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PHARMACEUTICAL COMPANIES
OF *Johnson & Johnson*



ATMP (CAR-T) release stories

Janssen Research & Development

Quality Assurance Clinical Supply chain – Elly Van Dun

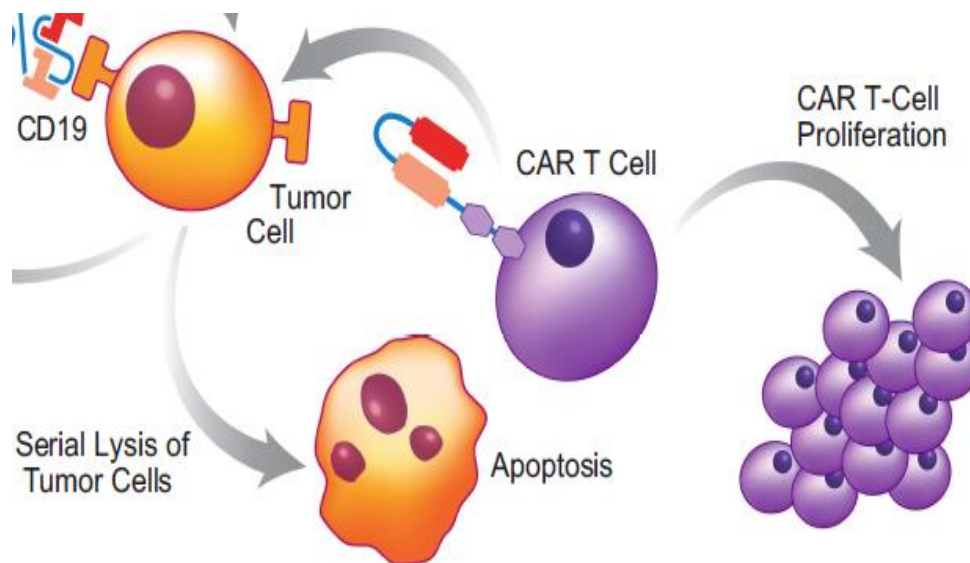


Agenda

- Introduction to Janssen CAR-T
- Status of the clinical trials
- Supply Chain overview
- QA and QP challenges

What is CAR-T

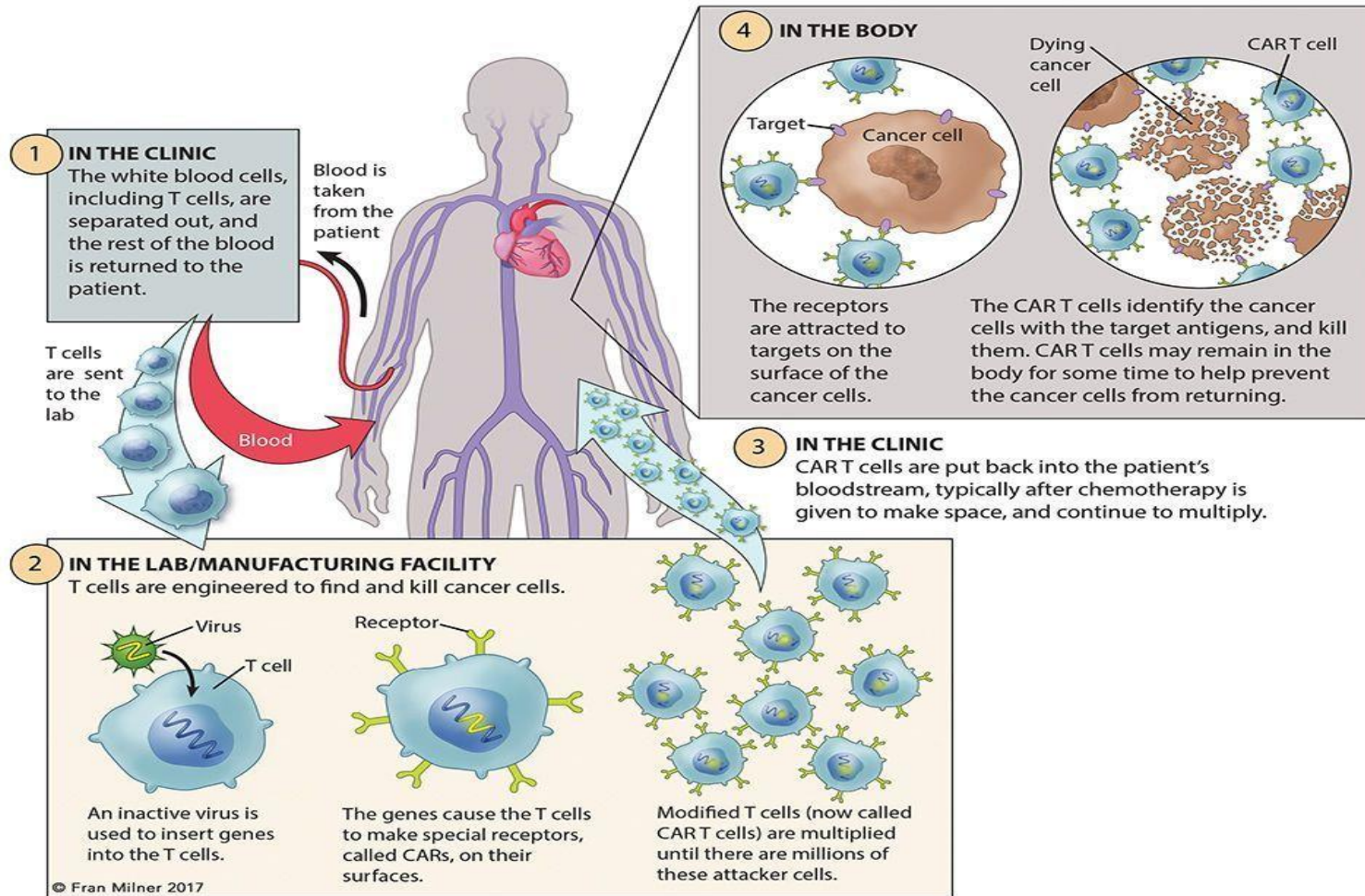
- Genetically engineered Chimeric Antigen Receptor (CAR) expressing T-Cells
- Concept introduced in 1989
- Cancer - Immunotherapy



1st Janssen CAR-T compound

- Partner: Legend Biotech (Nanjing, China)
 - Collaboration and License agreement
 - Indication: Multiple Myeloma
 - Ccompound: JNJ-68284528 - (BCMA*) CAR-T for Autologous use**
 - Clinical Trials:
 - Legend phase 1: 74 patients dosed. Completed
 - Legend China: ongoing
 - Janssen US Ph1b/2: started Aug 2018
 - Janssen EU will start Jan-2020
-
- **B-Cell Maturation Antigen (highly produced by tumor cells)*
 - ** *Involving one individual as donor and recipient*

Chimeric Antigen Receptor (CAR) T-Cell Therapy



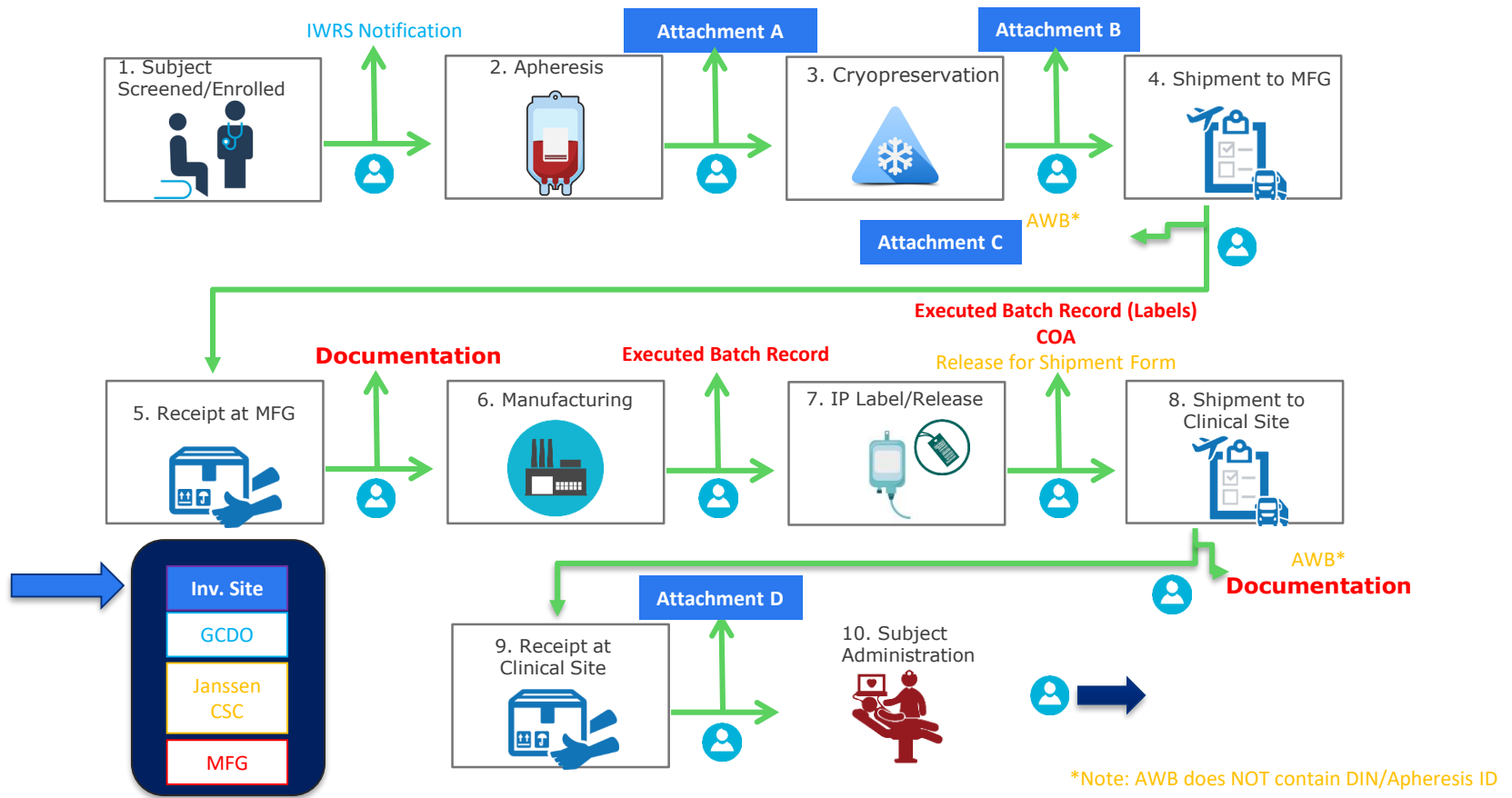
Chain of Identity/Chain of Custody (CoI/CoC)

- Chain of identity (CoI) for autologous cells ensures collection of apheresis material used in investigational product (IP) manufacturing is administered back to the same subject
- Chain of Custody is the permanent data capture from the start of tissue and/or cell collection through to product administration. The data identifies the staff that handled the product, actions performed by those staff, and the location/date/time of those actions.

COI/COC Tracking

- Throughout the CoI process for each subject, Janssen CSC will track two unique identifying elements at each step:
 - A distinct donation identification number (DIN) or apheresis identification (ID) number assigned to the product by the clinical site at the point of collection from the subject
 - A subject number assigned to the subject by the clinical site via interactive web response system (IWRS)
- Conditions of storage, handling and shipment will constitute the CoC.

CAR-T COC/COI Management Flow



Regulatory Framework

- For various steps in the supply chain, various legislation and guidelines are applicable:
 - GTP: Good Tissue Practices
 - GCP: Good Clinical Practices
 - GMP: Good Manufacturing Practices
 - GDP: Good Distribution Practices for distribution sites
 - GMO: Genetically Modified Organisms
 - Blood & Blood Products

Collection sites

- Audits and Quality Agreements with Collection sites
- Apheresis Product is considered a starting Material
 - Specifications are required for clinical manufacturing
- Collection sites:
 - FACT accreditation (US)
 - JACIE The Joint Accreditation Committee ISCT-Europe & EBMT (EU)
- Institution shall use
 - DIN: Donation Identification Number (US)
 - SEC-DIS/PIS: Single European Code- Donation Identification Code/Product Identification Code (EU)
- EU ATMP guidelines
 - 7.22 The donation, procurement and testing of human tissues and cells used as starting materials should be in accordance with Directive 2004/23/EC. For blood-derived cells, compliance with Directive 2002/98/EC regarding donation, procurement and testing is likewise acceptable. The accreditation, designation, authorisation or licensing of the supplier of starting materials as provided for under the legislation above-referred should be verified.

Cryopreservation lab

- MIA needed
- Manufacturing Operations
 - 1.3 Biological Medicinal Products
 - 1,3,1,1 Blood Products
 - 1,3,2 Batch Certification
 - 1,3,2,1 Blood Products
- Audit and Quality Agreement required

Manufacturing site: EU Regulation

1. Guideline Overview

Part I: Basic Requirements for Medicinal Products

Part II: Basic Requirements for Active Substances used as Starting Materials (APIs)

Part III: GMP related documents

- SMF
- ICH Q10 (PQS)
- ICH Q9 (QRM)
- MRA Batch Certificate
- Written Confirmation
- EMA Guideline (Shared Facilities)
- EMA-Guideline (Excipients)

Annexes 1-19 (products specific)

Glossary

Part IV: GMP Requirements for ATMPs

Other documents related to GMP

- Compilation of Community Procedures
- EU-GDP Guideline (medicinal products)
- EU-GDP API Guideline

PUBLIC HEALTH

European Commission > DG Health and Food Safety > Public Health > Vol 4: GMP Human & Veterinary

VOL 4: GMP HUMAN & VETERINARY

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively.

Introduction

- Introduction (07/02/2011)
- Commission Directive 2003/94/EC, of 9 October 2003, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Replacement of Commission Directive 91/356/EEC of 13 June 1991 to cover good manufacturing practice of investigational medicinal products.
- Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products.

Part I - Basic Requirements for Medicinal Products

- Chapter 1 - Pharmaceutical Quality System (into operation since 31 January 2013)
- Chapter 2 - Personnel (into operation since 16 February 2014)
- Chapter 3 - Premises and Equipment (into operation since 1 March 2015)
 - See transitional arrangement for toxicological evaluation on page 1 of Chapter 3
 - Previous version
- Chapter 4 - Documentation (January 2011)
- Chapter 5 - Production (into operation since 1 March 2015)
 - See transitional arrangement for toxicological evaluation on pages 1-2 of Chapter 5
 - Previous version
- Chapter 6 - Quality Control (into operation since 1 October 2014)
- Chapter 7 - Outsourced activities (into operation since 31 January 2013)
- Chapter 8 - Complaints and Product Recall (into operation since 1 March 2015)
- Chapter 9 - Self Inspection

Part II - Basic Requirements for Active Substances used as Starting Materials

- Basic requirements for active substances used as starting materials (August 2014)

Part III - GMP related documents

- Site Master File
- Q9 Quality Risk Management
- Q10 Note for Guidance on Pharmaceutical Quality System
- MRA Batch Certificate
- Template for the "written confirmation" for active substances exported to the European Union for medicinal products for human use (Version 2, January 2013)
- Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities
- Guidelines of 19 March 2015 on the formalized risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use (all language versions are available here). A risk assessment as set out in these guidelines should be carried out for excipients for authorised medicinal products for human use by 21 March 2016.

Annexes

Import and QP Certification

- 11.2 Qualified Person
 - QP-qualification acc. Directive 2001/83/EC Art. 49
 - Additional detailed product- & process-specific training & expertise including
 - Cell- & tissue-biology
 - Biotechnological techniques
 - Cell-processing, -characterization & „*potency testing*“
- 11.13. The QP has to verify and certify that each batch produced in the EU has been manufactured and checked in accordance with:
 - (i) the requirements of the marketing authorisation/clinical trial authorization
 - (ii) relevant regulations governing the manufacture of medicinal products, including GMP, and
 - (iii) relevant product specifications in the destination country (in the case of exports).
- 11.19 Conditions of storage and transport have to be checked before certifying any batch.

Handling of unplanned deviations

- Certification & release with unplanned Deviations
 - Presupposition:
 - Compliance with final product specification
 - Deviation related to manufacturing-process or QC-method
 - Deviation „unexpected“ - „unplanned“
 - In-deep assessment conc.
 - Impact on quality, safety & efficacy
 - Evaluation conc. additional on-going stability samples
- QP-certification & release possible!

Administration of out of specification products

- Administration of OOS-products can be done exceptionally
 - Immediate significant hazard for the patient
 - Take into account alternatives options
 - Evaluate consequences of not receiving the product
- Manufacturer notifies the treating physician of the OOS provides an evaluation of the risks
- The confirmation of the treating physician to accept the OOS batch needs to be documented and recorded by the manufacturer
- Manufacturer immediately has to inform the Sponsor
- The Sponsor has to inform the relevant Competent Authority
- No QP certification will be performed! QP 'release for shipment' will be performed.

Challenges

- Vein-to Vein time
- Local vs central cryopreservation
- Cost
- Quality oversight collection centres
- Collection centres: work on multiple CAR-Ts for multiple Pharma Companies: challenges regarding handling different paperwork, processes, labels,...
- QP oversight:
 - from apheresis to administration
 - CoI/CoC review: manual process



Thank You!

Q&A



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Back-up slides



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The Vineti System – What is it?

- Our CAR-T program requires a radically different supply chain than most conventional drugs.
- Vineti is a supplier of a Chain of Identity (CoI) and Chain of Custody (CoC) software for use in the tracking of personalized medicine. It includes logistics integrations and manufacturing scheduling/planning functionality.
- The Vineti system tracks the entire “Vein to Vein Process”. Where the product is, and who handled the product.
- The system will assign a unique CoI Number that will be associated to the blood product of a specific subject during a specific donation. This number will be tracked throughout the process.

The Vineti System – What is it?

- During specified points in the Chain of Custody the Vineti system will capture predefined data related to the blood product. The system makes use of barcode scanners to verify the identity of the product and minimize data entry along the way. The system will also generate Apheresis, Cryopreservation, Shipping and Final Product Labels.
- Scans and data entry will be associated with the system user performing the tasks. These actions will be registered with time/date stamps and electronic signatures upon completion of the data entry.
- The Vineti System provides a reportable audit trail for all of the CoI and CoC activity.

The Vineti System – What is it?

- In short, the Vineti system replaces the manual process that makes use of paper forms, loading and downloading those forms into a central repository, and the maintenance of a Excel spreadsheet used for central tracking.
- The Vineti system also alleviates the need to pre-print and ship labels to each of the sites. It also allows for the data captured in specific stages of the process to be included on the printed labels (rather than being handwritten).

Current U.S. Vineti Chain of Custody/Identity Map

