Good Manufacturing Practice for Clinical Trial of New Anticancer Drugs (Conventional vs New Generation Dosage Form, i.e Stem Cell-Based)

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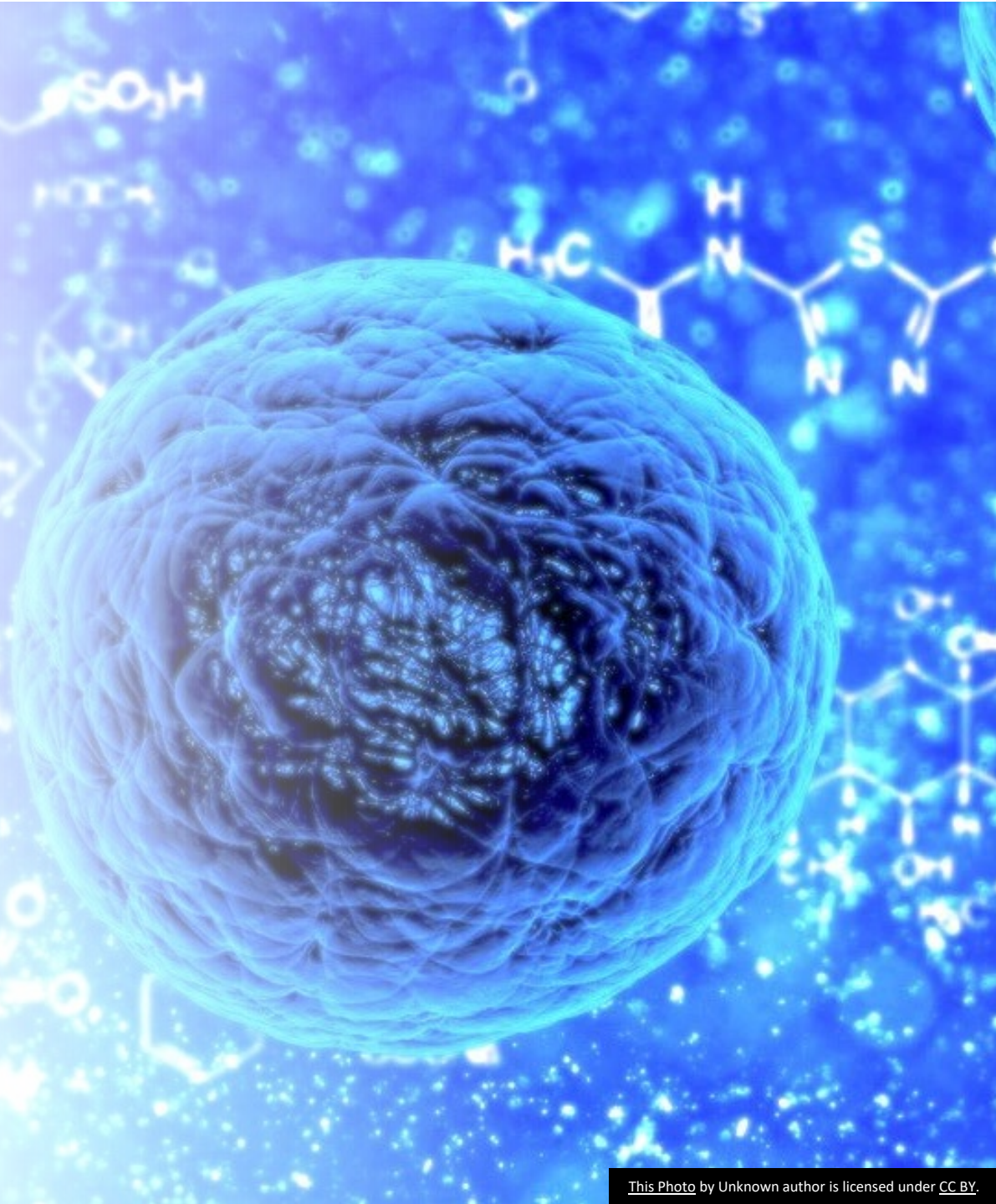
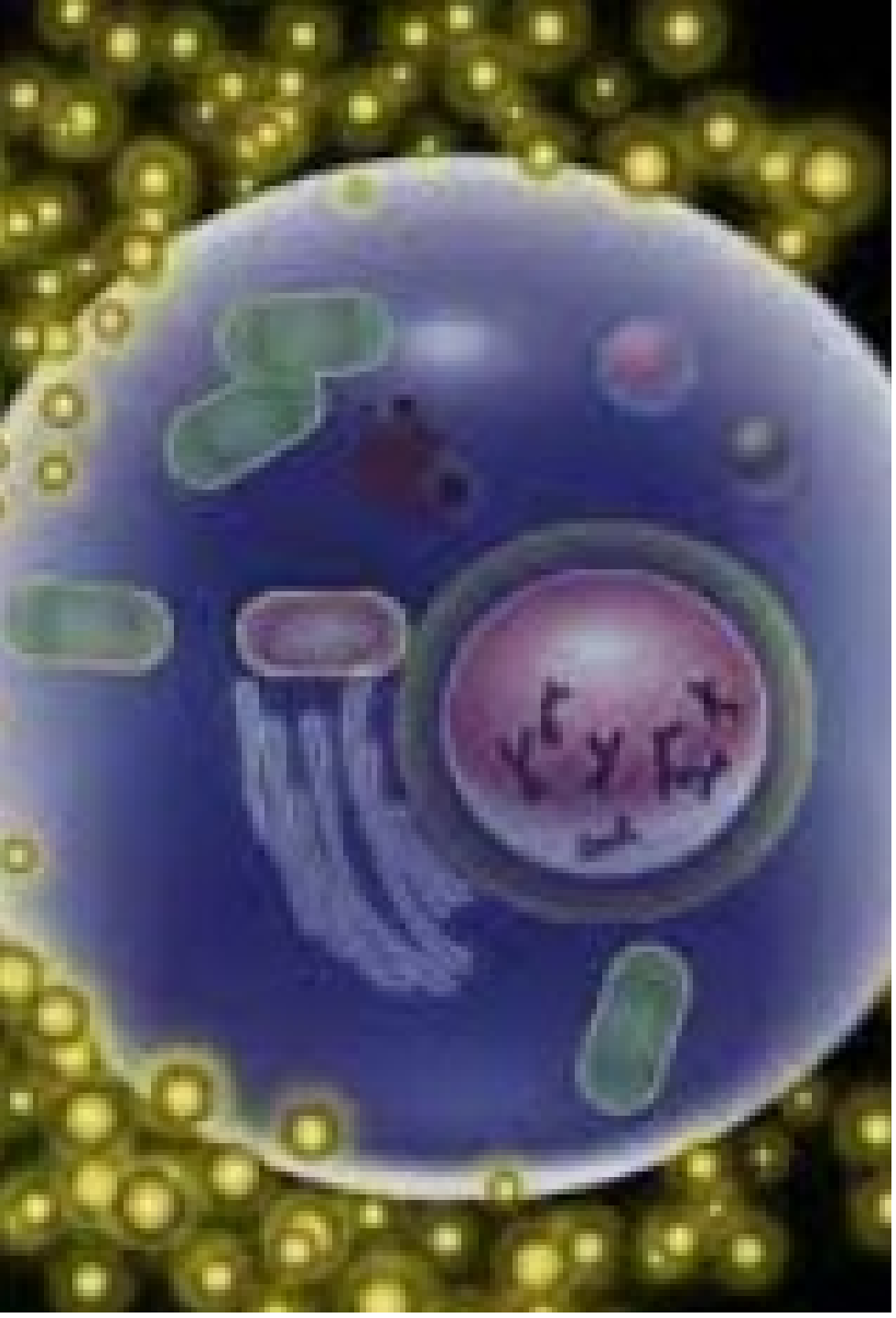




OUTLINE

Introduction

- Conventional Dosage Form
- Next Generation Dosage Form: Advanced Therapy Medicinal Product (ATMP)
- Drug R&D timeline

Introduction to Good Manufacturing Practice

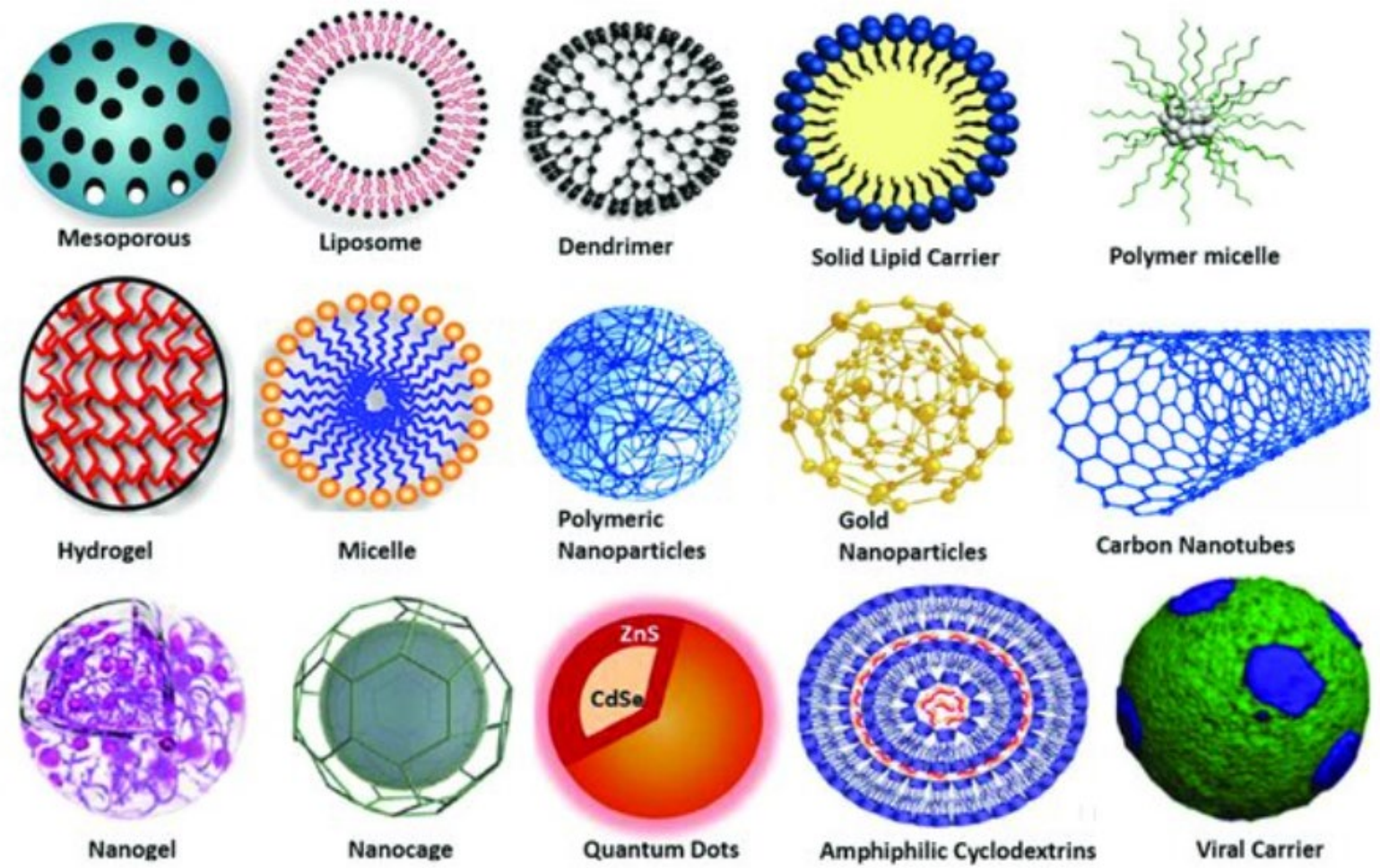
- Conventional vs ATMPs

Summary

Introduction – Conventional Dosage Form

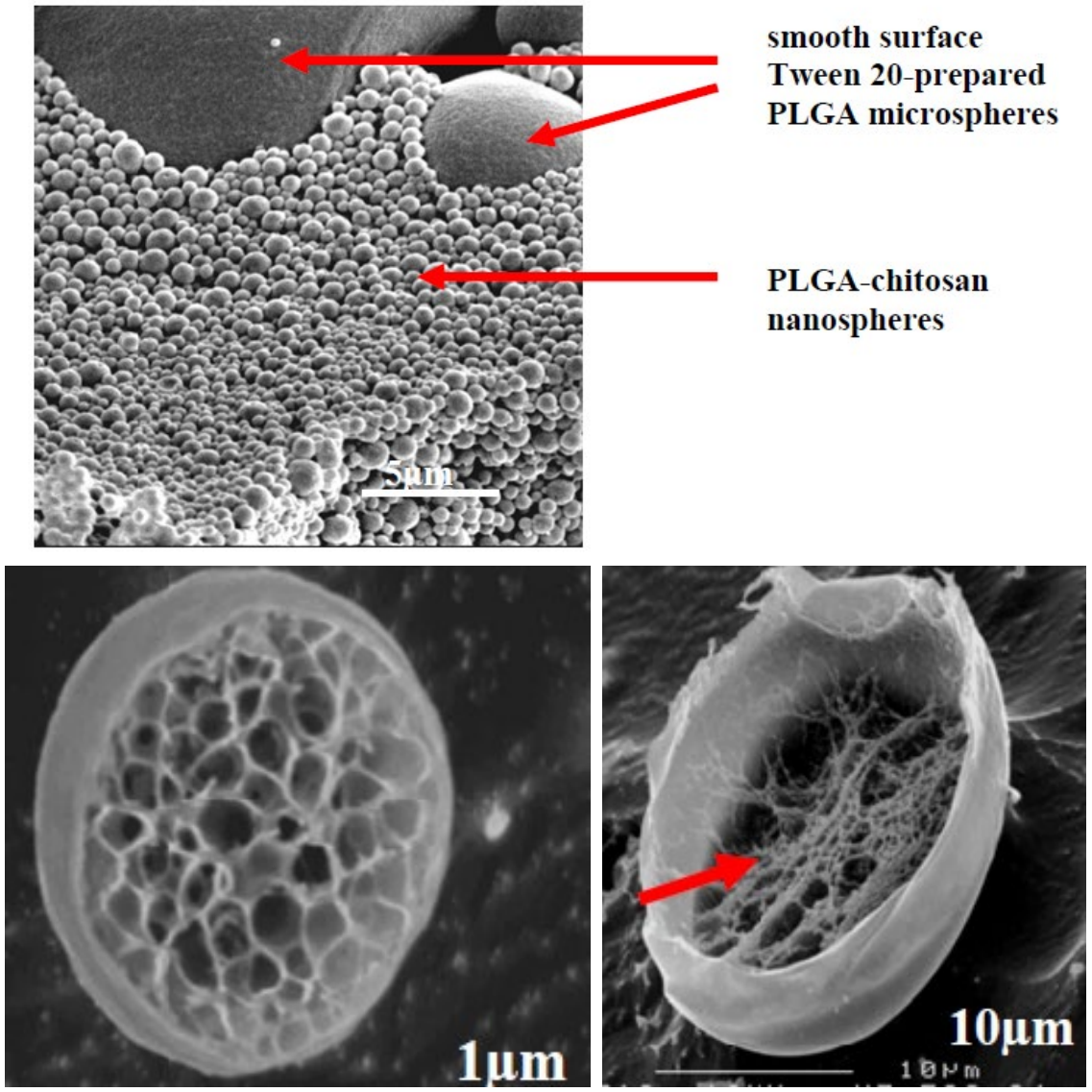
- Chemical or herbal-based, usually a single compound
- Non-sterile & sterile manufacturing condition
- Common product specifications according to dosage form (tablet, capsule, syrup, suspension, ointment, lotion, cream, capsule)

Introduction – Next Generation Dosage Form (NGDF)



Asim Ali Yaacob et al. 2020

Introduction – NGDF for Advanced Therapy Medicinal Products



Introduction

Advanced Therapy Medicinal Products (ATMPs) are innovative and complex

- Stem cells for cancer or for regenerative medicines

Pose challenges to the DESIGN and CONDUCT of clinical trials

- Manufacturing constraint (new design of GMP facility, huge investment, shelf-life, tight control on logistic)
- Difficulty in designing placebo, long-term follow-up, not always feasible to provide pre-clinical data

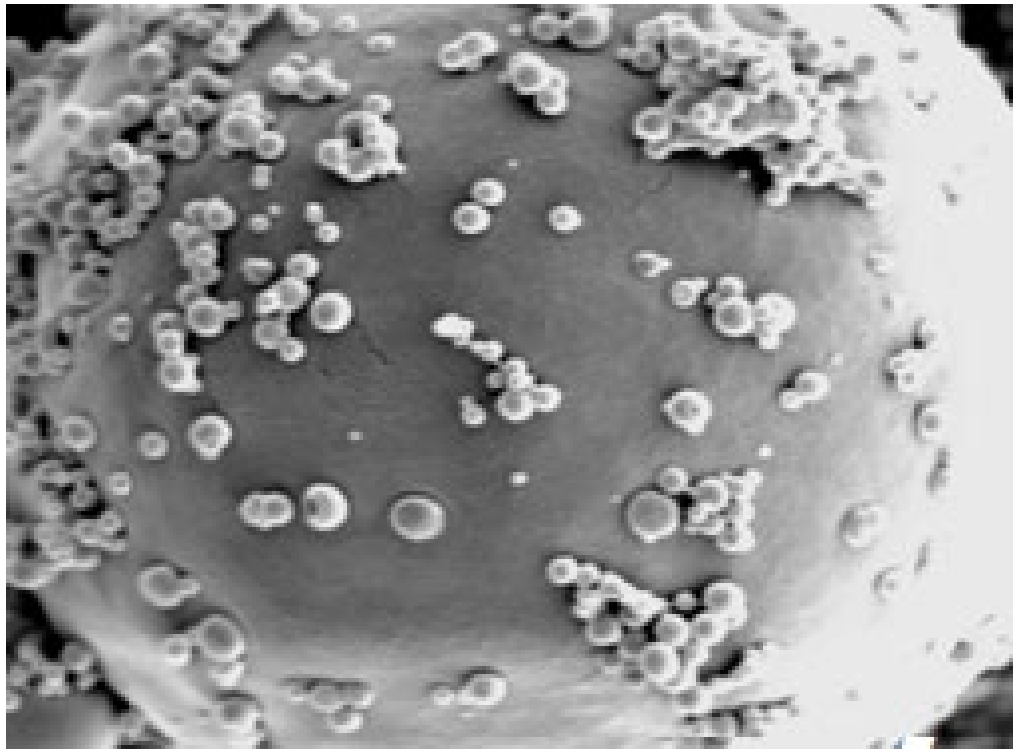
Introduction

4 classes of ATMP

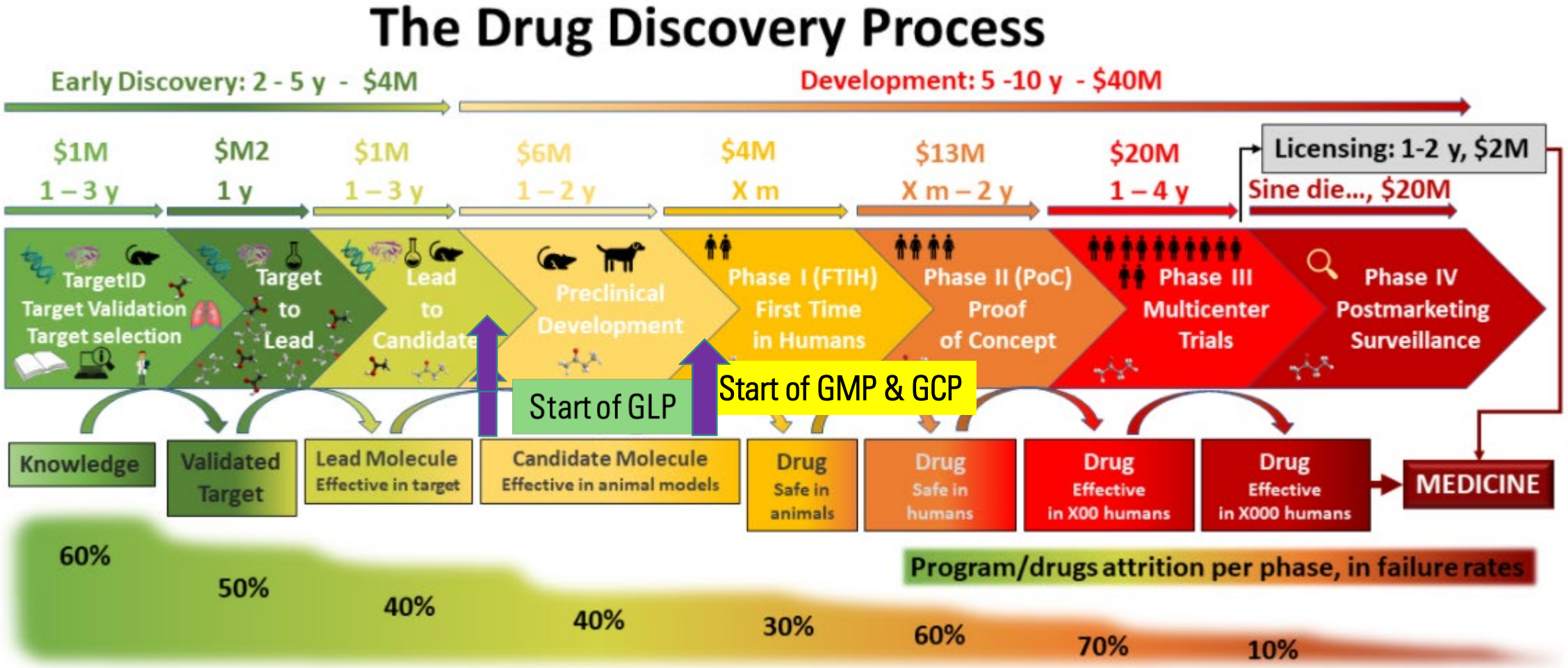
- Gene-Therapy Medicinal Products (GTMPs)
- Somatic Cell Therapy Medicinal Products (sCTMPs)
- Tissue-Engineered Products (TEPs)
- Combined ATMPs

Introduction – ATMP for cancer

- Gene-Therapy Medicinal Products (GTMP)
  - Gene silencing
  - Anti-sense therapy
  - RNA interference
  - Gene and genome editing
  - Somatic gene therapy
- Somatic Cell Therapy Medicinal Products (sCTMPs)

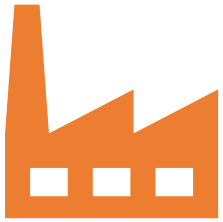


DRUG R&D TIMELINE



https://doctortarget.com/machine-learning-applied-drug-discovery/

Introduction



Good Manufacturing Practice (GMP)

Good Clinical Practice (GCP)

Good Laboratory Practice (GLP)

Introduction to Good Manufacturing Practice (GMP)

Is a concept that ensures product are consistently manufactured based on a controlled procedures under a controlled environment to yield consistent product quality based on appropriate quality standards

Source of References:

PIC/S
ICH Guidelines
ISPE Good Engineering Practice
US cGMP Guideline
EU GMP Guideline
Etc

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Pharmaceutical Inspection Co-operation Scheme

Leading the international development, implementation and maintenance of harmonised GMP standards and quality systems of Inspectorates in the field of medicinal products

About

PIC/S is the abbreviation and logo used to describe both the Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Inspection Co-operation Scheme (PIC Scheme) operating together in parallel.

PIC/S Committee Meeting, November 2019

11 - 12 November 2019

PIC/S Committee meeting which took place in Toyama (Japan), on 11-12 November 2019, hosted by Japan / MHLW & PMDA.

› more

All PIC/S documents publically available are listed below and appear in alphabetical order. Protected documents are for PIC/S Members-only and require a login.

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PIC/S GMP GUIDE (PART I: BASIC REQUIREMENTS FOR MEDICINAL PRODUCTS)	PE 009-15 (Part I)	Documents for Industry	PIC/S GMP Guide
PIC/S GMP GUIDE (PART II: BASIC REQUIREMENTS FOR ACTIVE PHARMACEUTICAL INGREDIENTS)	PE 009-15 (Part II)	Documents for Industry	PIC/S GMP Guide
PIC/S GMP GUIDE (RELATED ANNEXES)	PE 009-15 (Annexes)	Documents for Industry	PIC/S GMP Guide
PIC/S GMP GUIDE (ZIP)	PE 009-15	Documents for Industry	PIC/S GMP Guide

GMP Scopes

QUALITY CONTROL

PRODUCTION

ENGINEERING

QUALITY ASSURANCE

GMP- Quality Control

- Conduct testings on:
  - raw materials
  - packaging materials
  - finished product
  - water for manufacturing
  - air quality inside the plant

GMP- Production

+ Manufacture products according to an approved process
+ Conduct in-process quality control (IPQC) testing

GMP- Engineering

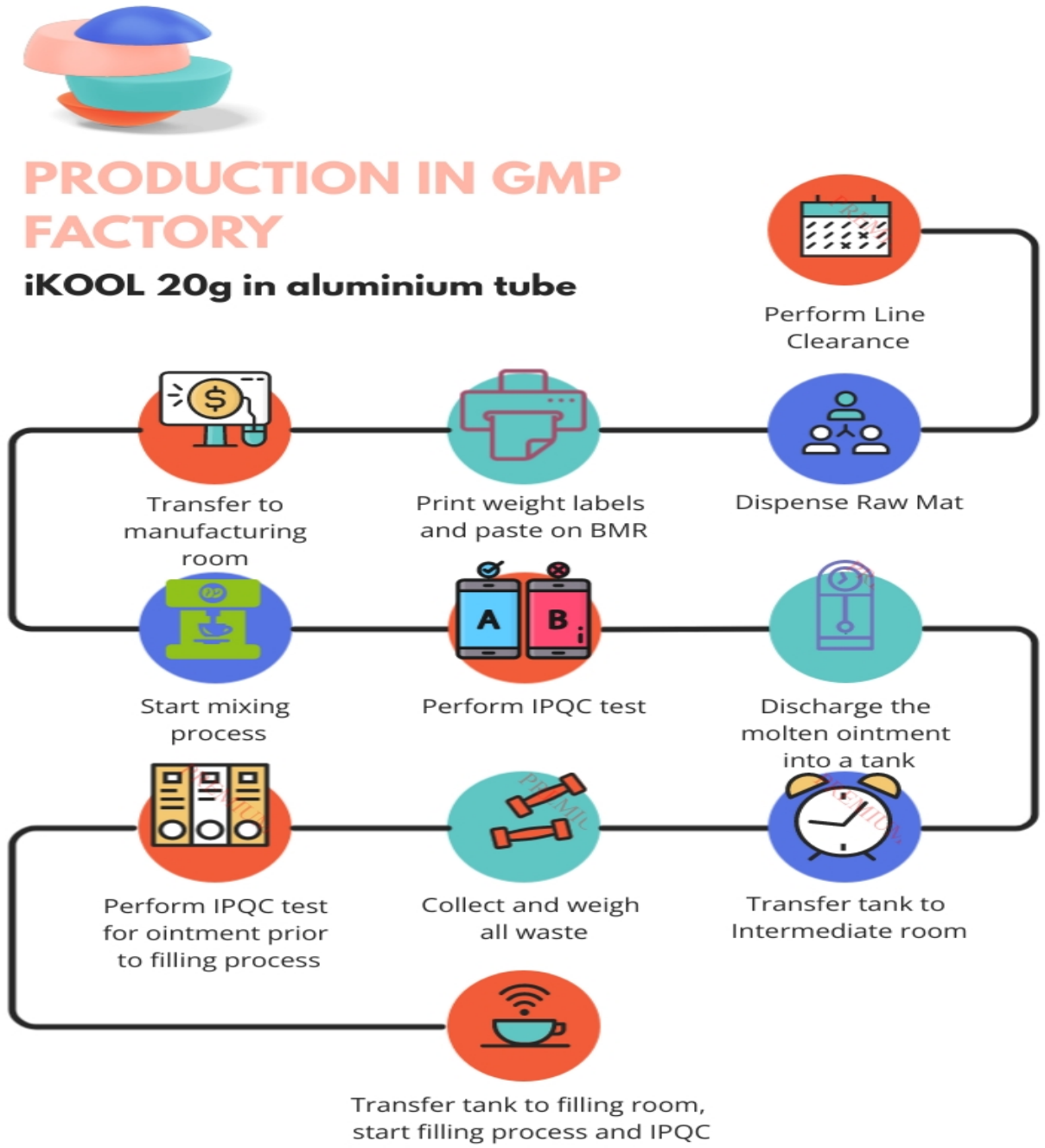
- Monitor quality of utilities:
  - Water Purification System
  - HVAC System – heating, ventilating & air-conditioning
- Monitor quality and status of production equipment
  - Calibration
  - Breakdown

GMP- Quality Assurance

- Managing Risk
  - Quality Risk Management
- Documentation
- Regulatory requirement
  - Product registration
  - Product complaint
- Personnel competency

Quality Control for in-coming materials (ikool™ as case example)

PRODUCTION PROCESS BASED ON APPROVED BMR AND BPR



QC TESTING FOR FINISHED PRODUCT

Assay of active ingredients

5 APIs

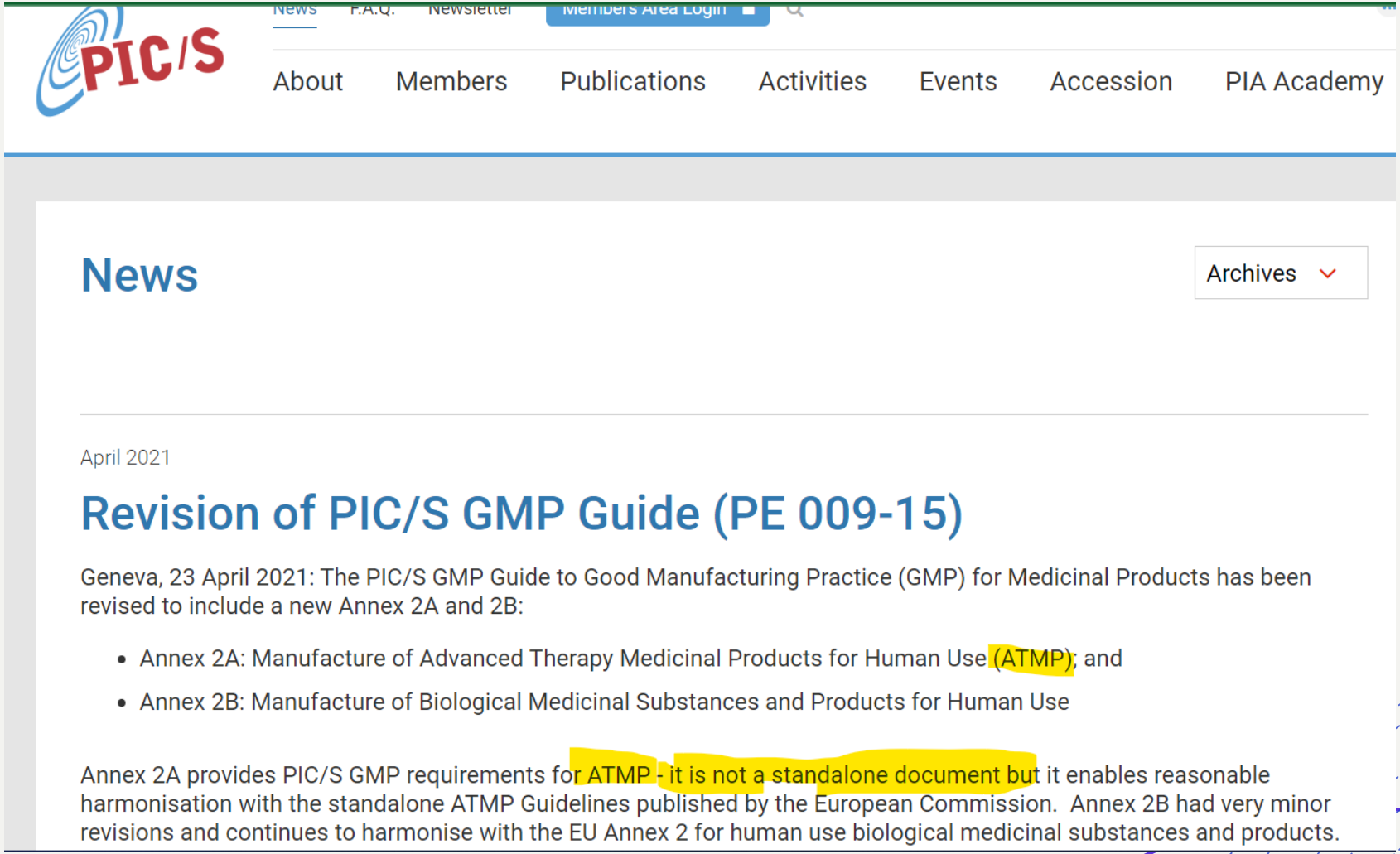
Microbial Limit test

TAMC
TYMC
S.aureus
E.coli

Minimum Fill weight

GMP for Advanced Therapy Medicinal Product (ATMP)

GMP for Advanced Therapy Medicinal Product (ATMP)



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April 2021

Revision of PIC/S GMP Guide (PE 009-15)

Geneva, 23 April 2021: The PIC/S GMP Guide to Good Manufacturing Practice (GMP) for Medicinal Products has been revised to include a new Annex 2A and 2B:

- Annex 2A: Manufacture of Advanced Therapy Medicinal Products for Human Use (ATMP); and
- Annex 2B: Manufacture of Biological Medicinal Substances and Products for Human Use

Annex 2A provides PIC/S GMP requirements for ATMP - it is not a standalone document but it enables reasonable harmonisation with the standalone ATMP Guidelines published by the European Commission. Annex 2B had very minor revisions and continues to harmonise with the EU Annex 2 for human use biological medicinal substances and products.

PIC/S GMP Guide - revised

PIC/S GMP GUIDE (INTRODUCTION)	PE 009-16 (Intro)	Documents for Industry	PIC/S GMP Guide
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Annex 2A- Manufacture of Advanced Therapy Medicinal Products (ATMP) for Human Use

Annex 2A- Manufacture of Advanced Therapy Medicinal Products (ATMP) for Human Use

GMP requirement is based on manufacturing method of ATMPs manufacture.

For example, for gene therapy ATMPs, genetic modifications can be obtained through a variety of methods (e.g. viral & non-viral vectors, mRNA, ex vivo and in vivo genome-editing tools).

Annex 2A- Manufacture of Advanced Therapy Medicinal Products (ATMP) for Human Use

The genetically modified cells can be of human origin (autologous or allogeneic) or of animal origin (xenogeneic cells), either primary or established cell lines.

In a medicinal product, the genetically modified cells or gene therapy products can be presented alone or combined with medical devices.

Appropriate application of Annex 2A

Example Products	Application of this Annex			
Gene therapy: mRNA	Linear DNA template preparation	In vitro cell free transcription	mRNA purification	Formulation & filling
Gene therapy: in vivo viral vectors	Plasmid manufacturing	Establishment of MCB and WCB	Vector manufacturing and purification	Formulation & filling
Gene therapy: in vivo non-viral vectors (naked DNA, lipoplexes, polyplexes etc.	Plasmid manufacturing	Establishment of bacterial bank	Fermentation and purification	Formulation & filling
Gene therapy: ex-vivo genetically modified cells	Donation, procurement and testing of starting tissue/cells	Plasmid manufacturing	Ex-vivo genetic modification of cells	Formulation & filling
		Vector manufacturing		Formulation & filling
Somatic cell therapy	Donation, procurement and testing of starting tissue/cells	Establishment of MBC and WBC or primary cell lot or cell proof	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination and filling
Tissue-engineered products	Donation, procurement and testing of starting tissue/cells	Initial processing, isolation and purification, establish MCB, WBC, primary cell lot or cell pool	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination and filling

Example of Approved sCTMP for cancer

- PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.
- Each dose of PROVENGE contains a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF
- The recommended course of therapy for PROVENGE is 3 complete doses, given at approximately 2-week intervals.
- PROVENGE is designed to stimulate the immune system

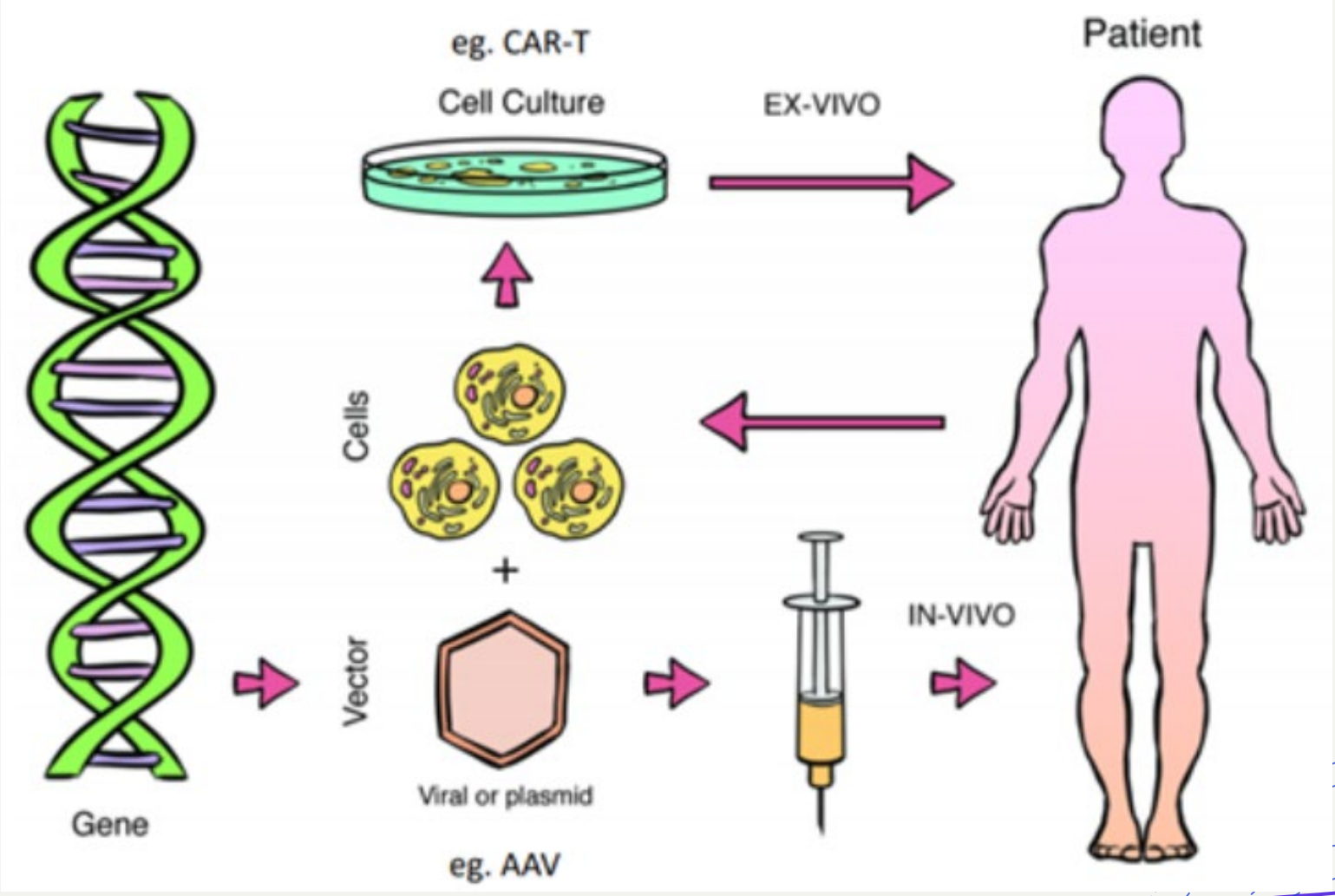
Example of Approved sCTMP for cancer

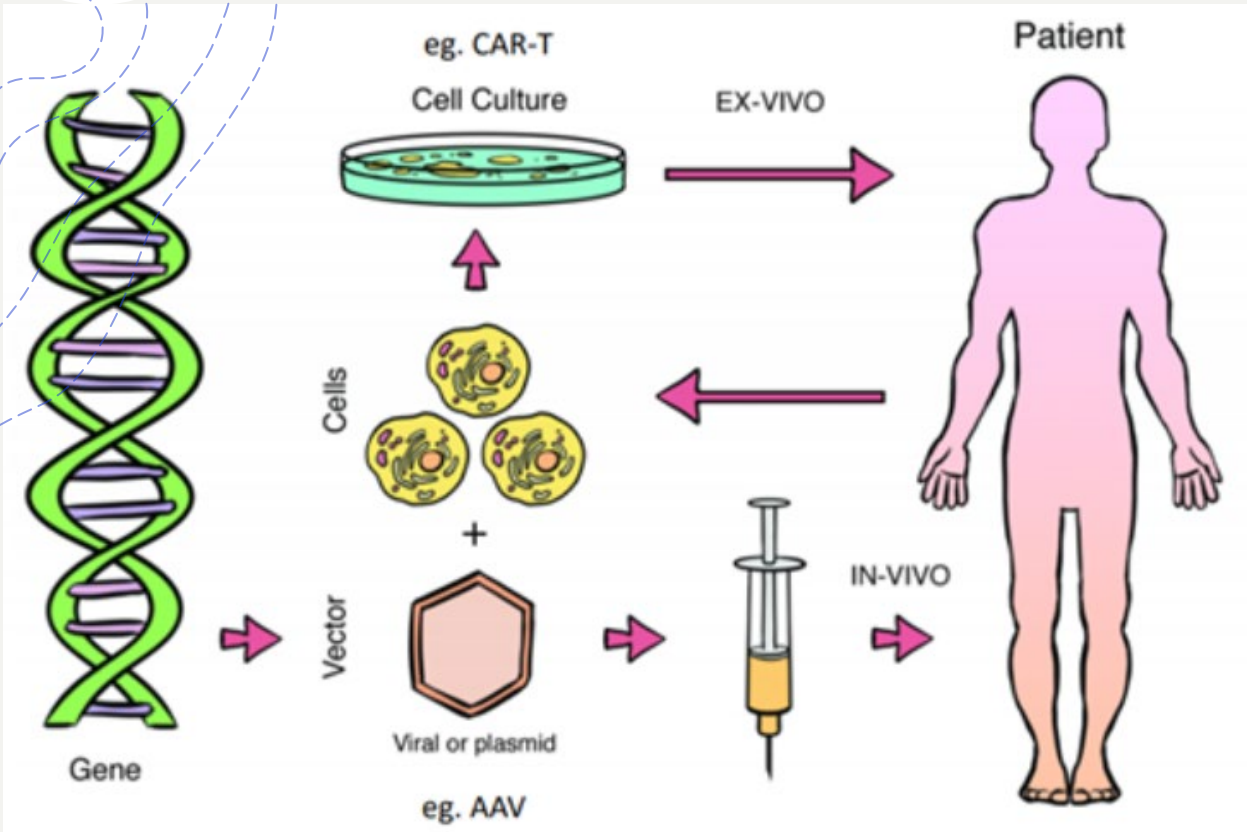
- Confirm Patient Identity - PROVENGE is intended solely for autologous use.
- Confirm the proper product has been received according to the label on the outside of the insulated polyurethane container.
- Prior to PROVENGE infusion, match the patient's identity with the patient identifiers on the Cell Product Disposition Form and the PROVENGE infusion bag.

Example of Approved sCTMP for cancer

- Confirm Product Release - Do not infuse PROVENGE until confirmation of product release has been received from Dendreon (GMP manufacturer of Provenge)
- Dendreon will send a Cell Product Disposition Form containing the patient identifiers, expiration date and time, and the disposition status (approved for infusion or rejected), to the infusion site.

Simplified Manufacturing Process Flow for ATMP





Manufacturing steps requiring GMP status for Gene therapy

Plasmid manufacturing	Establishment of MCB and WCB	Vector manufacturing and purification	Formulation & filling

Quality Control for ATMPs

+ ATMPs manufactured for exploratory, early phase clinical trials (phase I and phase I/II), are expected to be validated proportionately with the knowledge and the risk associated with the respective phase.
+ All aseptic and sterilisation processes as well as virus inactivation or removal for investigational and authorised ATMPs are expected to be validated.
+ The effectiveness of disinfection methods should be proven.

SUMMARY – GMP for conventional medicines vs ATMPs

5Ps of GMP – applicable for both

People
Comprehend role and responsibilities

Process
Properly documented simple, and consistent

Premise
Cleanliness and equipment well-maintained

Procedures
Guidelines for undertaking critical processes

Products
Clear specification at every stage of production