



**PROPHARMA
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Complex Challenges. Exceptional Solutions.

Regulatory Challenges in the landscape of cell and gene therapies

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Cell and Gene Therapy Landscape



What are ATMPs

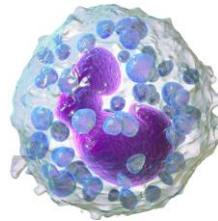
Medicines for human use that are based on genes, tissues or cells.

They offer groundbreaking new opportunities for the treatment of disease and injury.

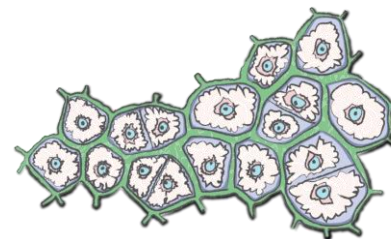
Note: in Europe, they are also known as “Advanced Therapy Medicinal Products” (ATMPs), falling into four categories:



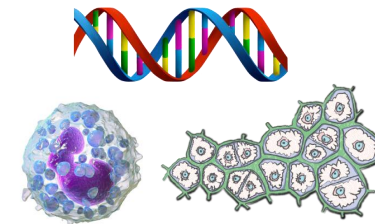
Gene therapy



Somatic cell
therapy



Tissue-engineered
therapy



Combined Device
ATMP

What are ATMPs

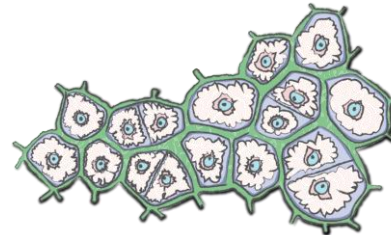


Gene Therapy Medicinal Product

Annex I, Part IV, 2.1 to
Directive 2001/83/EC

*Recombinant nucleic acid
administered with a view to
regulating, repairing, replacing,
adding or deleting genetic
sequence*

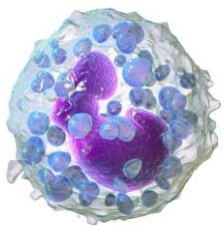
*Therapeutic, prophylactic or
diagnostic effect relates
directly to the recombinant
nucleic acid sequence it
contains*



Tissue Engineered Medicinal Product

Article 2.1.b in Regulation (EC) No.
1394/2007

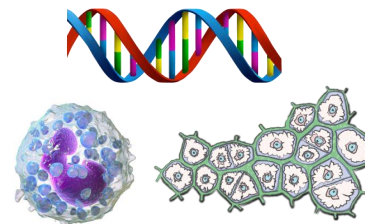
*Contains or consists of cells
or tissues administered with
a view to regenerating,
repairing or replacing a
human tissue*



Somatic Cell Therapy Medicinal Product

Annex I, Part IV, 2.2 to Directive
2001/83/EC

*Contains or consists of cells or
tissues used for prevention,
diagnosis and/or treatment of
diseases via pharmacological,
immunological or metabolic
actions*



Combined Device-ATMP

Article 2.1.d in Regulation (EC)
No. 1394/2007

*Contain as an integral part
of the product a
medical device*

The Valley of Death



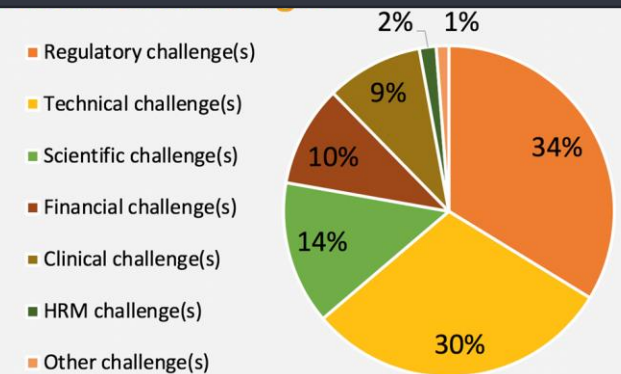
Is this your road to success or a drive
into the Valley of Death

Cell and Gene Therapy features:

- Complex products
- High variation in starting materials
- Complex manufacturing processes
- Complex analytical assays
- Frequently developed for small indications
- Often used in end stage patients
- Frequently developed by academia and start ups
- A complex Regulatory framework

Challenges in ATMP development

(Renske ten Ham, Utrecht University)

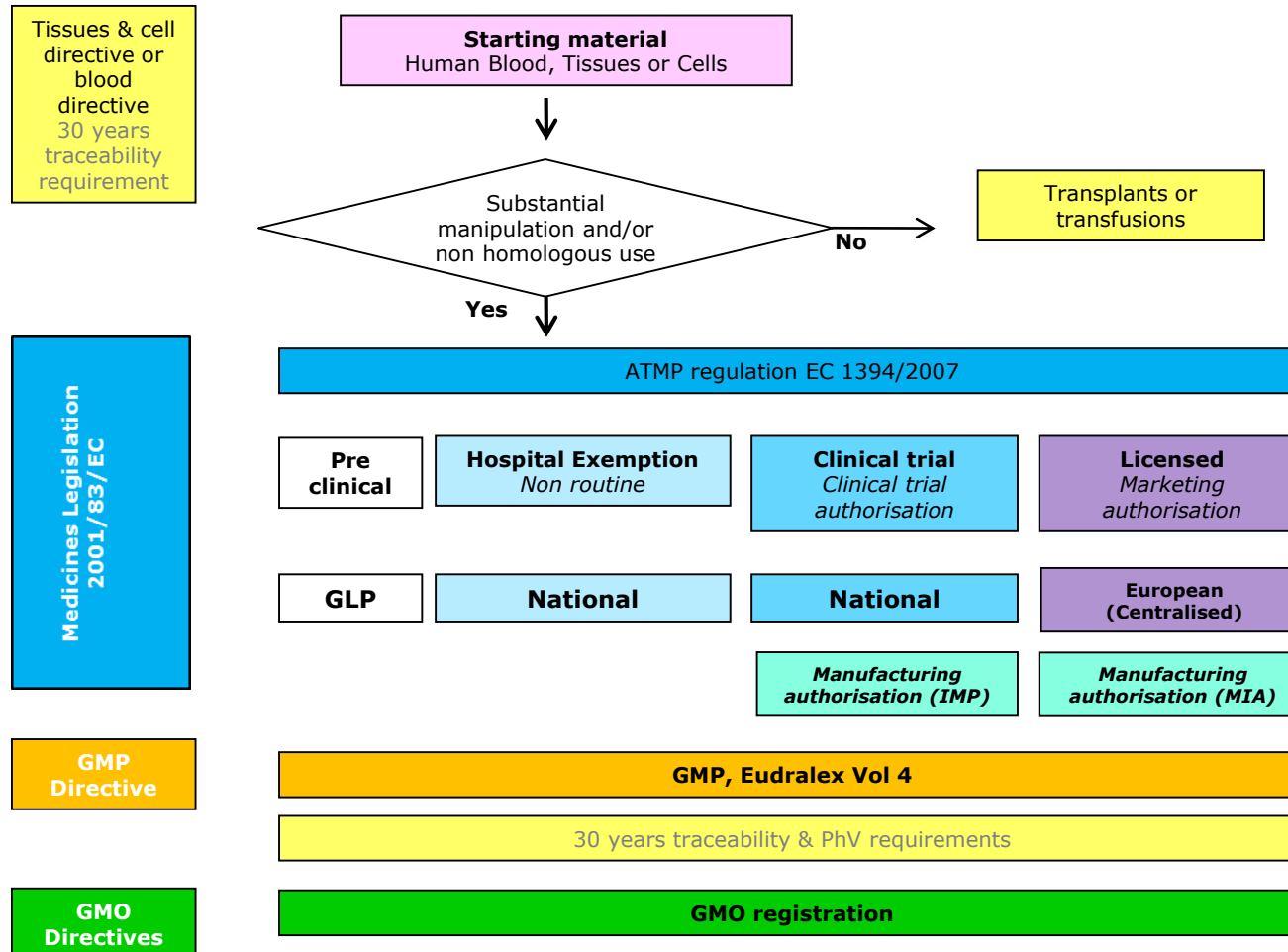


EU Regulatory landscape

- European Commission (EC) (DG SANTE)
 - Propose and amend legislation for the entire sector;
 - Regulations – self-executing and binding to all Member States, no national changes allowed*
 - Directives – required output is binding but transposition up to Member States to interpret locally*
 - Grants legally binding marketing authorisation valid in all EU
- European Directorate for the Quality of Medicines & Healthcare
 - Protects public health by enabling the development, supporting the implementation and monitoring the application of quality standards for safe medicines and their safe use which are recognised as a scientific benchmark and applied worldwide.
 - European Pharmacopoeia
- European Medicines Agency (EMA)
 - Coordination of scientific evaluation for Marketing Authorisation (ATMPs)
 - Developing guidelines in cooperation with expert committees and working groups
 - Product-specific scientific advice and early access pathways
- National regulatory authorities
 - Authorisation and oversight of clinical trials, blood, tissues and cells as well as GMO approval
 - Grants use under hospital exemption
 - Product-specific scientific advice to developers



EU Regulatory framework for ATMPs



Substantial manipulation

(Manufacture)

Manipulated during manufacturing process so that biological characteristics, physiological functions or structural properties have been modified to be relevant for their intended function

Non-homologous Use

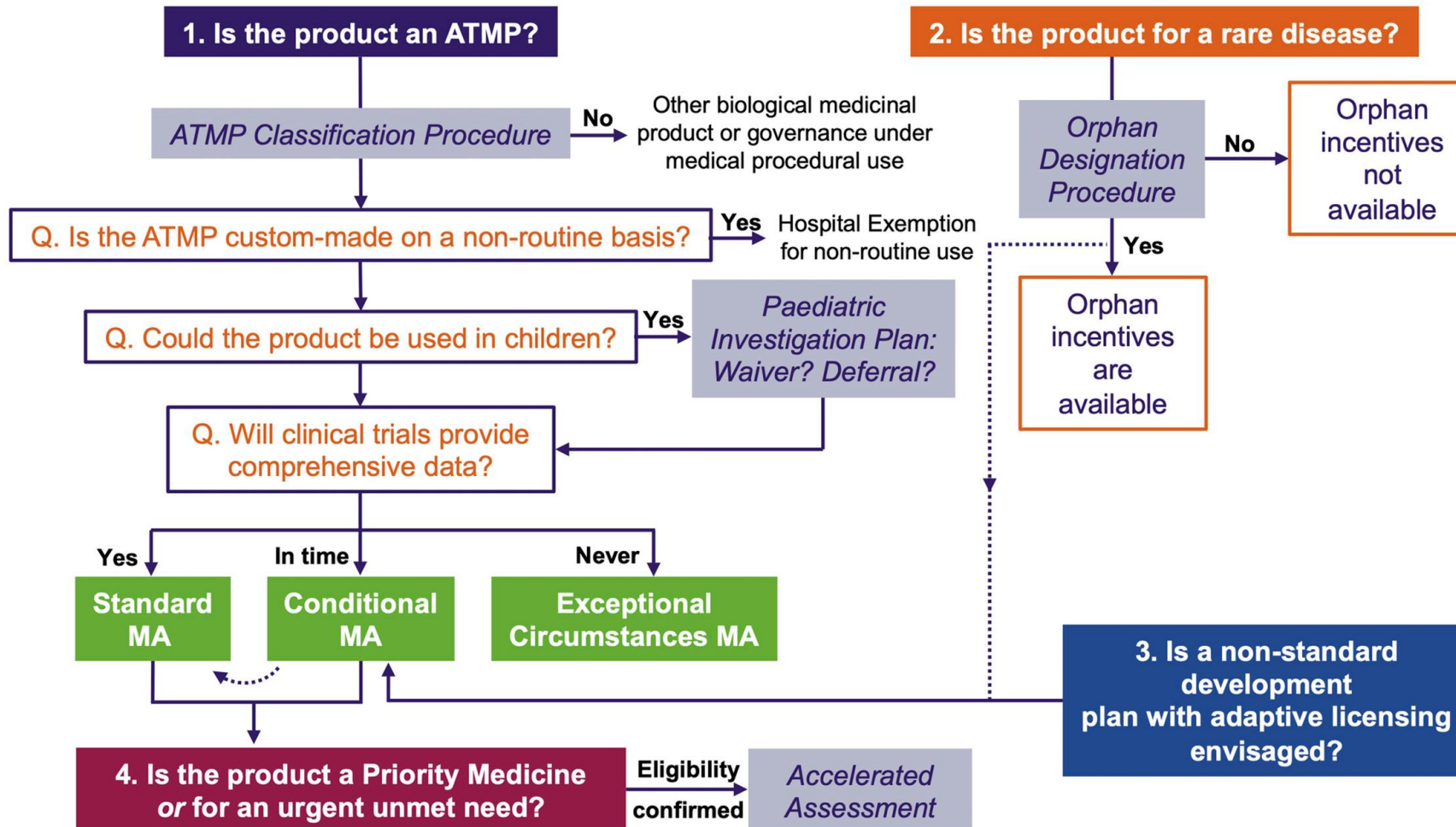
(Function)

Cells or tissues not intended to be used for the same essential function(s) in the recipient and the donor (may relate to function and/or location)

ATMP regulation

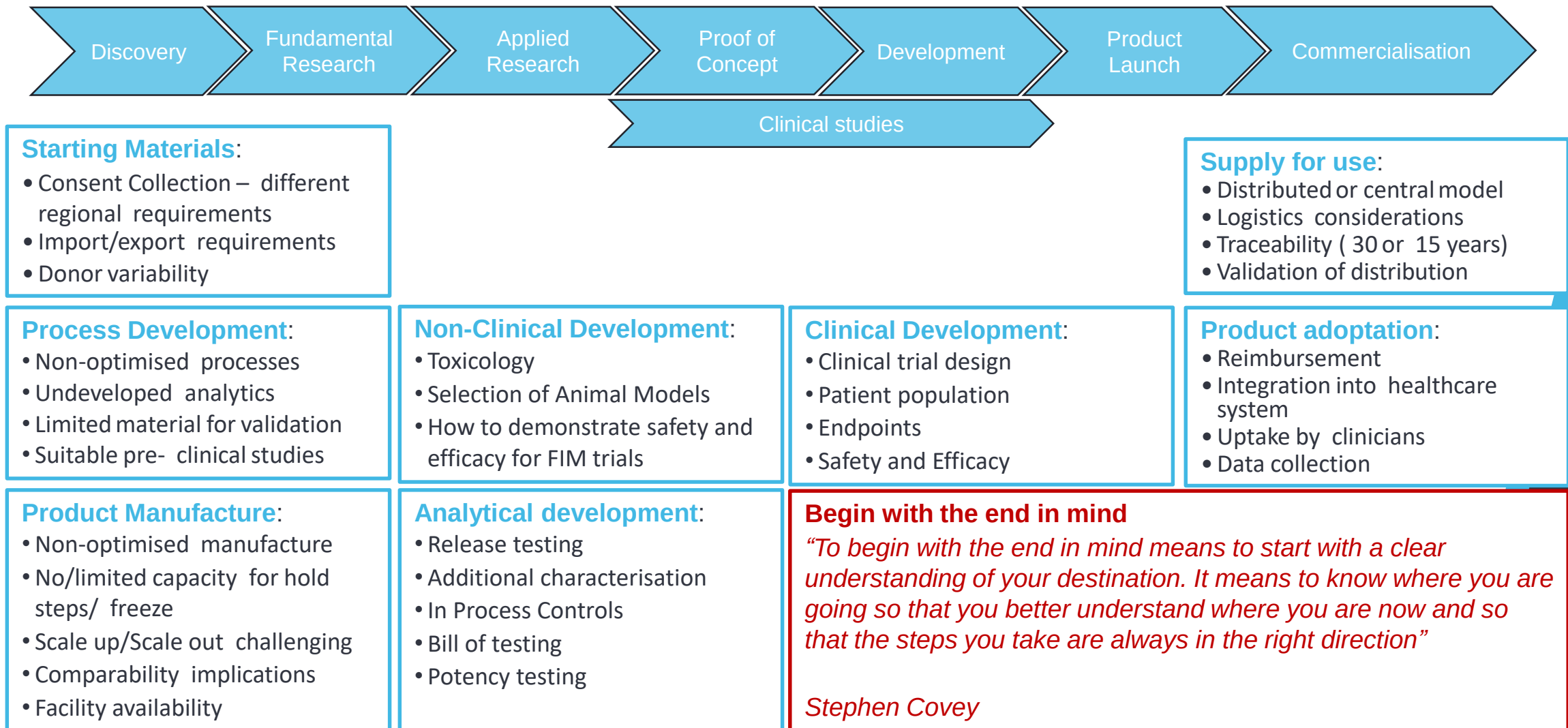
ATMPs are medicinal products
Authorized via centralized procedure
Assessed by the CAT
GMP, GCP adapted to ATMPs
Post authorisation and efficacy follow up

Regulatory pathways for Marketing Authorisation of ATMPs

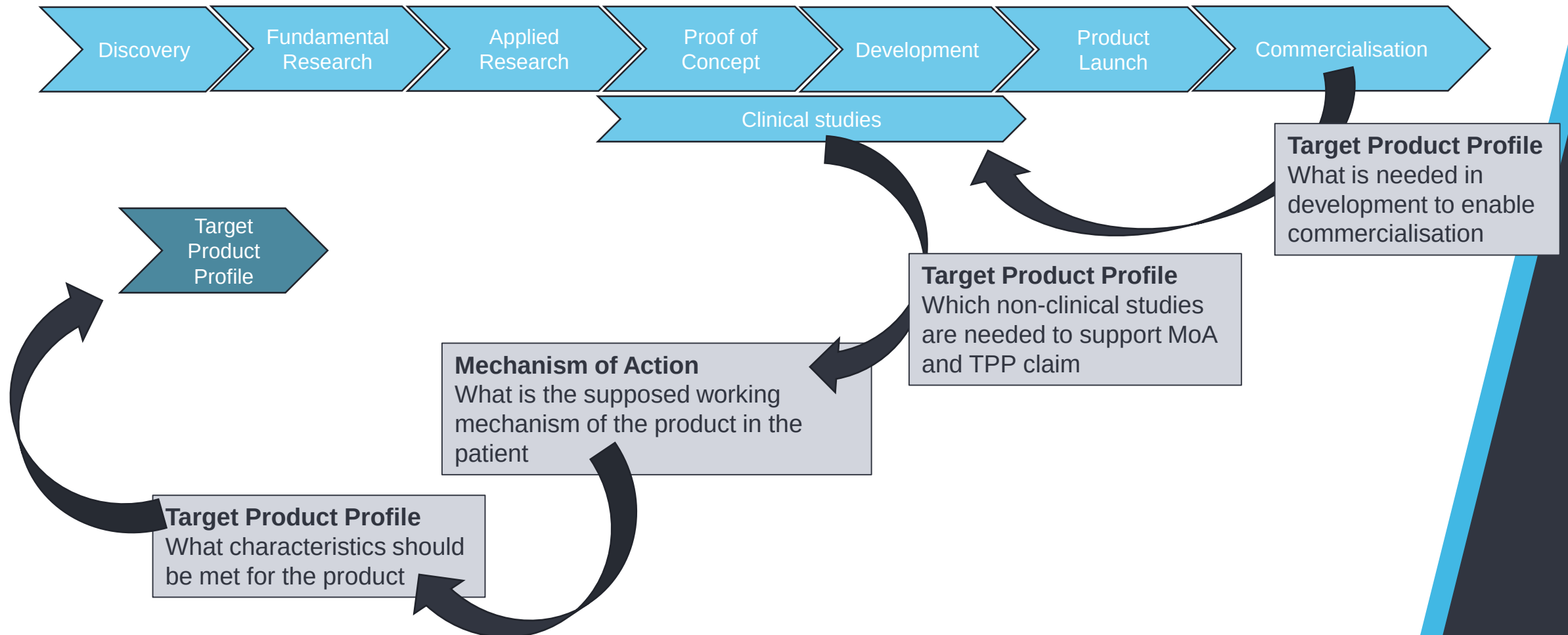


Detela et al,
2019
<https://doi.org/10.1016/j.omtm.2019.01.010>

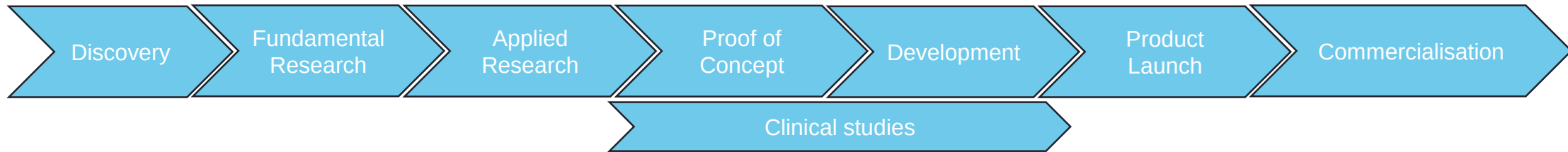
Regulatory considerations during ATMP development



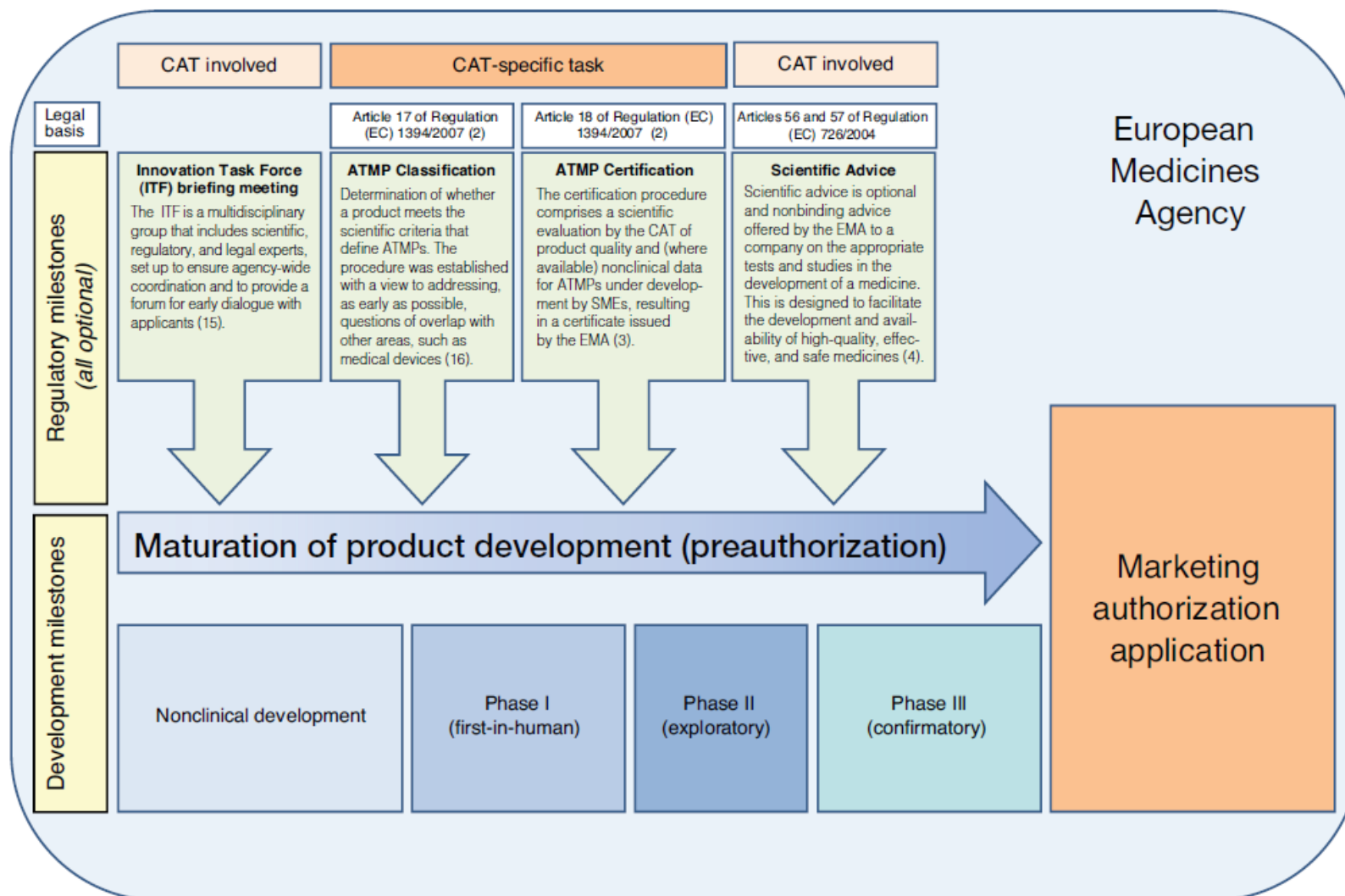
Begin with the end in mind



Begin with the end in mind



Regulatory Milestones for ATMP development



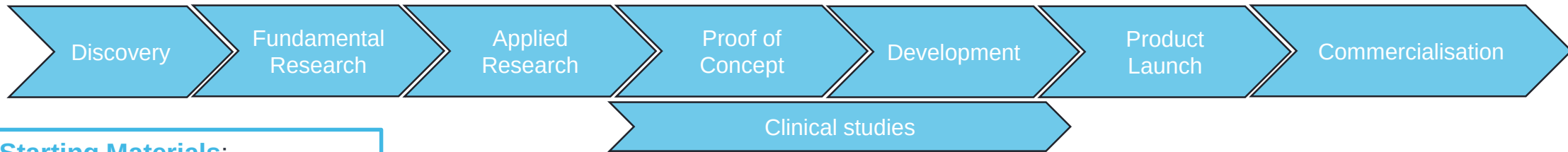
EU ATMP Marketing Authorisations 2009-2019

- Chondroselect®* Cultured chondrocytes for repair of knee cartilage defects (2009)
- MACI®*
- Spherox®
- Holoclar® Cultured corneal epithelial cells, limbal stem cell deficiency
- Provenge®* Metastatic prostate cancer
- Zalmoxis*® Stem cell transplantation, adjunctive treatment
- Alofisel® Crohn`s disease, complex anal fistula
- Glybera®* Familial LPL deficiency
- Imlygic® Injectable melanoma
- Strimvelis® Severe combined immunodeficiency ADA-SCID
- Yescarta® B-cell Lymphoma (DLBCL)
- Kymriah® B-cell Lymphoma (DLBCL), B-cell acute lymphoblastic leukemia
- Luxturna® Inherited retinal dystrophy, RPE65 mutation
- Zynteglo® Transfusion-dependent β -thalassaemia, not β^0/β^0 (4.2019)

Tissue engineered products Somatic cell therapies Gene therapies *no longer marketed

Why some ATMPs failed to be successful

CMC perspective



Starting Materials:

- Consent Collection – different regional requirements
- Import/export requirements
- Donor variability

Process Development:

- Non-optimised processes
- Undeveloped analytics
- Limited material for validation
- Suitable pre- clinical studies

Product Manufacture:

- Non-optimised manufacture
- No/limited capacity for hold steps/ freeze
- Scale up/Scale out challenging
- Comparability implications
- Facility availability

Analytical development:

- Release testing
- Additional characterisation
- In Process Controls
- Bill of testing
- Potency testing

The process is the product

Particularly for cell and tissue products this is often a challenge

Critical Quality Attributes

IPCs and specifications

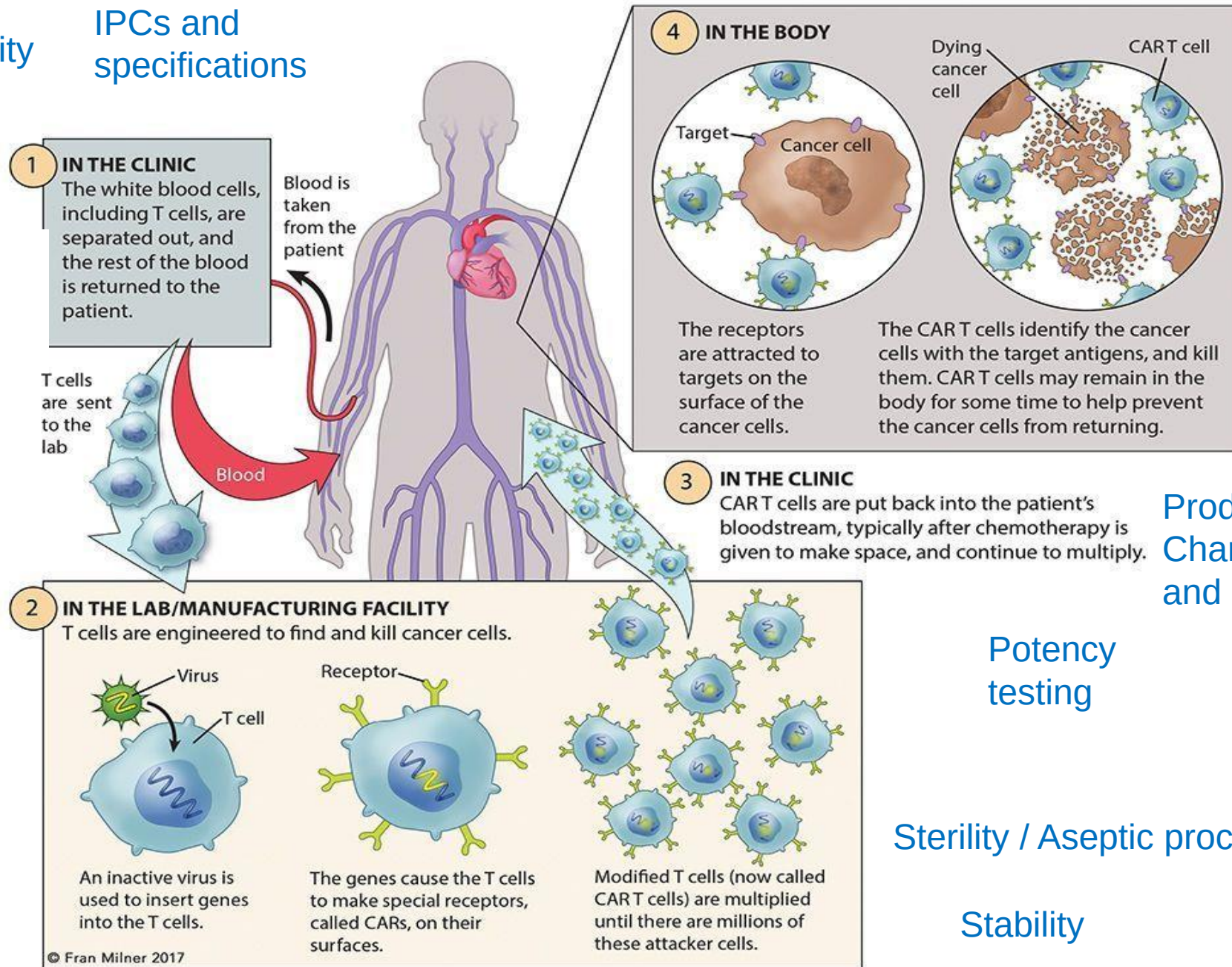
Starting material variation

Biological manufacturing system

Lot to Lot consistency

Analytics

Comparability



Mechanism of Action

Product Characterisation and release

Potency testing

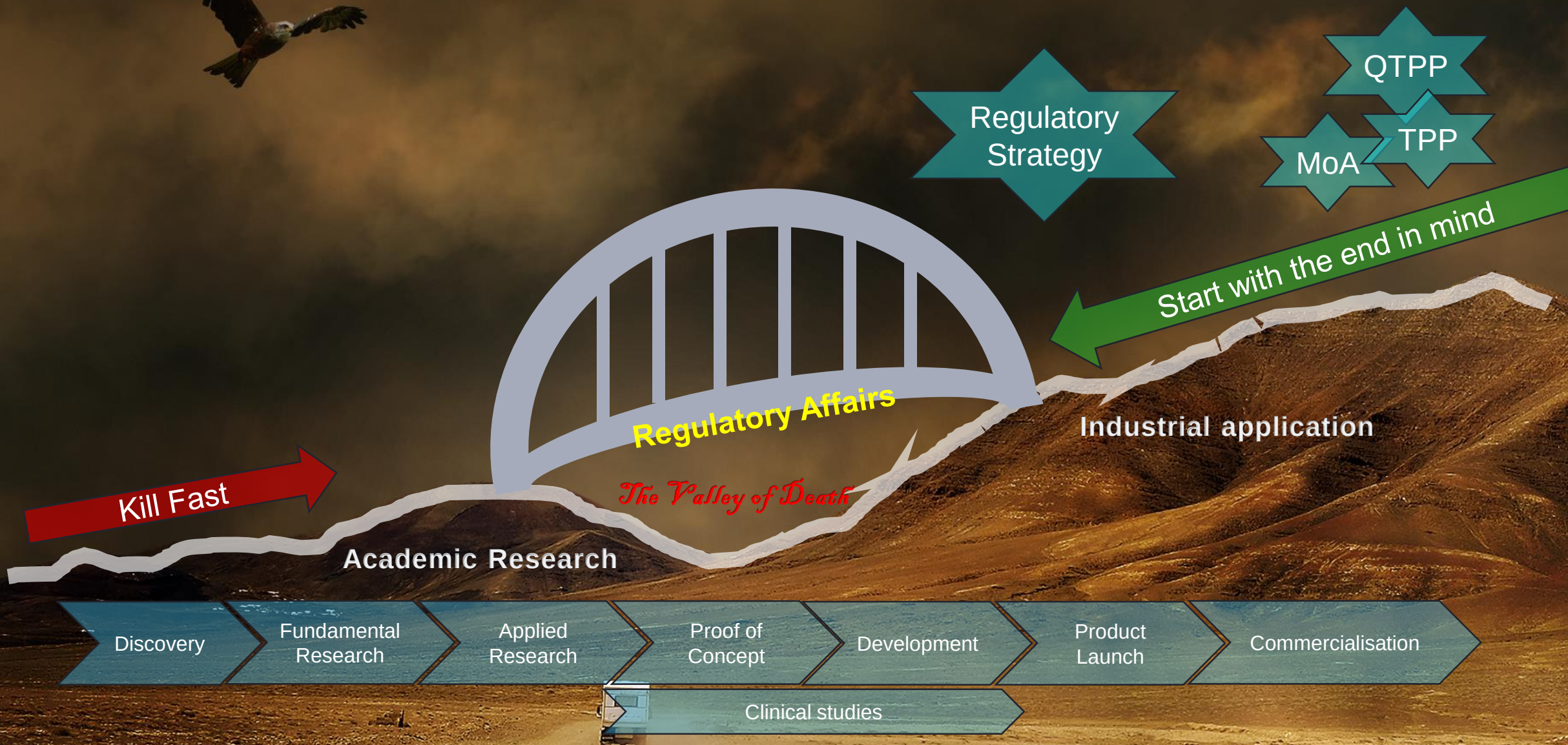
Sterility / Aseptic processing

Stability

Process Validation

Risk Based Approach

- Dir 2009/120/EC to enable a control strategy to adequately manage the risks of the product/manufacturing process (Marketing Authorisation & Clinical Trials)
- Prospectively planned strategy to justify the need for data in the MAA, proportionate requirements based on risk)
- How to do the risk/risk factor profiling?
- more flexible -less quality centred -include non-clinical and clinical considerations –risk mitigation measures
- GMP guide does not exclude tools for Quality risk management
- Seek for HA interactions during development





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Thank You

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