transfer, characterization studies, etc. The Bulk Drug Substance is released by QA/QP after review of the completed batch record, COA, environmental and water monitoring data, deviations and changes, the investigational new drug registration (e.g., IND, IMPD), and any other relevant information available in the product specification file as specified in the procedures for batch release. QA/QP can delegate the release of manufactured intermediates to other qualified personnel upon formalized agreements and acceptance.	

But, a Major Caution!

- ***We can adapt existing GMPs & Quality requirements/expectations from the recombinant protein and monoclonal antibody biopharmaceutical industry***
  - ***The greatest value here is understanding the 'why' of what is done***
- ***But in reality, the 'how' will require creative thinking, discussion and agreement between the developing ATMP industry and the regulatory authorities***
  - ***Example: aseptic process simulation (so many manual interventions, so many back-and-forth activities in the same room, equipment not designed for operation in a sterile room environment)***

"The process simulation test should follow as closely as possible the routine manufacturing process and it <u>should be conducted in the same locations where the production occurs</u>. The process simulation should focus on <u>all operations</u> carried out by operators involving open process steps."

EC ATMP GMP Guidelines 2017 (Section 9.5)

PDA Technical Report – in progress

Cell-Based Therapy Control Strategy

- ***Participants from over 10 companies involved with bringing these products through clinical development into the market***
- ***Reviewed by regulatory authority thought-leaders and PDA member companies involved in this field***
- ***Desire: to represent a risk-based approach useful to the developing ATMP industry (much like TR56 is for proteins)***

Cell-Based Therapy Control Strategy

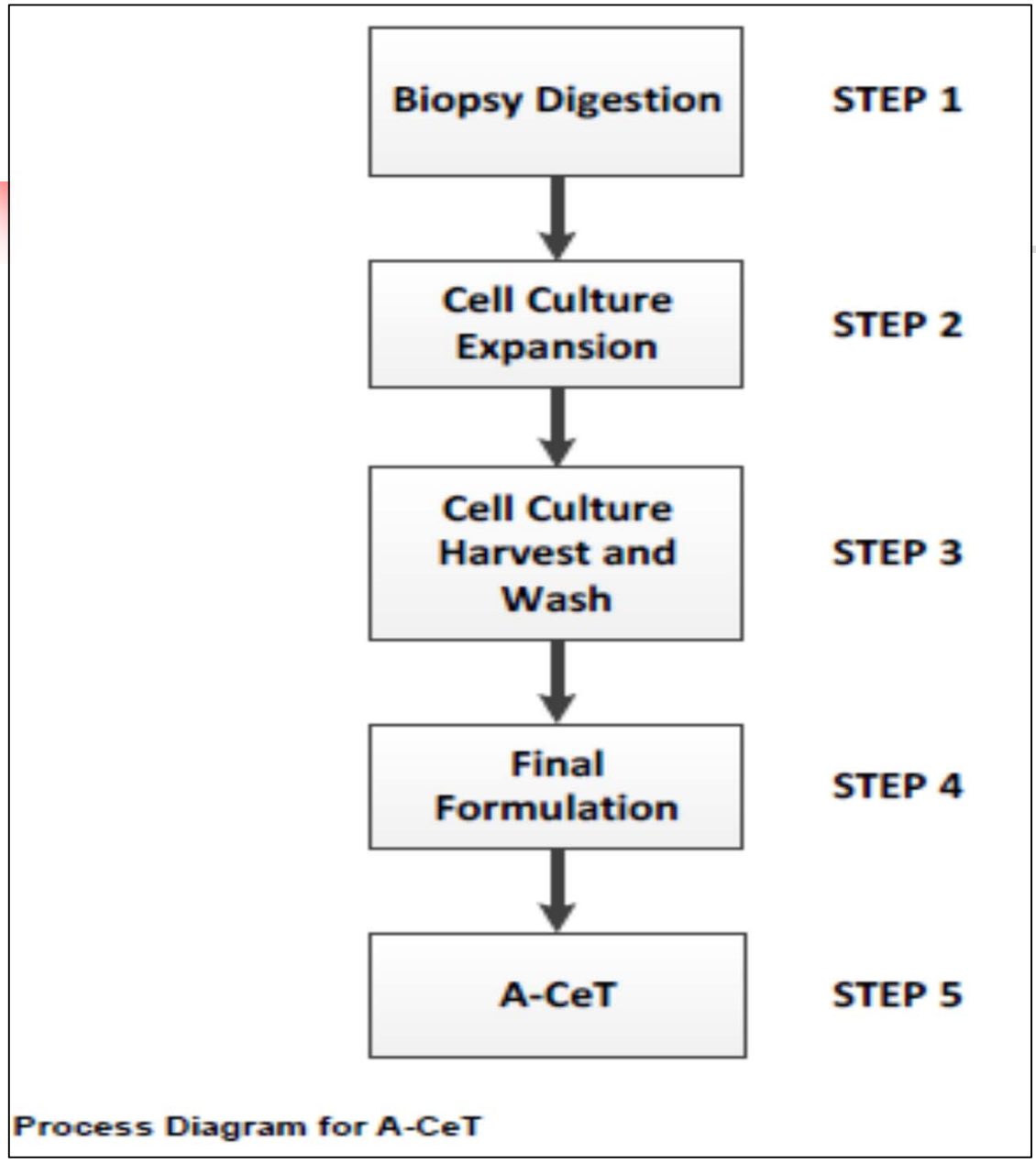
- ***Purpose**: highlights an approach for early-stage development based on established QbD elements (QTPP, CQA, CPP, etc.); proposes potential mitigation strategies for risks related to process or product and illustrates the design of a manufacturing control strategy for a product in early-phase clinical development*

- ***Content**: applies to autologous and allogeneic cell therapy applications, including cells with ex-vivo genetic modification (Gene therapy vectors for in-vivo dosing, however, are not within the scope of this report, though some concepts may be applicable to their development)*

"Regulatory expectations for development of cell and gene therapy products (CGTP) are no different than those pertaining to traditional biologic products in this regard."

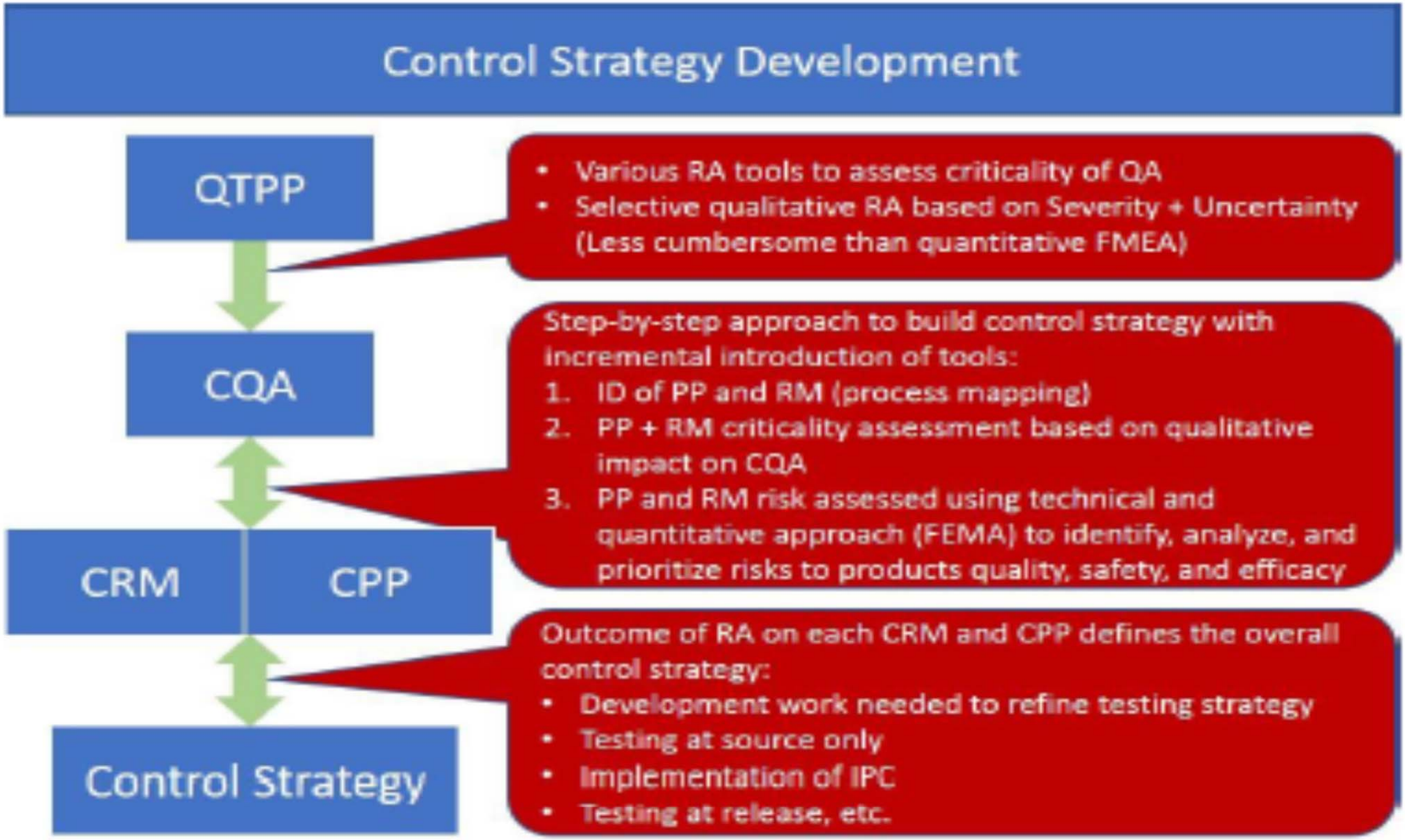
"Prospective science and a risk-based approach to product development of CGTP can increase the assurance of quality in the manufacture of CGTP just as it does for other biologics."

"By appropriately characterizing the risks and understanding how these risks influence or impact quality attributes of the products, a CGTP developer can effectively design a robust manufacturing control strategy and reliably ensure product quality"



Process Diagram for A-CeT

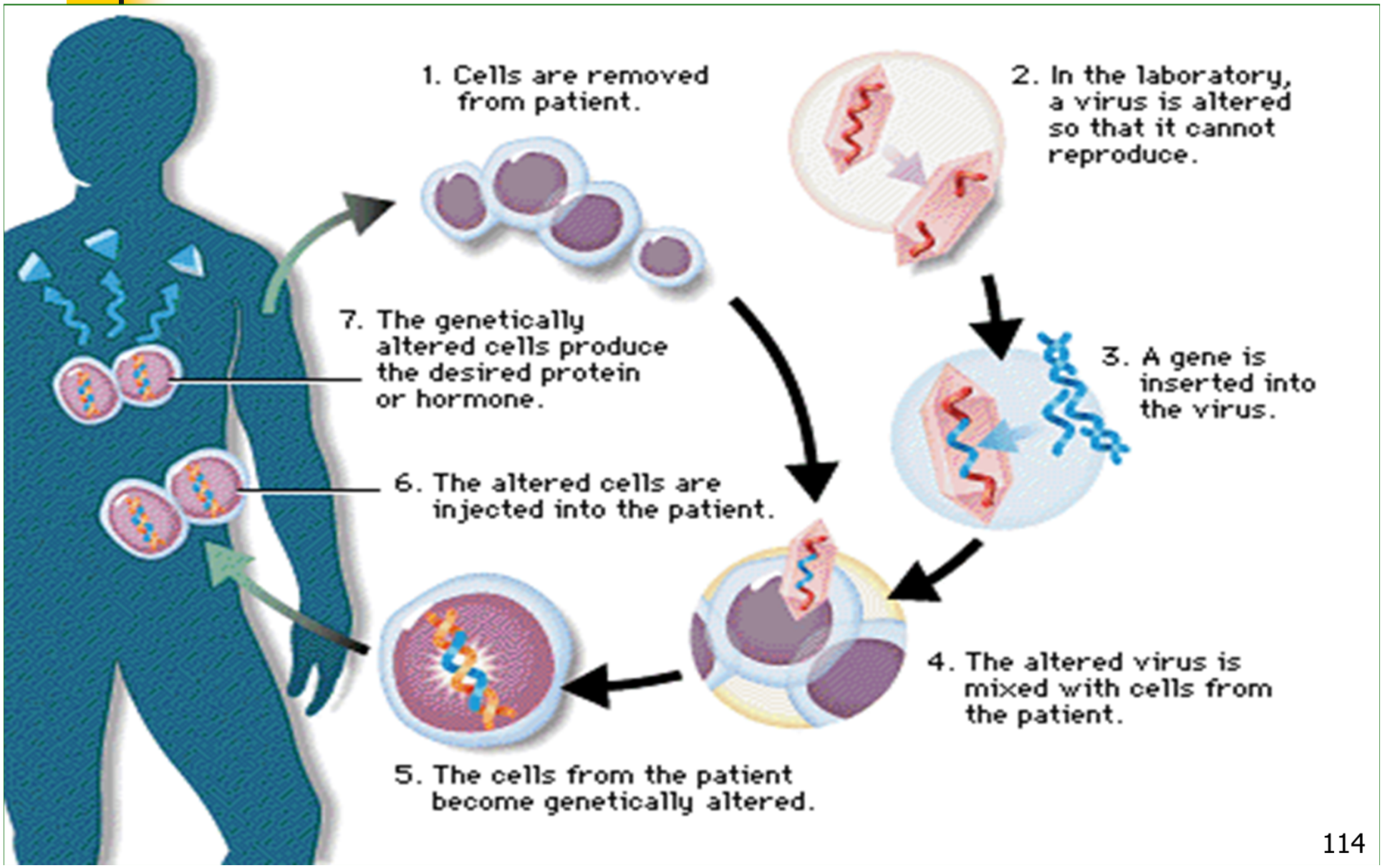
created a case study based on a fictional autologous ex vivo cell therapy product



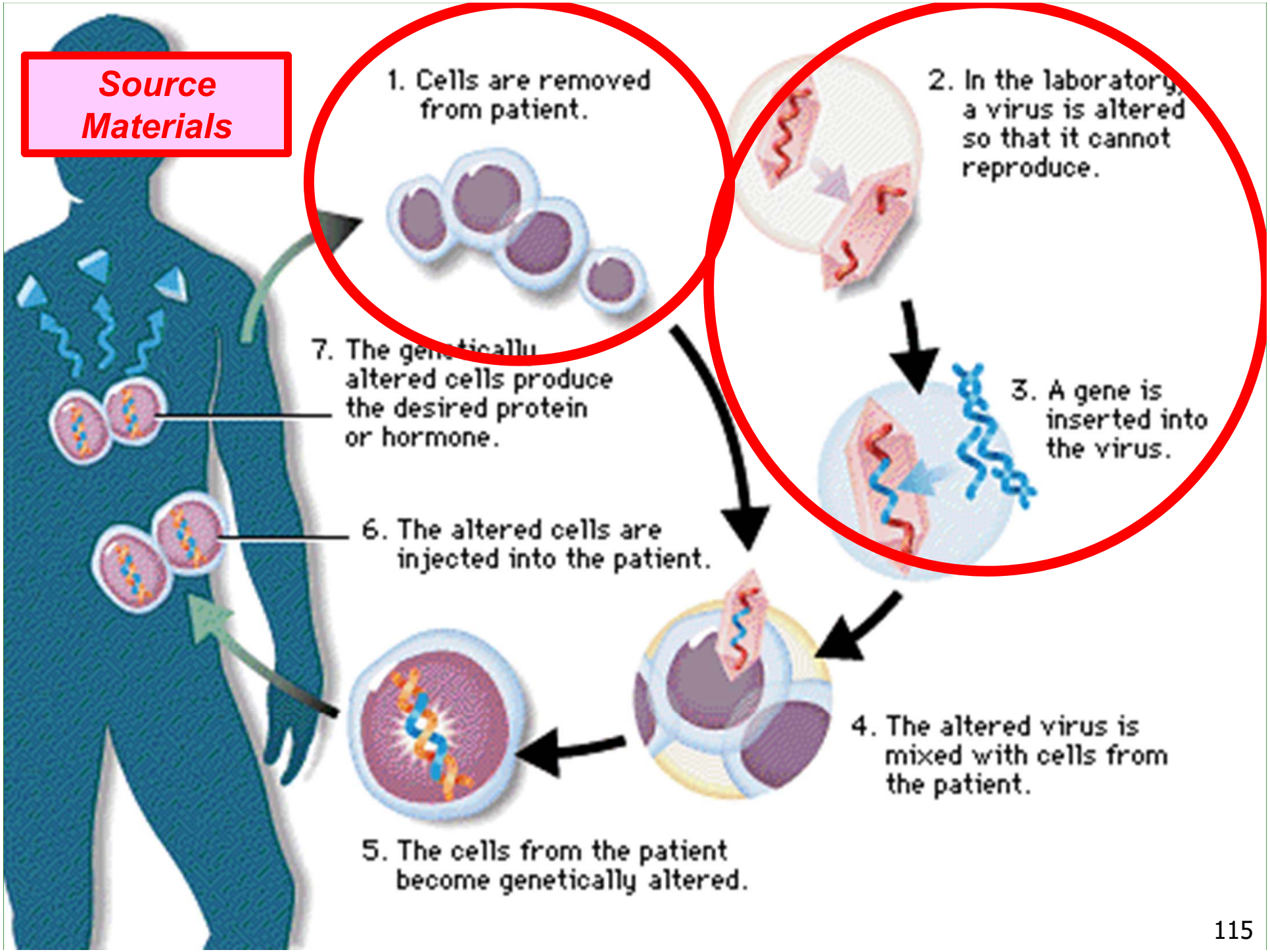
Control Strategy for Critical Quality Attributes

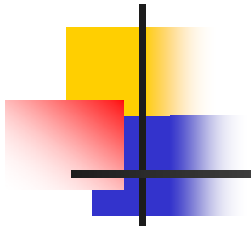
Lessons learned about the "how"

(from the companies moving ATMPs forward in clinical development)



Source Materials





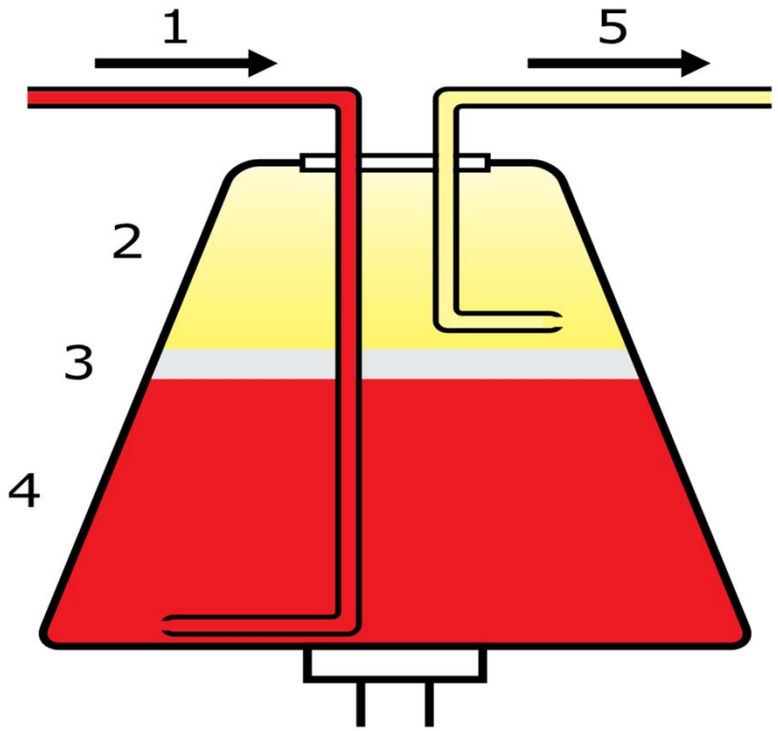
Patient cells are the source material for cell therapies and cell-based gene therapies

- *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*

Protein-based biopharmaceuticals → MCB/WCB are source materials; well-characterized for ongoing production

Cell collection – a contributor to quality variation

– ***Variability in cell type collection (apheresis)***

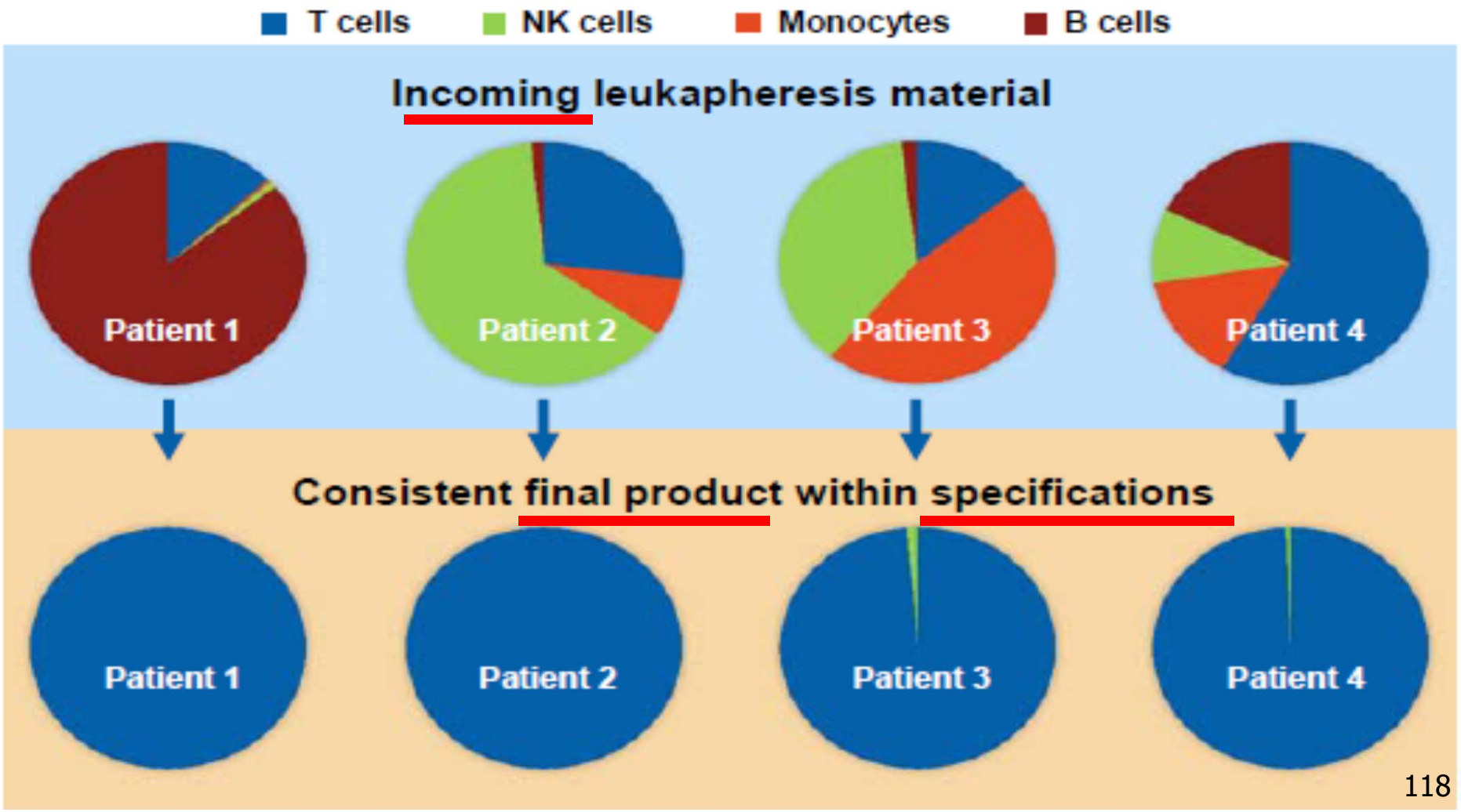


1 blood enters centrifuge
2 Plasma
3 Leukocytes (e.g., T cells)
4 Erythrocytes (red blood cells)
5 Selected components drawn off

Cell collection inconsistency impacts CQAs

Consistent T-cell product from individual patient material

NOVARTIS



Minimizing inconsistency from 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 cell type as possible***

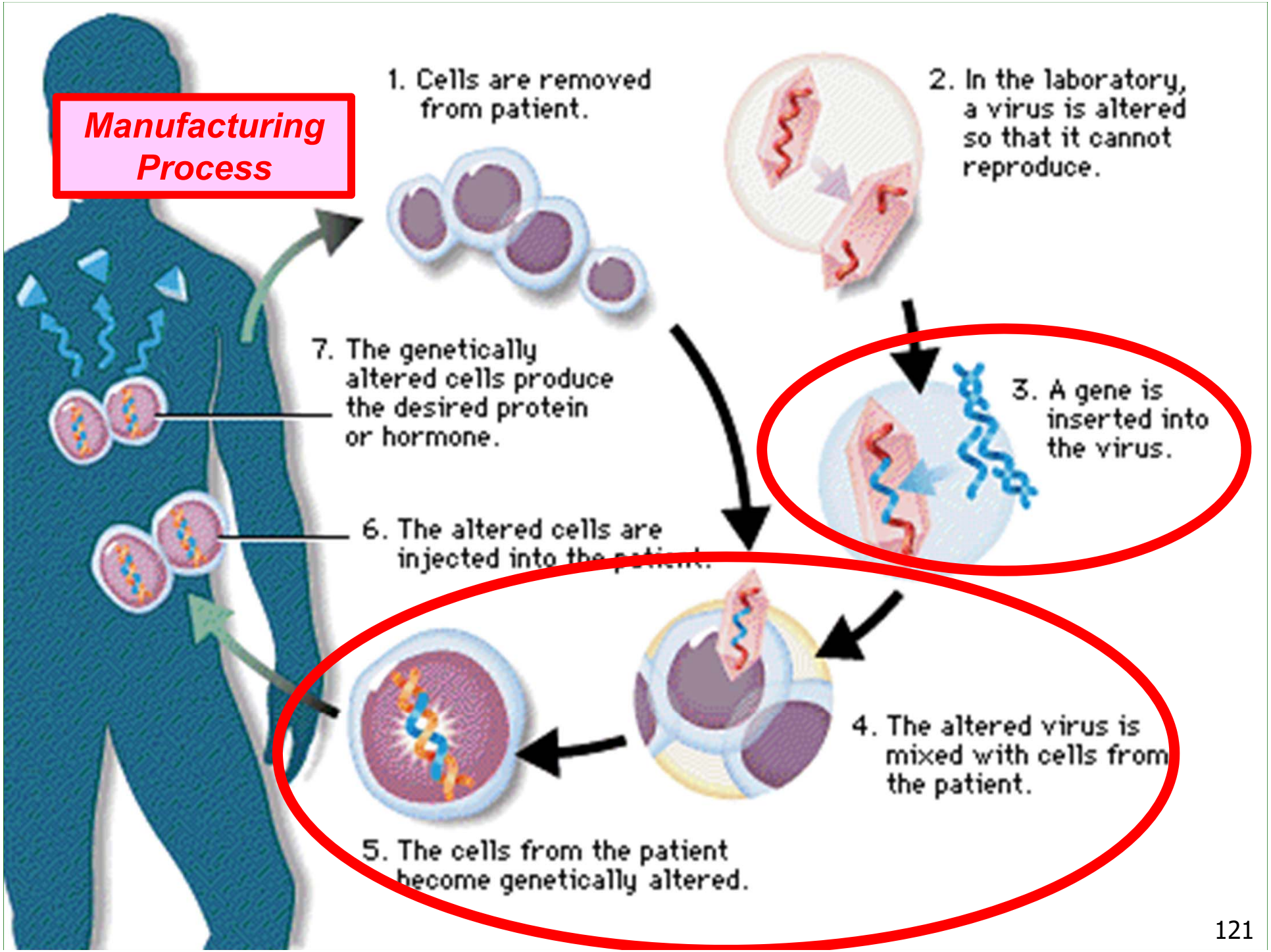
MCB and MVS are also source materials for genetically engineered viruses (either used in direct injection or as a virus vector for cells)

Master Cell Bank (MCB) for propagating the virus on cells; in order to lay down the Master Viral Seed (MVS) for production

All starting materials, including master and working cell banks and viral seeds should be thoroughly characterised and appropriately monitored (e.g. according to the concepts outlined in ICH Q5D). Evidence of freedom from contamination with adventitious agents is essential. For all starting materials, the absence of microbial/viral and fungal contaminants should be ensured through testing after expansion to the limit of in vitro cultivation used for production (see ICH guidelines Q5A).

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

23 March 2015
EMA/CAT/80183/2014

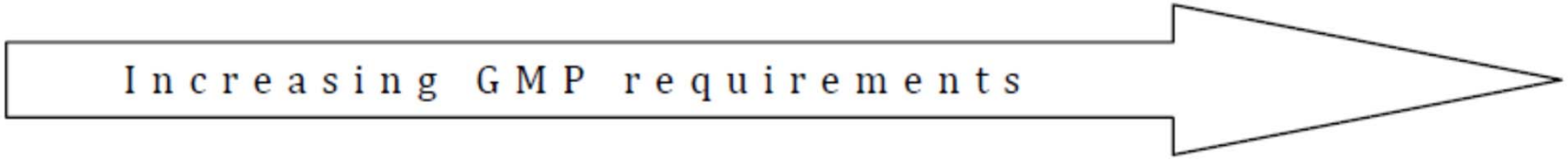

Manufacturing Process
1. Cells are removed from patient.
2. In the laboratory, a virus is altered so that it cannot reproduce.
3. A gene is inserted into the virus.
4. The altered virus is mixed with cells from the patient.
5. The cells from the patient become genetically altered.
6. The altered cells are injected into the patient.
7. The genetically altered cells produce the desired protein or hormone.

GMPs & Quality Applies to Virus Vectors!

(similar to protein manufacturing)

Grey – principles of GMP apply

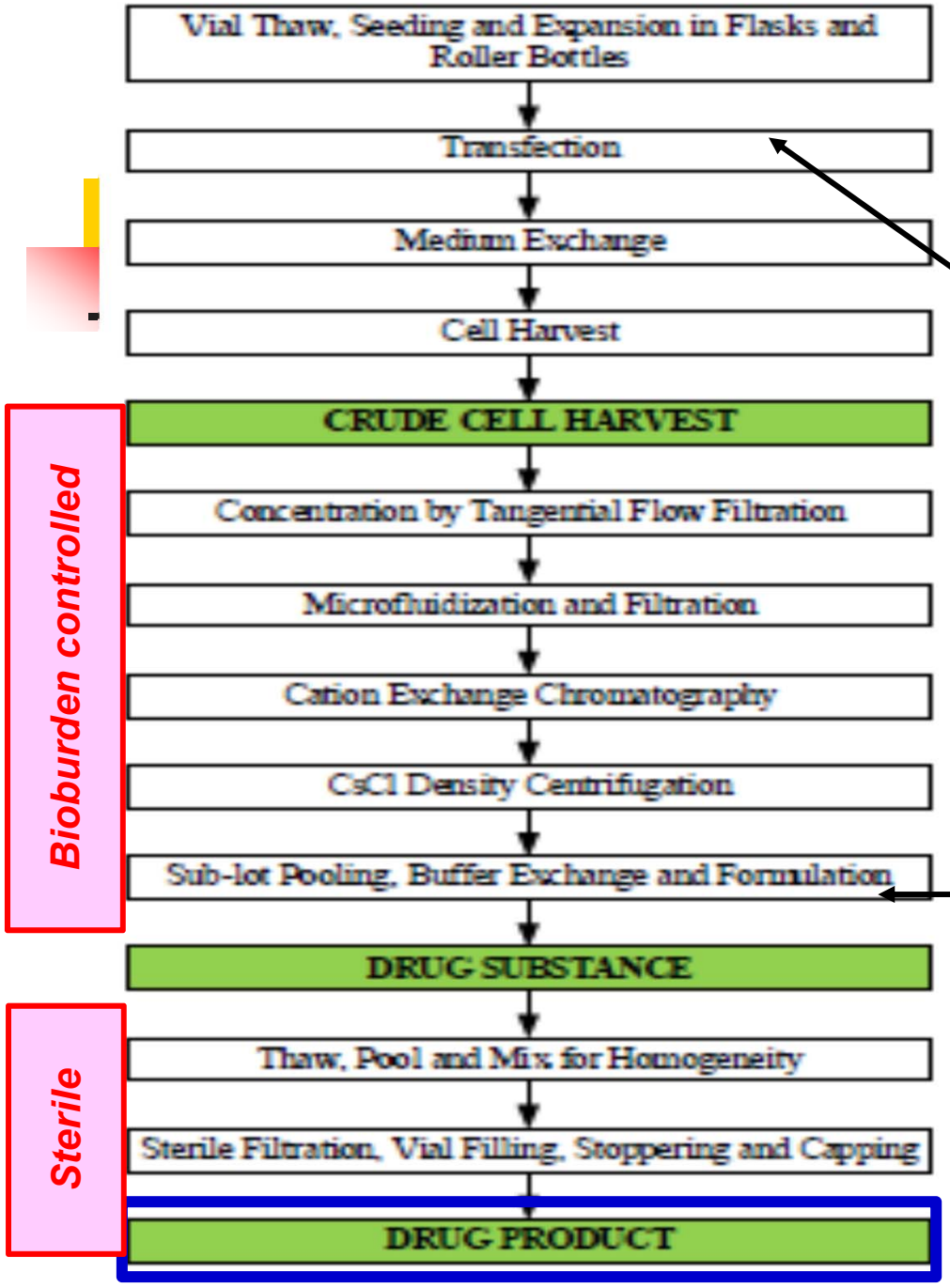
3. Biotech-nology - fermentation/ cell culture	Recombinant. products, MAb, allergens, vaccines Gene Therapy (viral and non-viral vectors, plasmids)	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and / or fermentation	Isolation, purification, modification	Formulation, filling



Annex 2

Manufacture of Biological active substances and Medicinal Products for Human Use

Volume 4
EU guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use



Key manufacturing process steps

genetically engineered virus

triple transfection of HEK293 cells

Spark THERAPEUTICS **Luxturna**

FDA Advisory Committee Meeting

October 12, 2017

formulation includes inactive ingredients sodium chloride, sodium phosphate, and poloxamer 188

"There are 40 release tests in place to ensure that each lot of voretigene neparvovec meets pre-defined criteria for safety, purity, and potency."

GMPs & Quality Applies to Cells!

(once cells are in the facility)

Grey – principles of GMP apply

7. Human and / or animal sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells[14]	Manufacture vector[13] and cell purification and processing,	Ex-vivo genetic modification of cells, Establish MCB, WCB or cell stock	Formulation, filling
	Somatic cell therapy	Donation, procurement and testing of starting tissue / cells[14]	Establish MCB, WCB or cell stock	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, fill
	Tissue engineered products	Donation, procurement and testing of starting tissue / cells[14]	Initial processing, isolation and purification, establish MCB, WCB, primary cell stock	Cell isolation, culture, purification, combination with non-cellular components	formulation, combination, fill

Increasing GMP requirements

Annex 2

Manufacture of Biological active substances and Medicinal Products for Human Use

Volume 4
EU guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Key manufacturing process steps

genetically engineered autologous cells

- 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.

The product must pass a sterility test before release for shipping.

Key manufacturing process steps

genetically engineered autologous cells

YESCARTA is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and activated with anti-CD3 antibody in the presence of IL-2, then transduced with the replication incompetent retroviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag. The product is thawed prior to infusion *[see Dosage and Administration (2.2), How Supplied/Storage and Handling (16)]*.

YESCARTA™ (axicabtagene ciloleucel) ***Kite Pharma FDA Package Insert***

Compare with the previous T cell process – how similar?

GMPs & Quality challenges of the manufacturing process specific for autologous genetically engineered cells

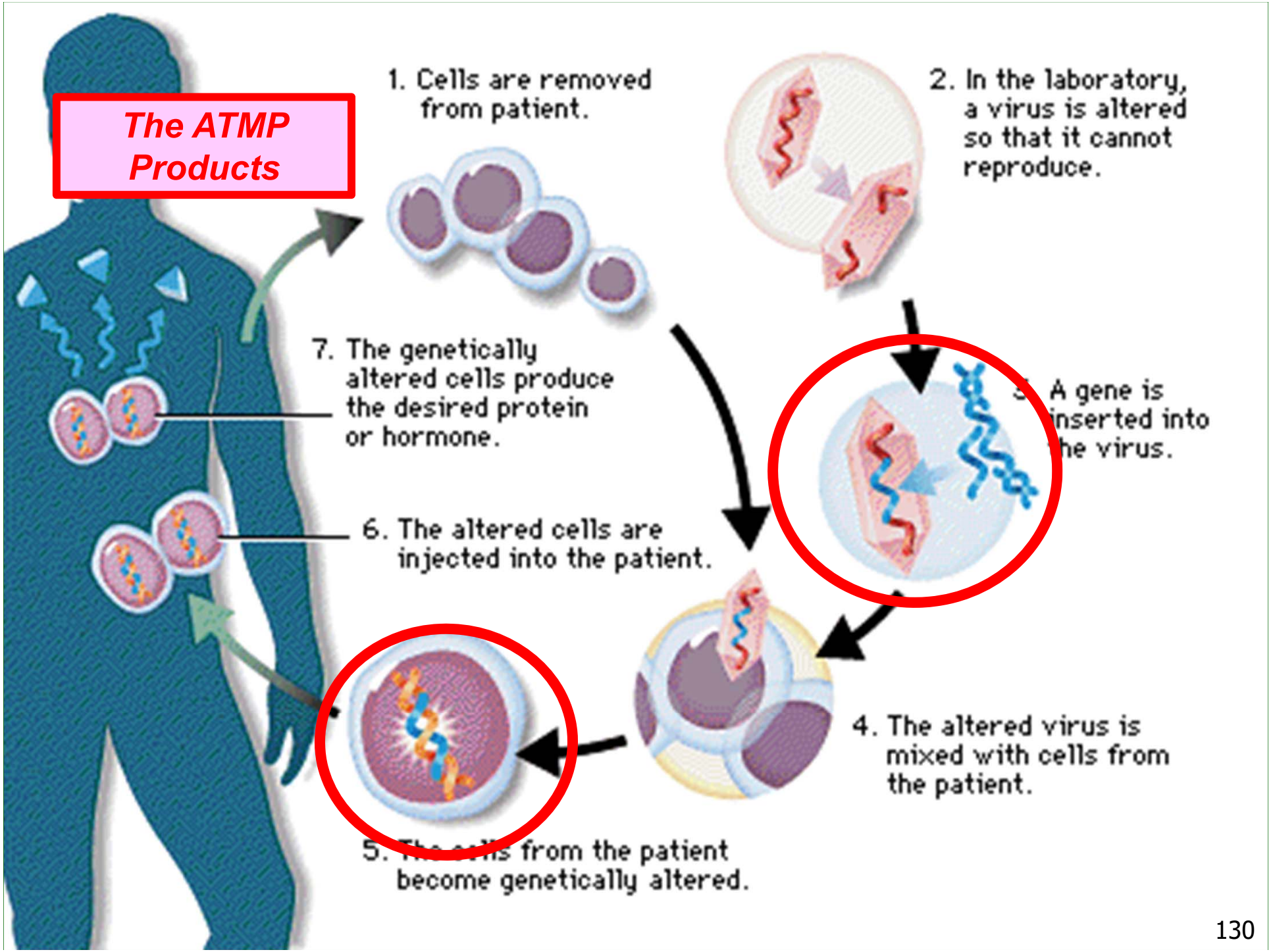
- ***Timeliness of initiating manufacturing process (must closely coordinate with clinical manager)***
- ***Patient (product) traceability through manufacturing process (1 batch = 1 patient)***
- ***Slow cell growth which limits batch supply (frequently just enough for patient + small amount left over for required QC testing and development assessment)***
- ***Timeliness of completing manufacturing process – patients depending upon 'their product'***

- *Protection of production staff from biohazard materials (patient cells, virus vectors)*
- *Risk assessment control over raw material sources for variation and impurities (no chromatography, primarily washing – 'what goes in, stays in')*
- *Assessment of manufacturing process parameters on impact of product critical quality attributes (CQAs)*
- *Completion of release tests prior to patient administration for short-lived, non-frozen cells*

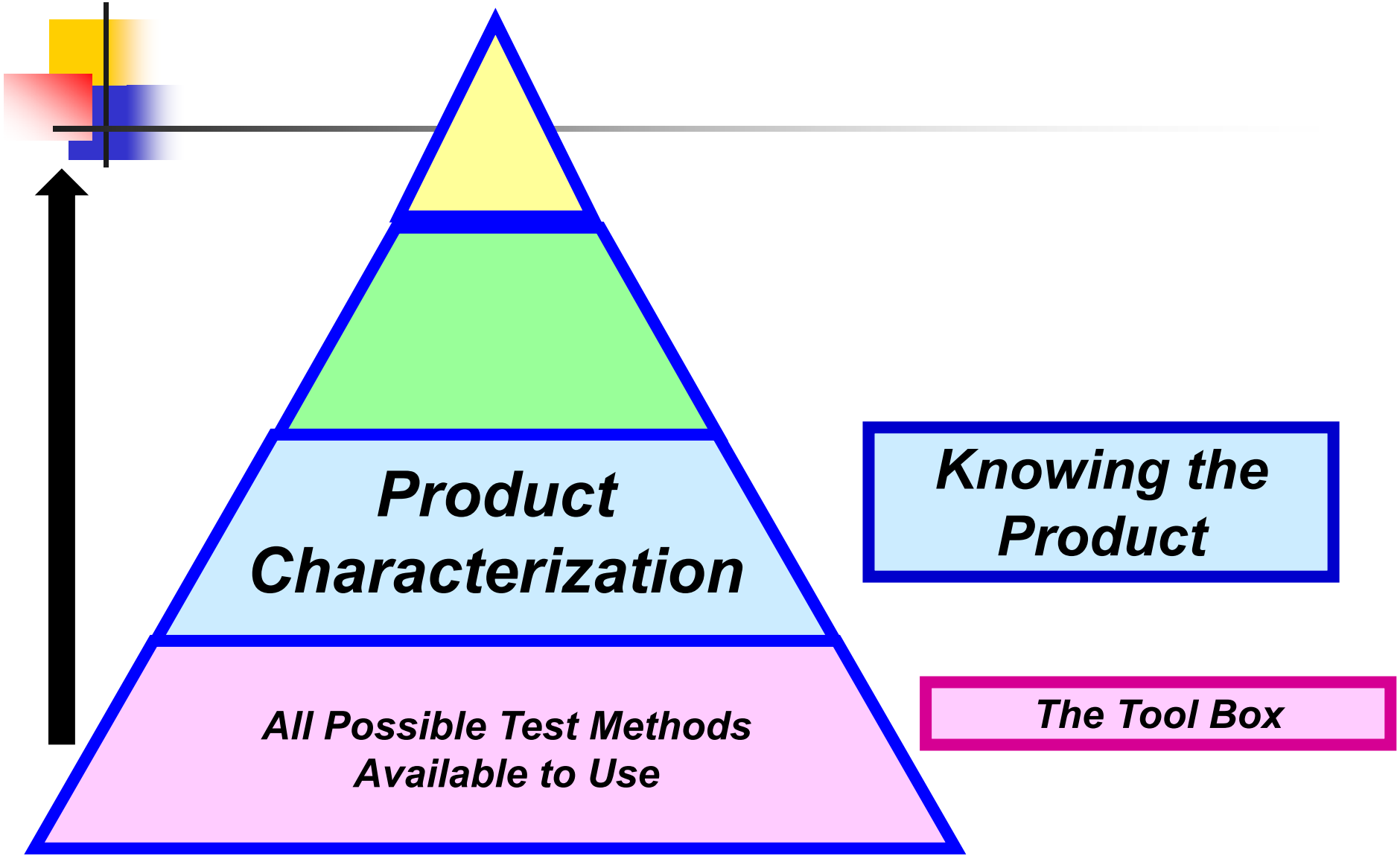
Thankful that today the following exists for these products:

- *sterile single use components*
- *modular facility design* →
- *rapid microbiological methods (RMMs)*

ATMP Facility Design YouTube


The ATMP Products
1. Cells are removed from patient.
2. In the laboratory, a virus is altered so that it cannot reproduce.
3. A gene is inserted into the virus.
4. The altered virus is mixed with cells from the patient.
5. The cells from the patient become genetically altered.
6. The altered cells are injected into the patient.
7. The genetically altered cells produce the desired protein or hormone.

Flow of Knowledge About the Product Through Testing



Product characterization is a journey

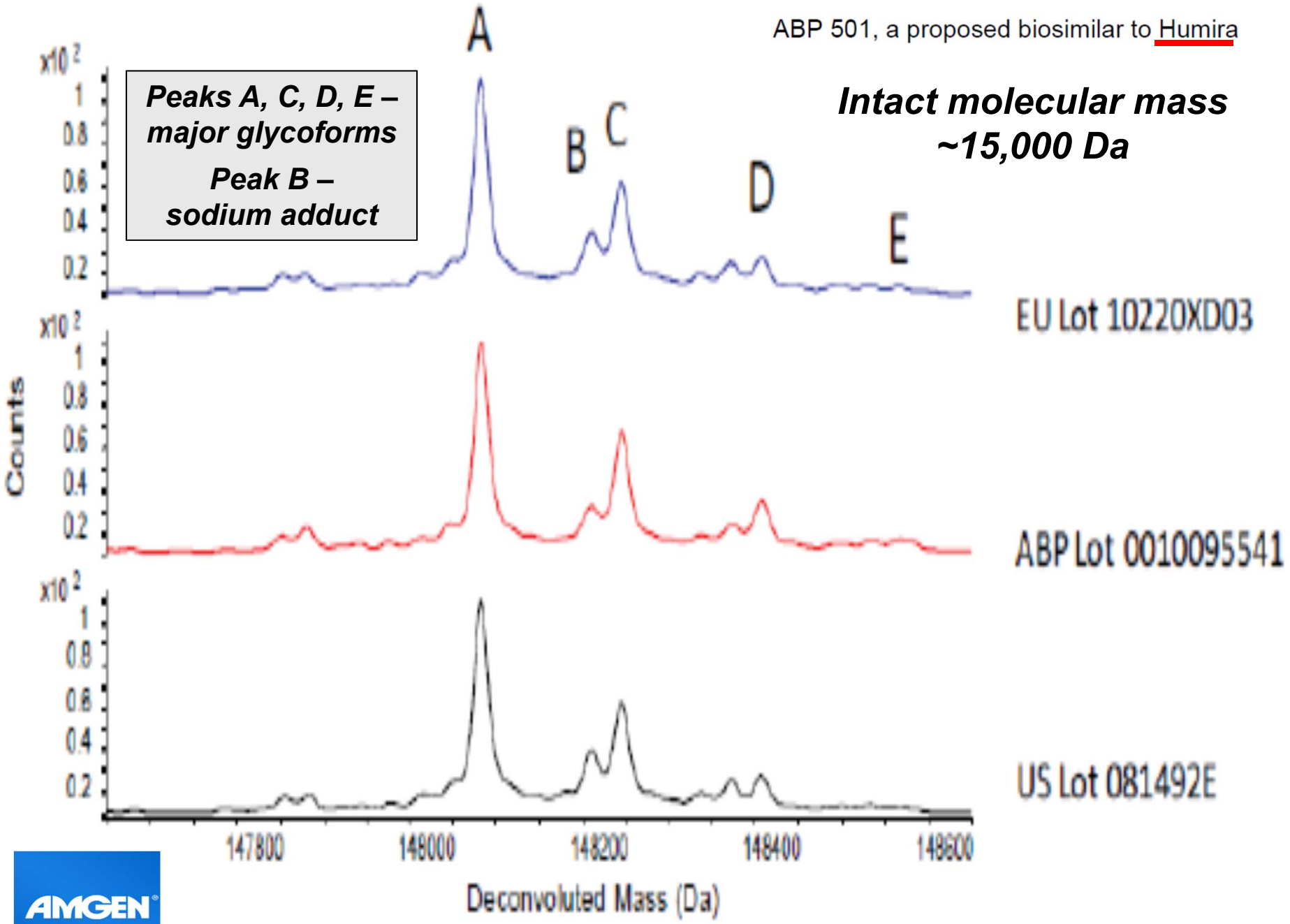
Biopharmaceutical	*Characterization Requirement*	*Status of Characterization Tools*
Recombinant Proteins & Monoclonal Antibodies	*Carried out during clinical development* ↓ *'Thorough' 'Comprehensive' 'Extensive' for market approval*	*Well developed*
Biosimilars (rProteins & MAbs)		

For these biopharmaceuticals, the advancement in analytical characterization tools has been astounding!

Biosimilar proteins illustrate 'thorough' characterization today

Quality Attribute	Recombinant Fusion Protein (etanercept) Innovator: Amgen (Enbrel) Biosimilar: Sandoz (Erelzi)	Monoclonal Antibody (TNF blocker) Innovator: Abbvie (Humira) Biosimilar: Amgen (Amjevita)
Primary Structure	• Peptide mapping with ultraviolet (UV) and mass spectrometry (MS) detection (reduced) • Amino acid analysis • Intact molecular mass (MALDI-TOF-MS) • Mass analysis of peptides (EIS-MS) • Post-translational modification (MS/MS) • Peptide mapping coupled with tandem mass spectrometry (MS/MS) • Disulfide bridging (non-red peptide mapping) • Free cysteines	• Peptide mapping with ultraviolet (UV) and mass spectrometry (MS) detection (reduced and non-reduced) • Amino acid analysis • Intact molecular mass (LC-MS) • Reduced and deglycosylated molecular mass (LC-MS)
Higher Order Structure	• Far and near UV circular dichroism • FT-Infrared • Differential scanning calorimetry • Hydrogen/deuterium exchange • 1D-NMR • X-ray crystallography	• Near UV circular dichroism • FT-Infrared • LC-MS (disulfide bond characterization) • Differential scanning calorimetry
Functional (Therapeutic) Biological Activity	• Apoptosis inhibition bioassay • TNF-α and TNF-β neutralization assay reporter gene assays • Surface plasmon resonance • Binding assays for Fc • Binding affinity assays for Fc • Binding assay for C1q • ADCC bioassay • CDC bioassay	• Apoptosis inhibition bioassay • ELISA binding assay • Cell-based binding assay • Binding assays for Fc • CDC and ADCC bioassay • Inhibition of induced IL-8 bioassay • Specificity against LTα bioassay • Inhibition of induced cell death • Inhibition of induced chemokines • Inhibition of T-cell proliferation

ABP 501, a proposed biosimilar to Humira



Peaks A, C, D, E – major glycoforms

Peak B – sodium adduct

Intact molecular mass ~15,000 Da

EU Lot 10220XD03

ABP Lot 0010095541

US Lot 081492E

(information obtained from FDA Advisory Committee briefing documents)

Product characterization is a journey

Biopharmaceutical	*Characterization Requirement*	*Status of Characterization Tools*
Recombinant Proteins & Monoclonal Antibodies	*Carried out during clinical development* ↓ *'Thorough' 'Comprehensive' 'Extensive' for market approval*	*Well developed*
Biosimilars (rProteins & MAbs)		
Genetically Engineered Viruses		*Developed*
Genetically Engineered Cells		*Under development*

For cells especially, the advancement in characterization tools is probably about 10 years behind protein characterization tools!

Genetically Engineered Viruses

Regulatory expectation for characterization

Characterisation studies should be conducted throughout the development process, resulting in a comprehensive picture and knowledge of the GTMP, which takes the individual components (including starting materials, intermediates, drug substance and drug product) into full consideration.

An extensive characterisation of the DS should be established in terms of genotypic and phenotypic identity, purity, biological potency/therapeutic sequence activity, infectivity/transduction efficiency and suitability for the intended use, unless otherwise justified.

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

23 March 2015
EMA/CAT/80183/2014

The complete sequence of the therapeutic and genetic elements required for selectivity/regulation/control of the therapeutic sequence should be provided. Restriction endonuclease mapping data should be provided to complement sequence data and transcription/translation elements and open reading frames analysed. It should be demonstrated that there is no inclusion of known oncogenic/tumorigenic sequences. Tests should be included to show integrity and homogeneity of the recombinant viral genome or plasmid and the genetic stability of the vector and therapeutic sequence. Phenotypic identity and analysis of the therapeutic sequences and selectivity/regulatory elements delivered by the vector should be included.

Physicochemical characteristics such as refractive index, particle or molecular size average and distribution, and aggregation levels should be determined in characterization studies.

Product-related impurities, such as vectors with deleted, rearranged, hybrid or mutated sequences should be identified and their levels quantified. The possibilities for co-packaged extraneous DNA sequences being present in the vector should be explored. Reference should be made to potential degradation during the manufacturing process affecting key properties of the vector such as infectivity/non-infectious forms, plasmid forms with reduced transduction efficacy, or degradation of nucleic acid complexes through, for example, oxidation or depolymerisation.

Case examples of characterization of genetically engineered viruses

Characterisation

Parameters investigated were composition (genome integrity and size, protein analysis and molecular mass, stoicometry of capsid proteins), physical properties (particle size, glycosylation state of the virus particle), primary structure (sequence confirmation, protein identification), higher order structure (TEM and analytical ultracentrifugation to determine mass, density and distribution profiles); biological activity was addressed by the infectious particle assay, ratio of full:infectious virus particles and potency.

19 July 2012
EMA/882900/2011 **Glybera** Alipogene tiparvovec Amsterdam Molecular Therapeutics

Characterisation

For characterisation of talimogene laherparepvec, the Applicant has considered viral structure (size, density, purity by SEC), genomic sequence, protein and glycan content, as well as biological characteristics. The studies are considered relevant and adequately conducted.

22 October 2015
EMA/734400/2015 **Imlygic** talimogene laherparepvec Amgen

Regulatory expectation for characterization

5.3. Characterisation

Rigorous characterisation of the genetically modified cell medicinal product (either alone or in combination with medical device) is essential. If genetically modified cells are combined with a medical device, characterisation should take into account the medical device itself and its contribution to the structure and function of the final product.

The use of a range of appropriately qualified molecular, biological, and immunological methods for the following characteristics should be addressed:

- identity, and viability
- sequence and integrity of transgene,
- identity and integrity of vector,

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

13 April 2012
EMA/CAT/GTWP/671639/2008

- gene copy number per cell,
- vector integration profile,
- transduction efficiency (e.g. percentage of transduced cells),
- vector/transgenes removal or elimination (when applicable),
- identity and activity of the expressed gene product,
- cell phenotype / morphology,
- homogeneity of the cell population (e.g. percentage of sub-populations),
- proliferation and/or differentiation capacity of the genetically modified cells,
- vector release from cells,
- vector replication competence and possibility of reactivation,
- genetic stability upon in vitro proliferation and/or differentiation.

Case examples of characterization of genetically engineered cells

Characterisation

Characterisation of the transduced CD34+ cells in terms of identity, purity and potency has been assembled through comparability studies and additional characterisation studies.

Characterisation methods together with their description and attributes are detailed.

Process-related and product-related impurities that could potentially impact safety and/or efficacy of Strimvelis have been identified and analysed.

GlaxoSmithKline

1 April 2016
EMA/CHMP/323455/2016

Strimvelis

CD34+ cells transduced with retroviral vector

Challenging characterization of cells

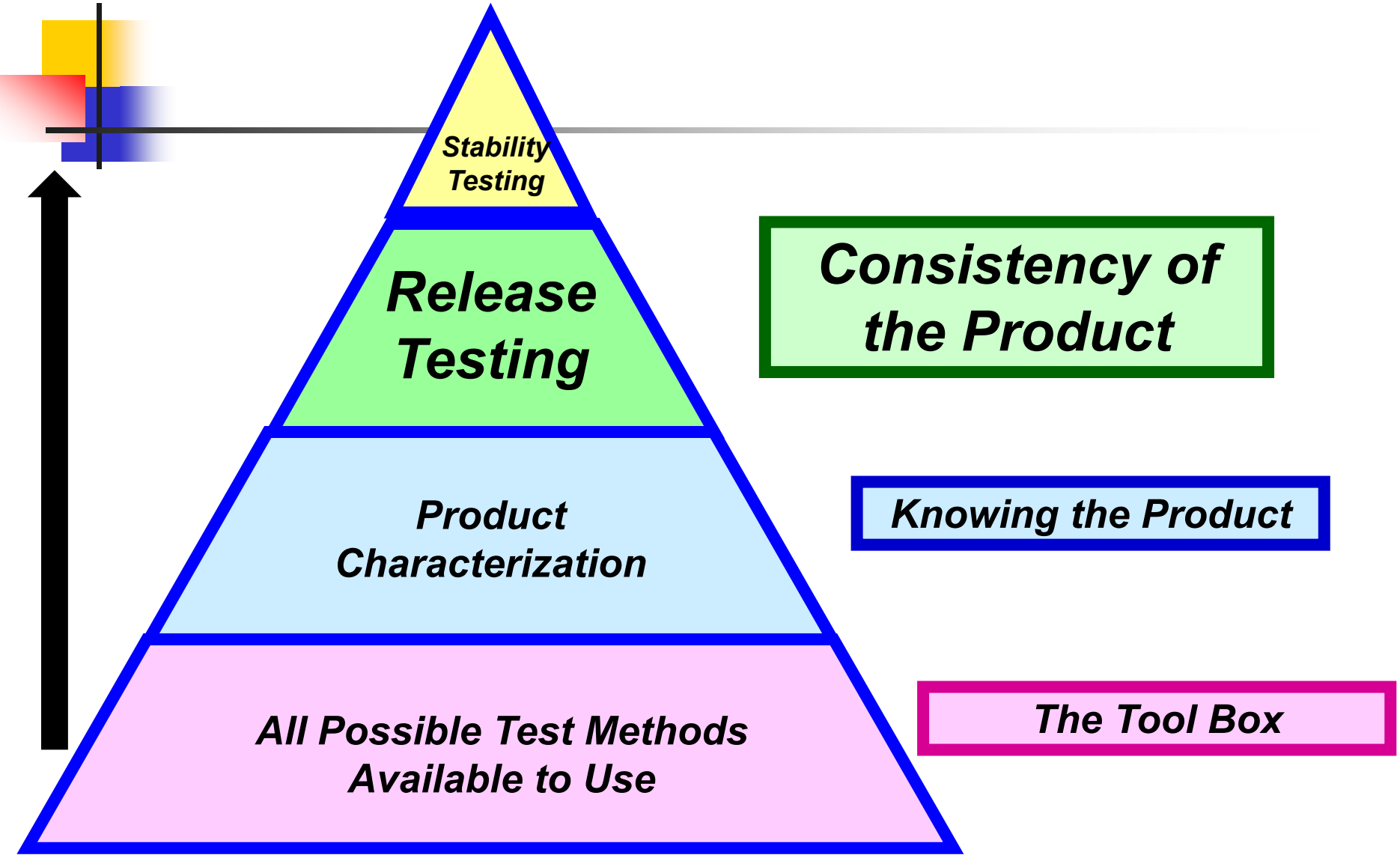
IDENTITY OF CELLS

- *Currently, identity for cell-based products is poorly understood*
- *Typically, it is demonstrated through the presence or absence of cell surface markers identified by flow cytometry.*
- *This approach may miss other informative markers whose expression varies during production or because of process changes*

POTENCY OF CELLS

- *Cells often act through multiple modes of action*
- *One single potency assay may not suffice, resulting in an assay matrix approach*
- *Potency assays take considerable time and effort to develop, qualify and eventually validate*

Flow of Knowledge About the Product Through Testing



Case Example: Genetically-engineered virus release testing

Assay	Test Site / Method Number	Acceptance Criteria
	Physicochemical	
Appearance (Visual Inspection)	Spark / QC028	Clear and colorless solution, free of visible
pH	Spark / QC020	(b) (4)
(b) (4)	Spark / QC019	(b) (4)
Concentration of Pluronic (µg/mL)	(b) (4)	(b) (4)
Extractable Volume (mL)	(b) (4)	(b) (4)
	Identity	
Vector Genome Identity by (b) (4)	Spark / QC067	Positive for hRPE65v2
	Concentration	
Vector Genome Concentration Assay (vg/mL)	Spark / QC062	(b) (4)

	Activity/Potency	
(b) (4)	Spark / QC069	(b) (4)
Gene Product Expression by (b) (4) Assay	Spark / QC033	Positive for hRPE65v2 gene
In Vitro Relative Potency of (b) (4) by (b) (4) Assay (b) (4)	(b) (4)	(b) (4)
In Vitro Relative Potency of (b) (4) Assay	(b) (4)	(b) (4)
	Purity	
Purity by (b) (4) Assay (b) (4)	Spark / QC003	(b) (4)
	Safety	
Endotoxin (IU/mL)	(b) (4)	(b) (4)
Particulate Matter	(b) (4)	(b) (4)
Sterility	(b) (4)	No Growth

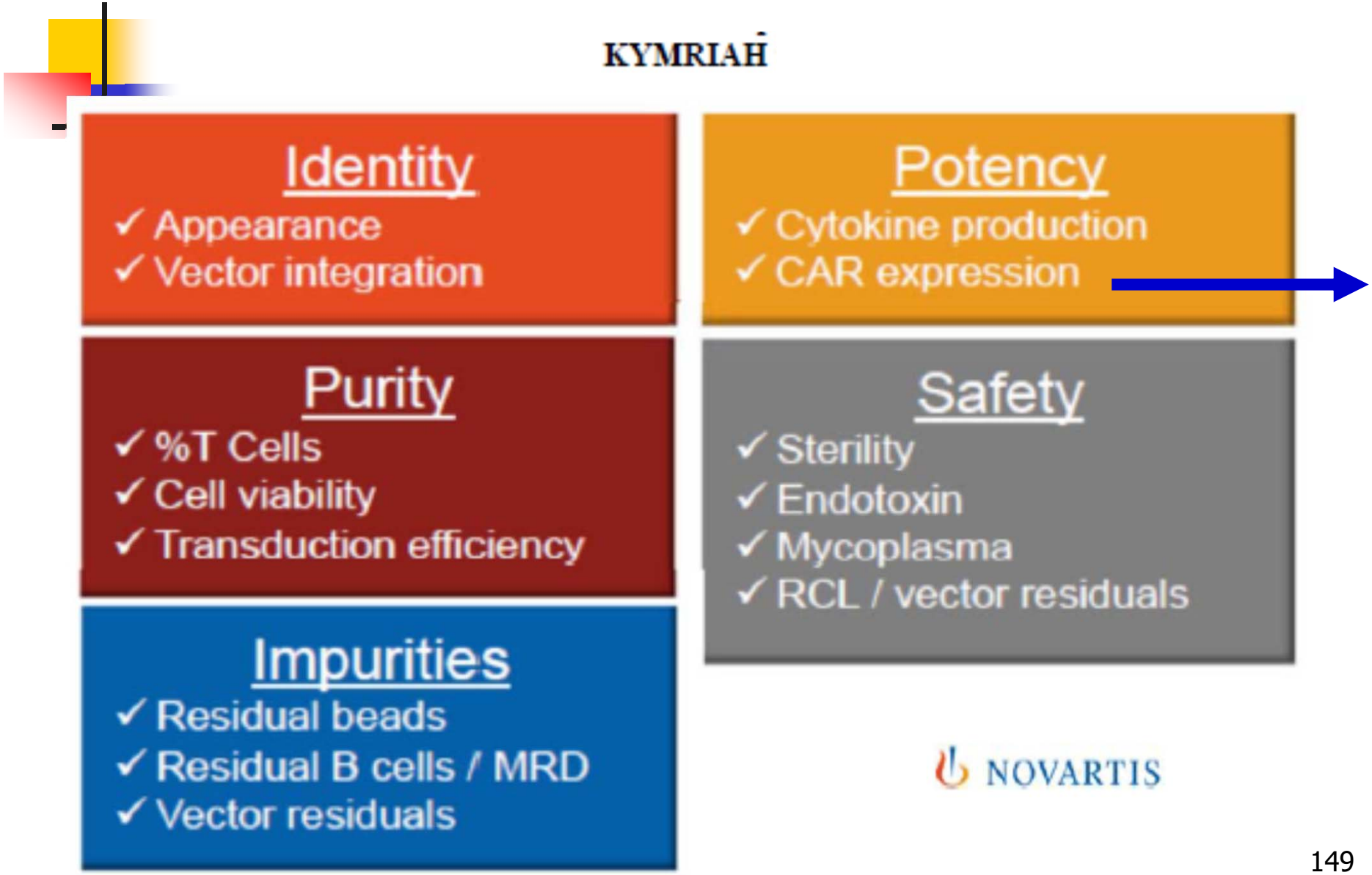
PDA TR Cell-Based Therapy Control Strategy

Case Example: Cell therapy CQAs (release testing)

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

Residual Fetal Bovine Serum	High	Medium	CQA	Levels in final product known to potentially impact safety
Dead Cells	Medium	Low	CQA	Presence of dead cells monitored through cell viability
			Potency	
Functional Activity	High	Low	CQA	Lack of function will inevitably result in a lack of clinical efficacy; expression of specific genes is measured as surrogate assay for function
			Strength/Dose	
Total Cell Number/ Dose Unit	Medium	Low	CQA	Link between dose and efficacy needs to be established during development; 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

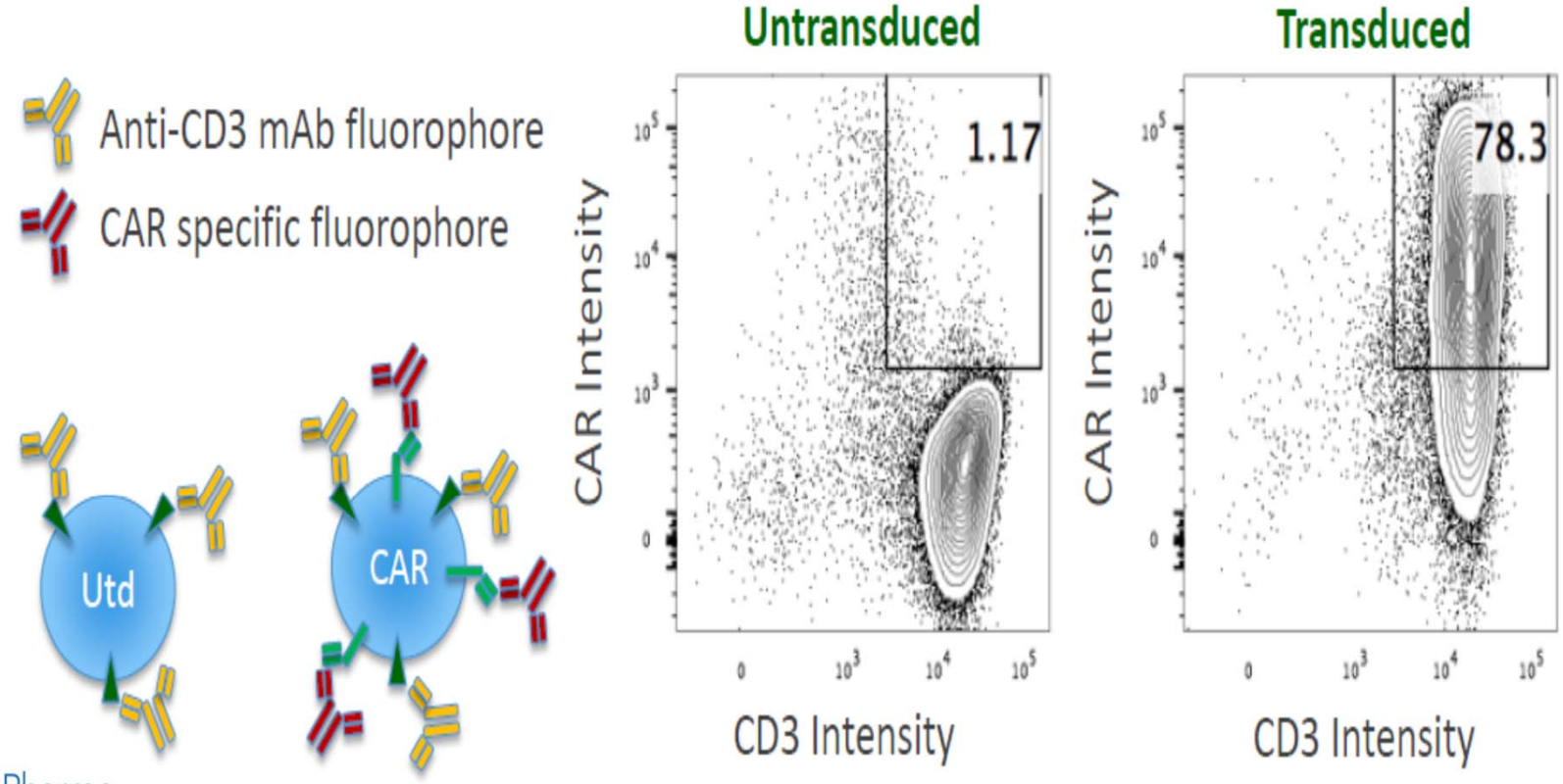
Case Example: Genetically-engineered T-cells release testing



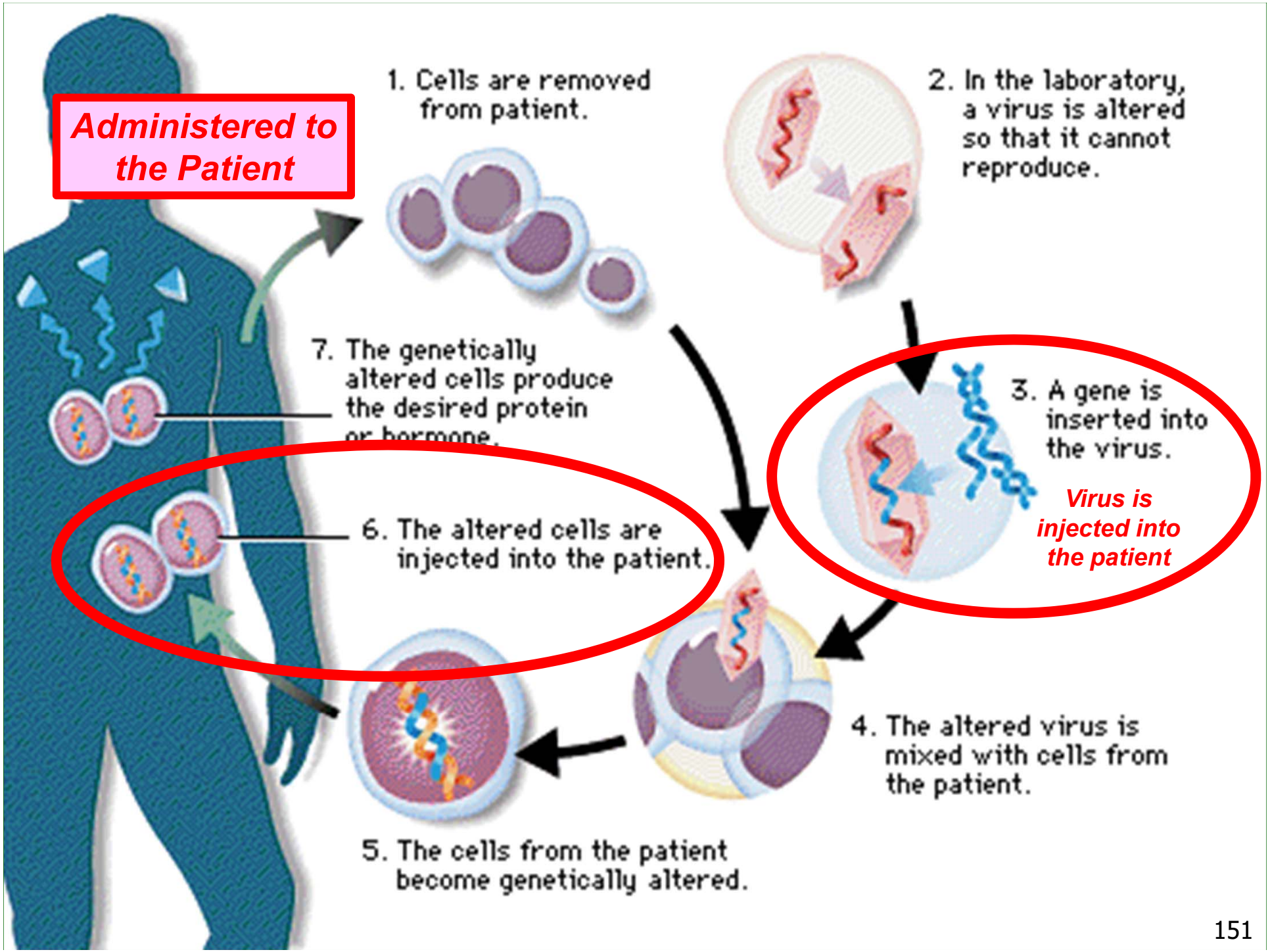
Final Product Potency: % CAR Expressing T Cells

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


Administered to the Patient
1. Cells are removed from patient.
2. In the laboratory, a virus is altered so that it cannot reproduce.
3. A gene is inserted into the virus.
Virus is injected into the patient
4. The altered virus is mixed with cells from the patient.
5. The cells from the patient become genetically altered.
6. The altered cells are injected into the patient.
7. The genetically altered cells produce the desired protein or hormone.

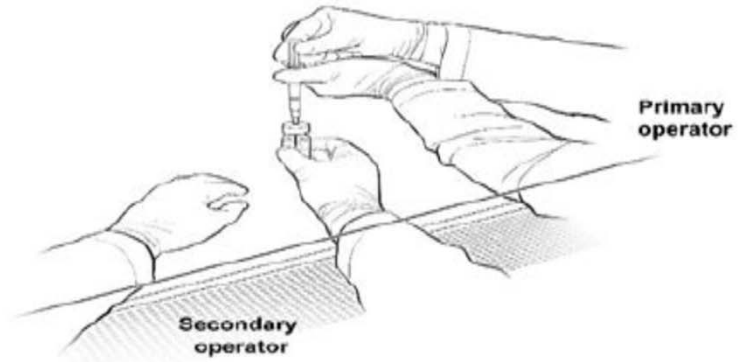
Genetically Engineered Virus

U.*S FDA Package Insert* *Patient Administration*

LUXTURNA (voretigene neparvovec-rzyl) is a suspension of an adeno-associated virus vector-based gene therapy for subretinal injection. LUXTURNA is a live, non-replicating adeno-associated virus serotype 2 which has been genetically modified to express the human *RPE65* gene. LUXTURNA is derived from naturally occurring adeno-associated virus using recombinant DNA techniques.

Each single-dose vial of LUXTURNA contains 5×10^{12} vector genomes (vg) per mL, and the excipients 180 mM sodium chloride, 10 mM sodium phosphate, and 0.001% Poloxamer 188 (pH 7.3), in a 0.5-mL extractable volume. LUXTURNA requires a 1:10 dilution prior to administration. After dilution, each dose of LUXTURNA consists of 1.5×10^{11} vg in a deliverable volume of 0.3 mL.

First Position of the Operators During Preparation of LUXTURNA Syringes



Prepare LUXTURNA within 4 hours of administration using sterile technique under aseptic conditions in a Class II vertical laminar flow biological safety cabinet (BSC).

Genetically Engineered Cells

U.S FDA Package Insert Patient Administration

A single dose of KYMRIAH may contain up to 2.5 x 10^8 CAR-positive viable T cells provided in a patient-specific infusion bag

KYMRIAH is supplied as a frozen suspension of genetically modified autologous T cells in one infusion bag labeled for the specific recipient. KYMRIAH is shipped directly to the cell lab associated with the infusion center in a liquid nitrogen Dewar. Product and patient-specific labels are located inside the Dewar. NDC 0078-0846-19

- Confirm patient identity upon receipt.
- Store infusion bag in the vapor phase of liquid nitrogen (less than or equal to minus 120°C) in a temperature-monitored system.
- Use closed, break-proof, leak-proof containers when transporting infusion bags within the facility.
- Thaw KYMRIAH prior to infusion *[see Dosage and Administration (2)]*.

GMP & Quality Challenges

Managing regulatory authority conservatism

- ***ATMPs are much less well known to regulatory reviewers than protein-based medicines – limited regulatory precedents***
- ***Put yourself in their shoes – 'do no harm'***
- ***<u>But</u> there always needs to be a balance between regulatory expectations and manufacturer's risk***

31 January 2017

Summary of the 5th annual regulatory conference organised by EBE, in collaboration with the European Medicines Agency (EMA) "Optimising the development of ATMPs to meet patient needs" – *London, 16th December 2016*

The real-life experience of carrying out clinical trials with ATMPs in a clinical setting can mean battling **multiple and often ridiculous barriers**, depending on the **different protocols used in different clinical settings and countries**. One example is bio-safety levels (BSL) attributed to an ATMP candidate by competent authorities, which can differ widely within the EU. In the case of Talimogene-Laherparepvec (TVEC) immunotherapy treatment, a BSL2 designation was given in Austria and Germany, but BSL1 in Spain. While BSL2 information is well defined for the laboratory research, there is no available information on its requirements in clinical settings to aid healthcare professionals with their hands-on work with patients. Study start-up was also markedly quicker in countries without BSL2 designation, it was noted.

If in doubt, seek regulatory authority advice!

Committee for Advanced Therapies (CAT) Certification

The certification system aims at giving SMEs an incentive to develop ATMPs and, although it is independent from any application from marketing authorisation, it could facilitate the evaluation of any future application for clinical trial and marketing authorisation based on the same data.

SAWP/CAT Scientific Advice

European Medicines Agency Guidance for applicants seeking scientific advice and protocol assistance

PDUFA Type A, B, C Meetings

Center for Biologics Evaluation and Research (CBER)

Office of Tissues and Advanced Therapies (OTAT)

Crystal ball YouTube

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

Summary

- ***ATMPs are the next wave of new medicines; they are more highly complex medicines than proteins, as well as living medicines***
- ***Phase-appropriate GMP & Quality are critical for patient safety***