CAR T

CMC challenges in autologous CAR T products

Industry Perspective

ASGCT 2019 Pre-Approval Commercialization Workshop

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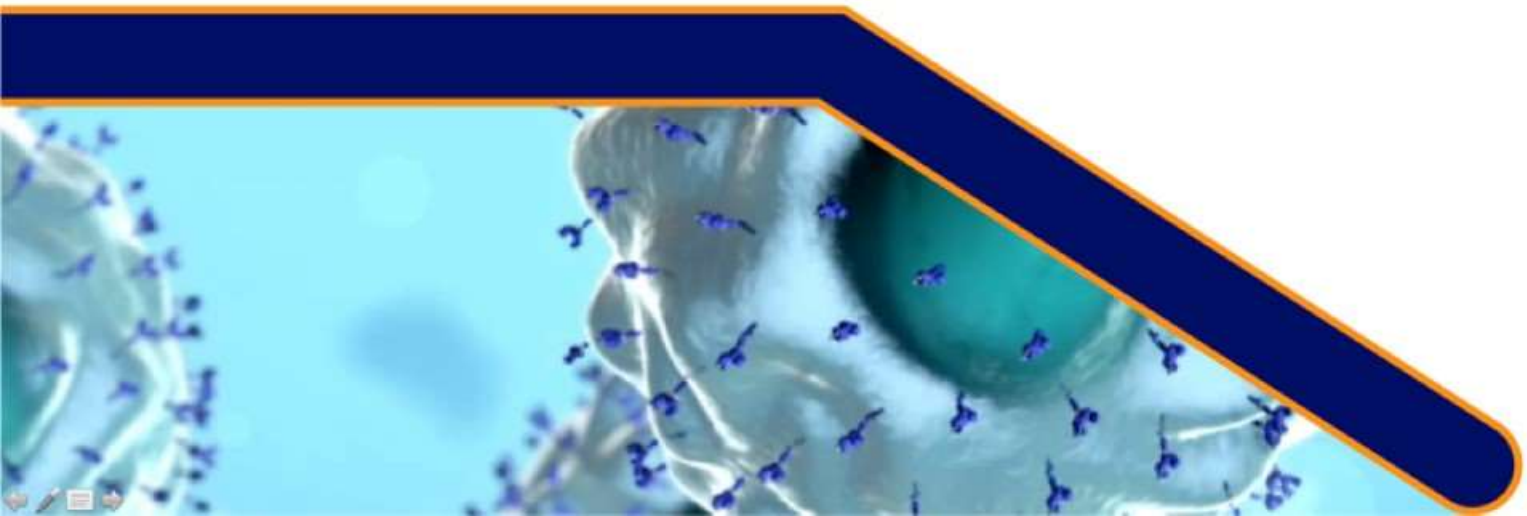
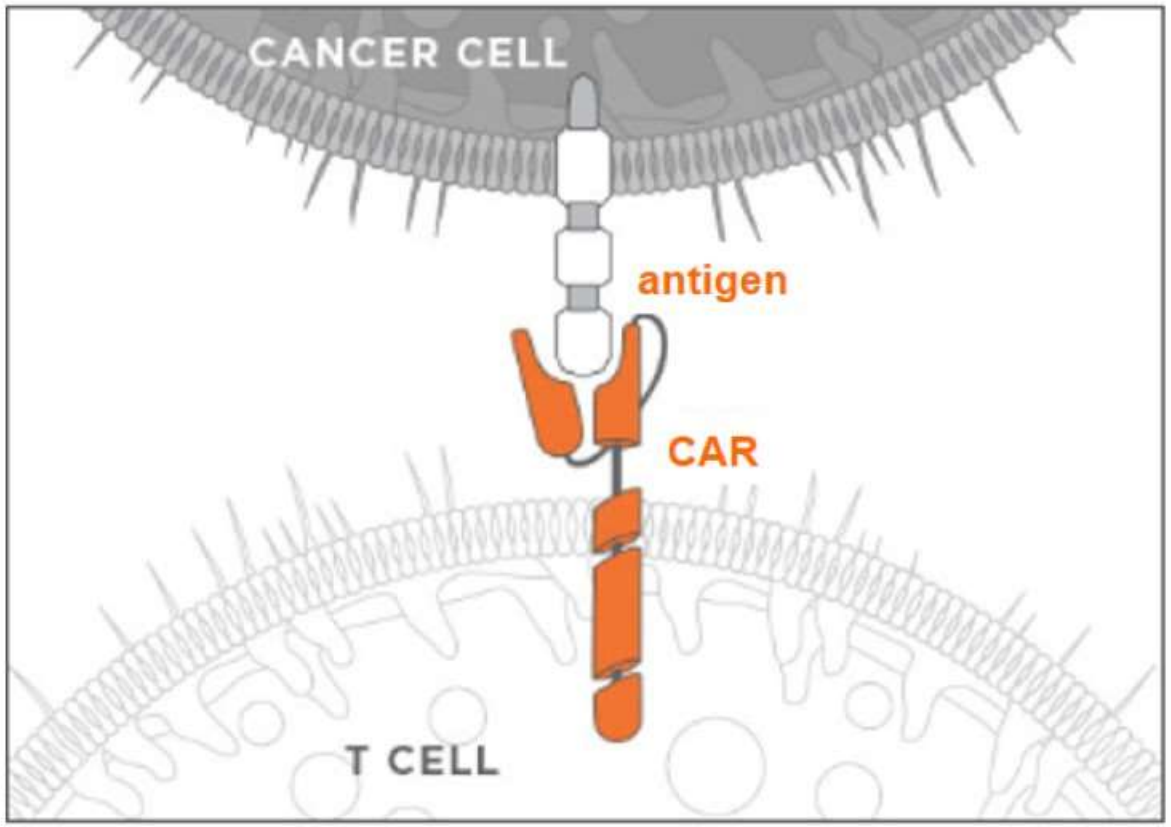


CAR T cell therapy



- Transformative potential
  - Rapid clinical development to help patients in need
  - Field in early stages

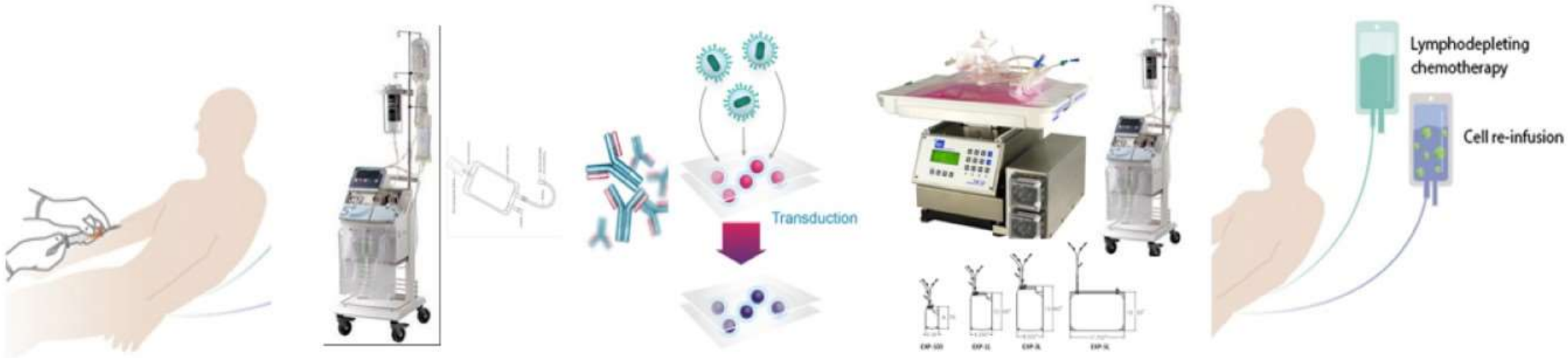
Region-specific regulations for genetically modified cells

Additional measures to ensure environmental and patient safety prior to clinical trial initiation

- US
  - FDA and NIH required initial registration of a gene therapy protocol and updates
  - Aug 2018: Deletion of the NIH registration and reporting requirements proposed
- EU
  - GMO applications required per country
- Japan
  - Strategic Consultations required prior to a Clinical Trial Notification for Regenerative Medicine products
  - Confirm product is not subject to the Cartagena Act in Japan

Understanding region-specific needs is critical for enabling global development

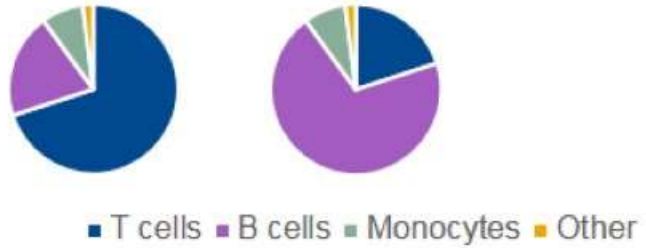
Autologous CAR T cell manufacturing



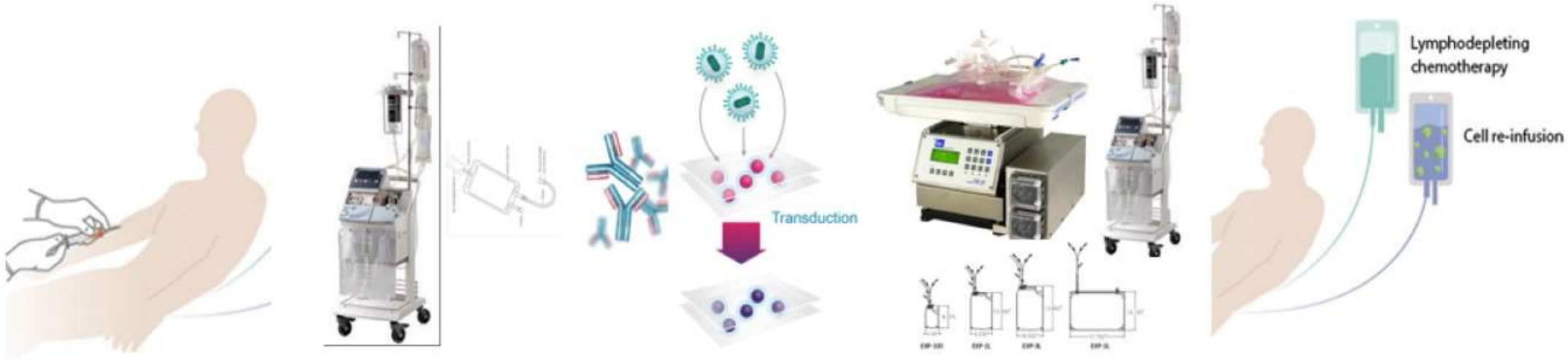
Leukapheresis	PBMC Isolation	Cell Activation, and Transduction	Cell Expansion, Harvest, Cryopreservation	Infusion
Apheresis material obtained from patient via standard leukapheresis collection	PBMCs isolated	Culture initiated, T cells activated, and transduced with vector to insert CAR sequence	CAR T cells expanded to therapeutic dose, formulated and cryopreserved. QC/QA release	CAR T cells infused into patient after lymphodepleting chemotherapy

Process development challenges

- Variability in starting cell composition
  - Wide process variability
- Limited starting cell material
  - May require different approaches for process characterization and product characterization
  - Begin commercial planning while still in learning phase
- Vector manufacturing and cell processing require optimization in order to enable consistent commercial supply of the CAR T product
- Final product is a cell suspension for infusion
  - Sterile filtration of final product is not possible



Raw materials used in cell therapy products



Leukapheresis → PBMC Isolation → Cell Activation, and Transduction → Cell Expansion, Harvest, Cryopreservation → Infusion

- Apheresis process
- Shipping
- Vector
- Human-derived raw materials
- Disposables
- Analytical reagents

Challenges:

- Single source/vendors, custom reagents
- High comparability risks → long development times
- Requirements for in vitro *vs.* in vivo *vs.* clinical data

Raw materials of biological origin

Requirements for blood/plasma-derived and animal-derived raw materials differ between each country/region

- US
  - Typically fewer requirements than the EU and Japan
- EU
  - European Pharmacopeia 5.2.12
  - EU Directive 2006/17/EC
- Japan
  - Standards for Biological Materials

Development of international standards accepted by all regional health authorities is desirable for rapid development

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Keys to success

- Prioritization of CMC changes and implementation prior to pivotal trial
  - Addition of manufacturing sites?
  - Fresh or frozen starting cells?
  - Raw materials of biological origin to be replaced and/or dual sourced?
  - New analytical methods?
- Retain sufficient samples
- Proactive discussions with Agencies as needed

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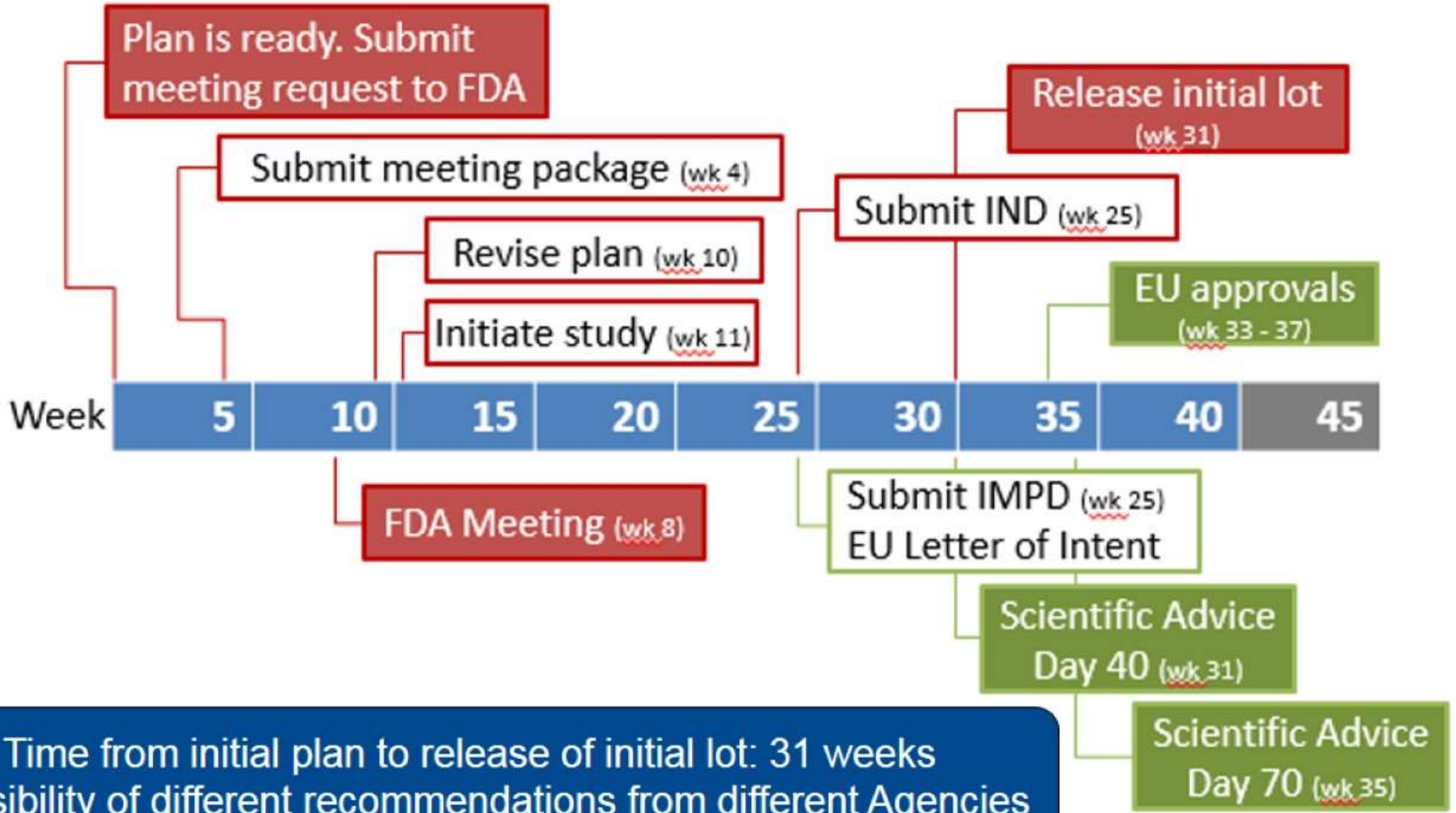
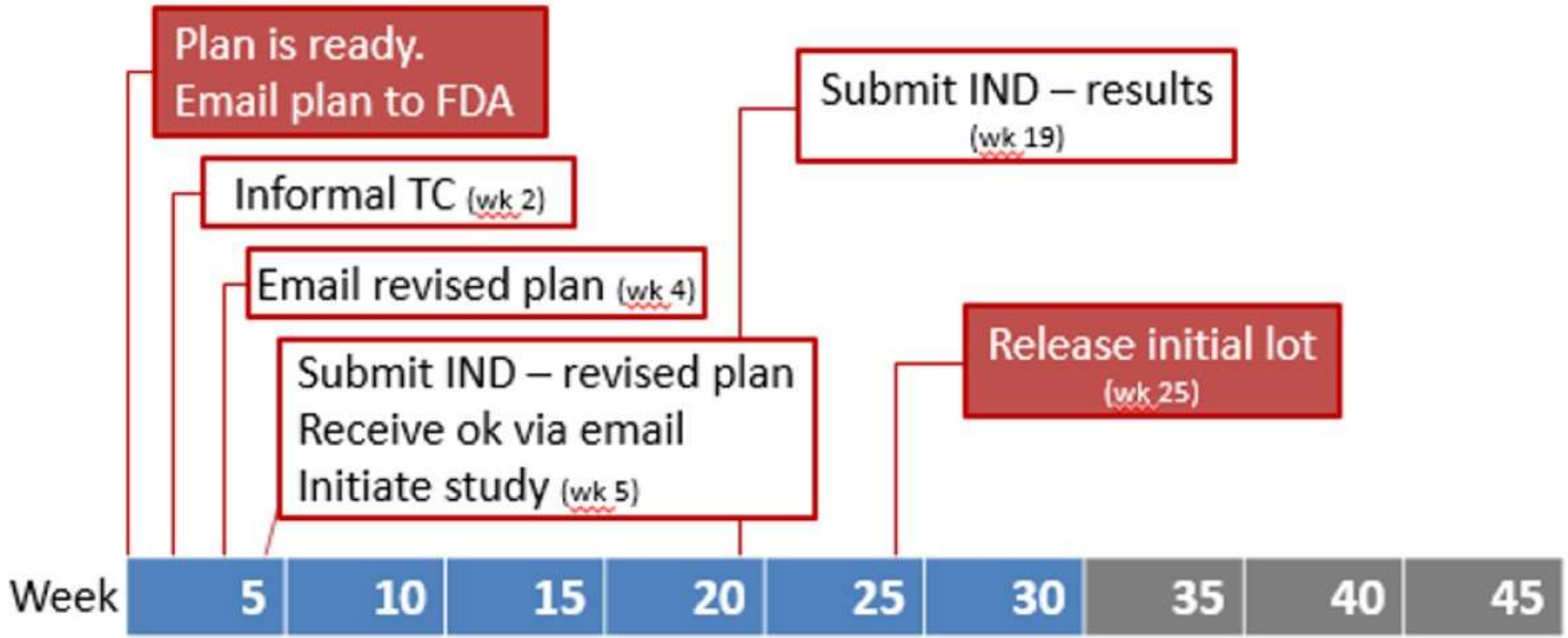
Typical interaction during development



Time from initial plan to release of initial lot: 31 weeks
Possibility of different recommendations from different Agencies

Proactive, frequent interactions with Health Authorities



Time from initial plan to release of initial lot: 25 weeks
Less risk due to confirmation of revised plan prior to execution
Input from one Agency only

* Scenario is also applicable for EU member states, Canada

Summary

- CAR T products have transformative potential
  - Rapid clinical development to help patients in need
  - Field in early stages
- Enabling fast-to-market cell and gene therapy products
  - Development and adoption of international standards
  - Good understanding of region-specific needs
  - Prioritization of CMC changes and implementation prior to pivotal trial
  - Maximize regulatory mechanisms to have active dialogue with Agencies where needed

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