Australian Government
Department of Health
Therapeutic Goods Administration

GMP for new and emerging technologies: Advanced Therapy Medicinal Products (ATMPs)

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TGA GMP^2 Forum Melbourne, November 2019

TGA Health Safety Regulation

Australian Government
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What we will discuss:

- GMP inspections for ATMPs
- Overview of current GMP codes across the world
- The journey of Annex 2 revision
- Questions of particular interests
- Different pathways to harmonisation
- What’s coming next

Inspections of manufacturing site ATMP and traditional biotech

ATMP

Biotech

Current GMP codes for ATMP - major markets

- 21 CFR part 211 (phase 1 investigational drugs exempt under 21 CFR 210.2(c))
- Guidelines on Good Manufacturing Practice specific to advanced therapy medicinal products (ATMPs) (Eudralex part IV)
- PIC/S GMP Guide (PE 009-14)
- Regulation on Good Manufacturing Practices (GMP) for Medicinal Products & Guideline on Manufacture and Quality Control of Cell Therapy Products
- Good, gene, Cellular and Tissue-based product manufacturing Practice (GCTP) (regenerative medicine products)

The real issues in existing GMP codes for ATMPs:

- Implications of Point of care/Decentralised manufacturing
  - AP release/time to release
  - Processing environment
- Outsourcing to non GMP facilities
- PQR
- GMP boundaries between API/Critical Material/Finished Product
- Release of OOS product (making it available)
- Importance of chain of custody/chain of identity
- New technologies

PIC/S annex 2 revision

- Working Group established to **revise the Annex 2 (Manufacture of biological medicinal products for human use) of the Guide to Good Manufacturing Practice of Medicinal Products PE 009-14 (Annexes)**
- TGA (chair), WHO and EMA amongst participants
- Objectives:
  - The revision of the requirements for ATMPs will remain an integral part to the existing GMP guidelines and will not be a standalone code
  - The WG will draft a separate Annex specific to ATMP
  - Efforts will be made, with the aim at maintaining as close harmonisation as possible, to use the language of the "Guidelines on Good Manufacturing Practice (GMP) specific to Advanced Therapy Medicinal Products (ATMP)" where possible. PIC/S and WG represented stakeholder's concerns will guide the final language.
  - Efforts will be made to accommodate language that address challenges such as **"diffuse manufacturing"**
  - Efforts will be made to accommodate language that will permit the standard **to facilitate cross border movement of ATMP**. The standard will aim to be bridging across the expectations for these products through all jurisdictions, even the ones that will not formally adopt it

PIC/S annex 2 revision

News

Archives

September 2019

Focused stakeholders consultation on revised draft PIC/S GMP Guide Annex 2A (Manufacture of Advanced Therapy Medicinal Products for Human Use) and Annex 2B (Manufacture of Biological Medicinal Substances and Products for Human Use)

Geneva, 20 September 2019

A draft revision of the PIC/S GMP Guide Annex 2 (Manufacture of biological medicinal substances and products for human use) has been prepared by the PIC/S Working Group on revision of Annex 2 established with WHO, led by Francesco Cicirello, Australia / TGA, and by the PIC/S Sub-Committee on GMDP Harmonisation, led by Paul Gustafson, Health Canada.

This revision is subject to a focused stakeholder consultation which includes **both consultation questions and an opportunity to comment** on:

- **a draft Annex 2A** (PS/INF 25/2019 (Rev. 1)): Manufacture of Advanced Therapy Medicinal Products for Human Use; and
- **a draft Annex 2B** (PS/INF 26/2019 (Rev. 1)): Manufacture of Biological Medicinal Substances and Products for Human Use.

Vector manufacturing

Question #1: Scope of Guidance Document	
PIC/S Question	What are your views on ATMP guidance applying to the manufacture of ATMP products as described in the following illustrations (line 58 of the consultation document)? As an alternative, should plasmid manufacturing and/or virus manufacturing be in scope of this document, if yes in what form?

Illustration 2-1 Type and source of Material: Human and or animal sources

Example product	Application of this guide to manufacturing steps shown in grey			
Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells[1]	Vector manufacturing; cell isolation, culture and purification	Ex-vivo genetic modification of cells, Establishment of MCB, WCB or primary cell lot	Formulation, filling
Somatic cell therapy	Donation, procurement and testing of starting tissue / cells[1]	Establishent of MCB, WCB or primary cell lot or cell pool	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, fill
Tissue engineered products	Donation, procurement and testing of starting tissue / cells[1]	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, fill

Illustration 2-2 Type and source of Material: Non Human and/or animal sources

Gene Therapy: in Vivo Viral Vectors by stable producer cell lines	Plasmid manufacturing[1]	Producer cell lines manufacturing	Vector Manufacturing	Formulation, filling
Gene Therapy: in Vivo Viral Vectors by transient production system	Virus manufacturing[1]	Cell system manufacturing	Vector Manufacturing	Formulation, filling

[1] Separate GMP requirements may apply where required under national law.

Product quality review

Considering the **length of time** that some advanced therapy **investigational** medicinal products (ATIMP) could be in clinical trial phase; is there a need to **include** requirements to periodically perform a **Product Quality Review proportionate to the development stage**?

Less stringent processing environment?

What are your views on the expectation for the working environment requirements when processing is not performed in a closed system?

A less stringent environment may be acceptable where approved by the competent authority.

- Manufacturing alternatives do not exist or are not suitable
- The environment must be specified and justified
- It must be demonstrated that the chosen environment is suitable for maintaining critical quality and safety attributes

Equipment use when manufacturing extends into hospitals

Performing a manufacturing step in premises that are not under direct control of the MAH or Sponsor, (including for example placing equipment used to perform manufacturing steps in an hospital wards or theatre), is permissible provided that **the MAH or Sponsor demonstrates that the process maintains its validated status** utilising the provisions of Annex 15 and any derogation from the mandated standards are justified utilising QRM principles described Annex 20, and subject to approval by the competent authority.

Batch release when manufacturing extends into hospitals

Addressing batch release when certain steps of manufacturing are decentralized or occur at the point of care

The steps of the batch certification and release process should be laid down in a standard operating procedure (SOP). The following conditions need to be respected:

(a) A "responsible site", should be identified. The responsible site is responsible for the oversight of the decentralised sites. The responsible site:

i. must have availability of an Authorised Person,
ii. **those involved** in the batch certification and release process **are adequately qualified and trained** ,
iii. should **perform audits**
iv. must ensure that there are written arrangements to:
   - **timely report quality defects, deviations or non-conformity**
   - ensure deviations are investigated
   - **ensure deviations are approved** by a responsible person with **the involvement of the Authorised Person** as appropriate.

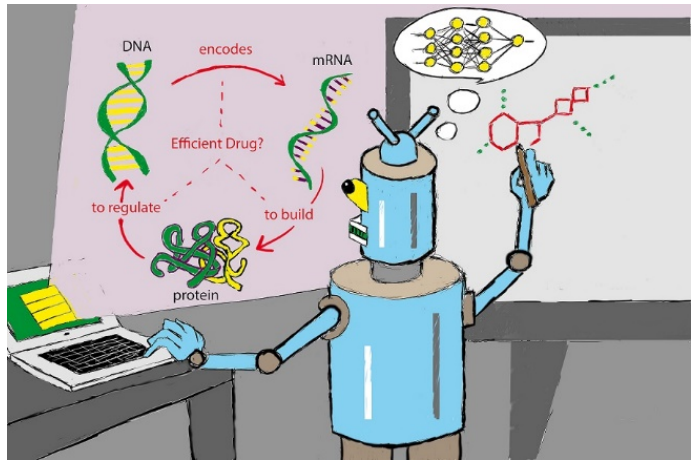
Batch release when manufacturing extends into hospitals (2)

i) The Authorised Person should have ultimate responsibility for the batch certification (responsibility cannot be delegated). **In certain exceptional cases the Authorised Person may delegate the release** to personnel at the decentralised site, under the following conditions:

i) There is a detailed algorithm that determines the cases when the product can be released without the preliminary approval of the Authorised Person, i **If technology permits this step can be performed by a validated computer system**;

ii) The Authorised Person **reviews all releases** that have occurred at the sites **to confirm the adequacy including:**

- **if any product needs to be recalled or going through hazard alert**
- **if any provision in the release procedure and /or technical agreement needs modification; and**
- **the product has not been released without Authorised Person authorisation when required.**



Batch release when product does not comply with specification

5.46 Where authorised by national law, the administration of a product that does not meet the release specification, might be performed in exceptional circumstances. **The responsibility and the decision of the patient treatment are solely on the treating physician and are beyond the remit of this GMP guide.**

Outsourcing to non GMP licensed third party in exceptional circumstances

Collection of **starting materials** and **highly specialised testing** in the jurisdictions that are subject to licensing(e.g. karyotype testing, exome sequencing) can be outsourced to non GMP licensed third party, as allowed by national law, provided that:

a) **There is a rationale and a justification in the quality system**

b) **The contract giver takes responsibility** to ensure that the contract acceptor demonstrates an appropriate level of GMP commensurate to the risk to the product and the activity/ies performed using the principles of Annex 20

c) **That proportionate qualifications/validations as appropriate are conducted** (with reference to Annex 15 and Annex 20) to demonstrate that the activity/ies is **not detrimental** to the quality of the product manufactured

Press release: PIC/S meetings in Geneva (Switzerland)

From 8 to 10 April 2019, the following meetings took place in Geneva (Switzerland): PIC/S Committee and PIC/S Executive Bureau.

A new Working Group for the development of a **PIC/S Aide Memoire on Tissues and Cellular Therapy Products Inspections** was established. This future Aide Memoire is intended for inspection of minimally manipulated human tissues and cells for human applications (ATMPs will not be within its scope).

PIC/S Involvement in the ICH GMP Guide on APIs

- PIC/S Involvement in the ICH GMP Guide on APIs

PIC/S Conference in Canberra 1996:
- consensus obtained to prepare international GMP.

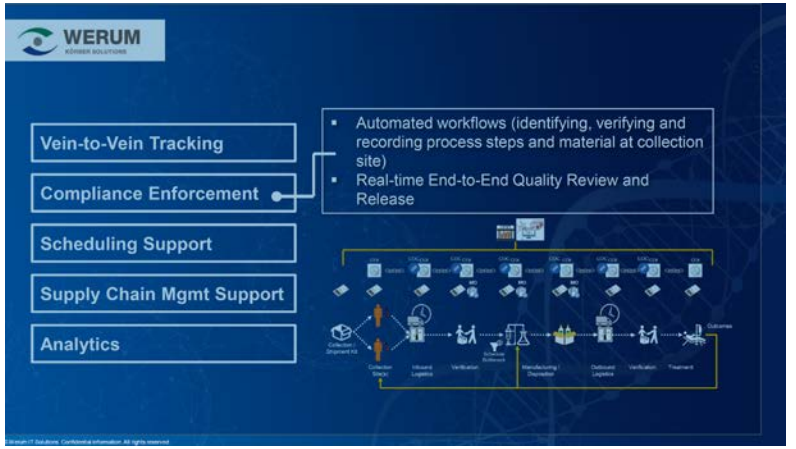
PIC/S draft document prepared during ‘97 & ‘98.

ICH Q7 took over the work of PIC/S mid-1998 to enable industry to become involved

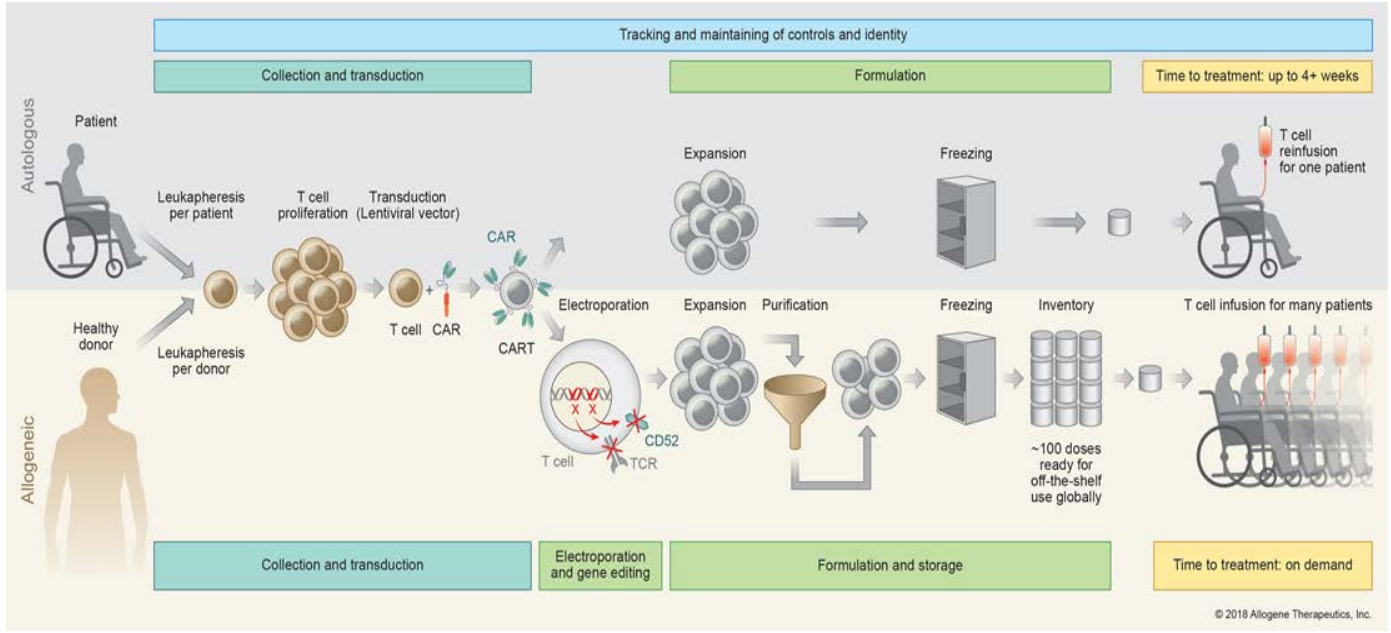
Most countries have adopted ICH document as a GMP requirement for APIs by 1st April 2001 (EU)

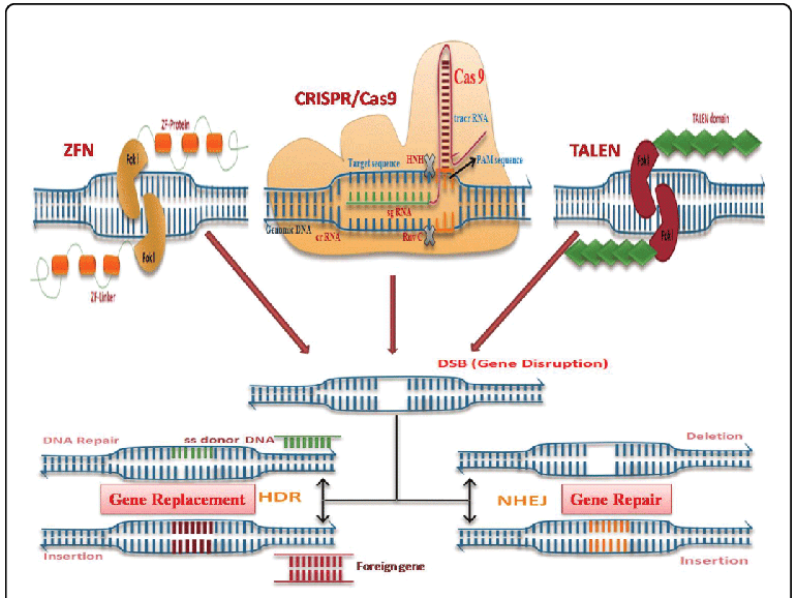
ICH document became Part II of PIC/S GMP Guide in 2007

What is coming next


WERUM
Vein-to-Vein Tracking
Compliance Enforcement
Scheduling Support
Supply Chain Mgmt Support
Analytics
Automated workflows (identifying, verifying and recording process steps and material at collection site)
Real-time End-to-End Quality Review and Release


TERUMOBCT
FINIA


Tracking and maintaining of controls and identity
Collection and transduction
Formulation
Time to treatment: up to 4+ weeks
Autologous
Patient
Leukapheresis per patient
T cell proliferation
Transduction (Lentiviral vector)
T cell
CAR
CAR
CART
Expansion
Freezing
T cell reinfusion for one patient
Healthy donor
Leukapheresis per donor
Electroporation
Expansion
Purification
Freezing
Inventory
T cell infusion for many patients
CD52
T cell
TCR
~100 doses ready for off-the-shelf use globally
Allogeneic
Collection and transduction
Electroporation and gene editing
Formulation and storage
Time to treatment: on demand
© 2018 Allogene Therapeutics, Inc.


ZFN
CRISPR/Cas9
TALEN
Cas 9
DSB (Gene Disruption)
DNA Repair
ss donor DNA
Gene Replacement
HDR
NHEJ
Gene Repair
Deletion
Insertion
Foreign gene
Insertion

Questions

Question 1

- **Do you support handing over at some point Annex 2A to ICH as a way to achieve harmonization?**

Question 2

- **Do you think that equipment such as the one showed in the presentation, if demonstrated that it is closed, should be treated as an isolator (Grade D processing background)?**

Questions

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