Regulatory Approval of Modern Gene-Based Cancer Immunotherapies – CAR T Cells

A product perspective

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U.S. Food and Drug Administration
FDA Approves First CAR T Cell Therapies

First cancer 'living drug' gets go-ahead

By James Gallagher
Health and science reporter, BBC News website

30 August 2017 | Health -BBC

Modified T cells that attack leukemia become first gene therapy approved in the United States


axicabtagene ciloleucel
YESCARTA™

NDC 71287-119-01

FOR AUTOLOGOUS & INTRAVENOUS USE ONLY
No U.S. standard of potency

Dose: One sterile bag for infusion.
Contents: Maximum of 2 x 10⁸ autologous anti-CD19 CAR T cells in approximately 88 mL suspension containing 5% DMSO USP.

Gently mix the contents of the bag while thawing
See package insert for full prescribing information and instructions for administration
Ship and store in vapor phase of liquid nitrogen ≤ -150°C

DO NOT FILTER
DO NOT IRRADIATE

Manufactured with gentamicin
Not evaluated for infectious substances
Preservative free

Manufacturer: Kite Pharma, Inc., El Segundo, CA 90245
Phone: 1-844-454-KITE U.S. Lic. #2064

www.fda.gov
Overview

• Introduction of CAR T cells – Genetically modified immunotherapy
• General requirements for a biologics license application (BLA)
• Manufacturing process control strategy
• Specific CMC considerations for a CAR T cell BLA
• Summary
CAR T Cells: Chimeric Antigen Receptor T Cells

• Genetically modified T cell immunotherapy
  – Targets antigen on the cell surface
  – Independent of MHC

• “Living Drug”
  – Dynamic cell population during manufacturing process
  – Expands and differentiates after administration
Structure of CAR

• Extracellular recognition domains
  – Antibody-derived scFv
  – Specific for tumor antigen
  – On-target, off-tumor effects

• Intracellular signaling domains
  – T cell-derived domains
  – T cell activation: CD3ζ
  – Co-stimulation signal: generally CD28 or 4-1BB
How Does a CD19-Directed CAR T Cell Work?

• CAR scFv binds to CD19 on B cell tumors
  – Not restricted by HLA
• Binding of CAR to CD19 leads to T cell activation
  – Promotes cell expansion and differentiation
  – Triggers effector functions:
    • Lysis of CD19+ cells
    • Cytokine signaling
    • Stimulation of bystander immune cells
Manufacturing Process

Cancer Gene Therapy (2015) 22, 79–84

www.fda.gov
Personalized Medicine: A different manufacturing paradigm

Conventional Drug/Biologic

1 product lot

Raw materials

cGMP Manufacturing

In Process and Lot Release

Testing

Distribution

Many patients

CAR T cell

1 product lot

One patient
Biologics License Application (BLA) Approval

- Clinical safety and efficacy
- Post marketing requirement (PMR)
  - Risk evaluation and mitigation strategy (REMS)
    - Cytokine Release Syndrome
    - Neural toxicity
  - Non-interventional registry
    - Delayed adverse events
- Post marketing commitment (PMC)
- Validated manufacturing process & capacity under CGMPs
- Pre-license inspections
- Labeling

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Regulatory Basis for BLA

• Request for permission to introduce a biologic product into interstate commerce (21 CFR 601.2)

• Demonstration of safety, purity and potency
  • Section 505 of the Food, Drug and Cosmetic (FDC) Act
  • Section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262)
  • Title 21 Code of Federal Regulations chapter 600 – 680 (21 CFR 600)
  • 21 CFR 1271

• Manufacturing facilities meet standards designed to assure that the biological product continues to be safe, pure, and potent (21 CFR 210 and 211 (CGMP))

• Labeling (21 CFR 610.60, 610.61, 610.62)
Multidiscipline Review Team

• Chemistry, Manufacturing and Controls (CMC)
  - Product/Manufacturing information
  - Capable of consistently producing a safe, pure and potent product with defined stability

• Pharmacology and Toxicology
  - Proof of concept
  - Safety (prior to clinical studies)
  - Dose determination

• Clinical
  - Safety (clinical studies)
  - Efficacy
Manufacturing Controls – Product Development

• Process Design – Safety and quality built into the process
• Process development for improvement – Comparability and change controls
• Control of raw materials and components – Qualification programs
• Tracking of product – Chain-of-identity
• Stability – for storage, shipping and post-thaw time
Manufacturing Controls – Later Phase Product Development

• Pivotal trials and commercial production
  - Defined critical process parameters (CPPs)
  - Critical quality attributes (CQAs)
  - Unit operations time limits
  - In-process controls
  - Lot release specifications

• Process validation

• Analytical test method validation

• Stability – for expiry dating, storage & shipping time
Raw Materials and Components

- Risk assessment and qualification programs
- Identity test (21 CFR 211.84) and review of vendor’s CoA
- Animal derived components (including human): Adventitious agents testing
- Human derived components: donor eligibility screen and testing

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Raw Materials and Components

- Leukapheresis materials
  - Suitability for further manufacturing (T cell # and composition)
  - Aseptic process step is used for cryopreservation
- Gene transfer vector is a critical component required for product activity
  - Assure identity, safety (including RCR test), purity, and potency
  - CGMP conditions and subject to inspections
  - Stability
  - Validation of manufacturing process, test method and shipping
In-process and Lot Release Tests

• Selection of CQAs for in-process and lot release tests
• Validation of analytical test methods
• Justification of test acceptance criteria based on manufacturing data
  • Late stage manufacturing data may be more reliable and a better reflection of commercial process
  • CAR T cells may have lot release acceptance criteria with wide ranges
    • Should be statistically justified
    • Should reflect clinical lots shown to be safe and effective
Potency Considerations

• At the final cell product level
  • Biological potency assay – mode of action (e.g., cell killing)
  • Cytokine production
  • Transduction efficiency
  • Vector copy number

• At the vector product level
  • Biological potency assay – mode of action
  • Infectious titer (critical for MOI determination at the transduction steps)
    • In Target cell and / or In a surrogate cell line
Process Validation

• Confirm that the process is capable of consistently producing a quality product for its intended purpose

• Validation plan
  • Stage 1: Process design
    • Process control strategy
    • CPPs, CQAs, statistically established acceptance criteria
  • Stage 2: process qualification
    • Qualification of facility and equipment
    • Process performance qualification (PPQ)
      • Prospective PPQ protocols
      • Execution and reports
  • Stage 3: Continued process verification
    • Protocol to continually monitor and ensure the state of control
Chain-of-Identity

- Ensure the right product goes back to the same patient from which the cells are derived
- Establish unbroken chain-of-identity through physical container closure labels and computer based electronic tracking systems
- Validate the systems to ensure no mix-up can occur throughout the entire manufacturing process from enrollment to final infusion
- Use at least two patient identifiers to define unique patient/product identity
- Have a contingency plan in place if the electronic system is down
Summary

• Key to manufacturing control is to minimize variations from all possible sources
• Demonstrate process control through process development, improvement, optimization, in-process and lot release testing, formal validation and continuing monitoring
• Vector is manufactured under CGMP conditions, tested for potency and subject to inspection
• Track cell product identity through validated chain-of-identity system
• Address issues early with FDA through various meetings during product development
  • Pre-BLA meeting: All issues and questions should be discussed
FDA Guidance Documents


• Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) [https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm091345.pdf]


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