CAR T

Managing Accelerated Development Industry Experience

CASSS 2019 Cell & Gene Therapy Products Symposium

Yoko Momonoi, M.S.
Global Regulatory CMC, Celgene Corporation

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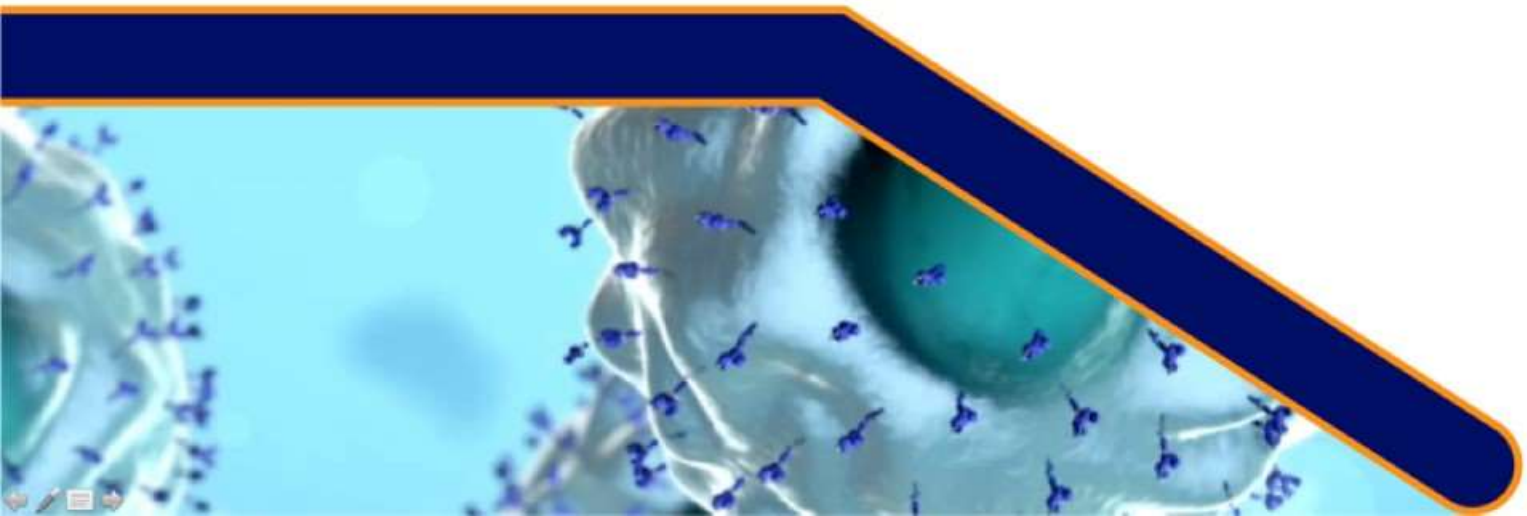

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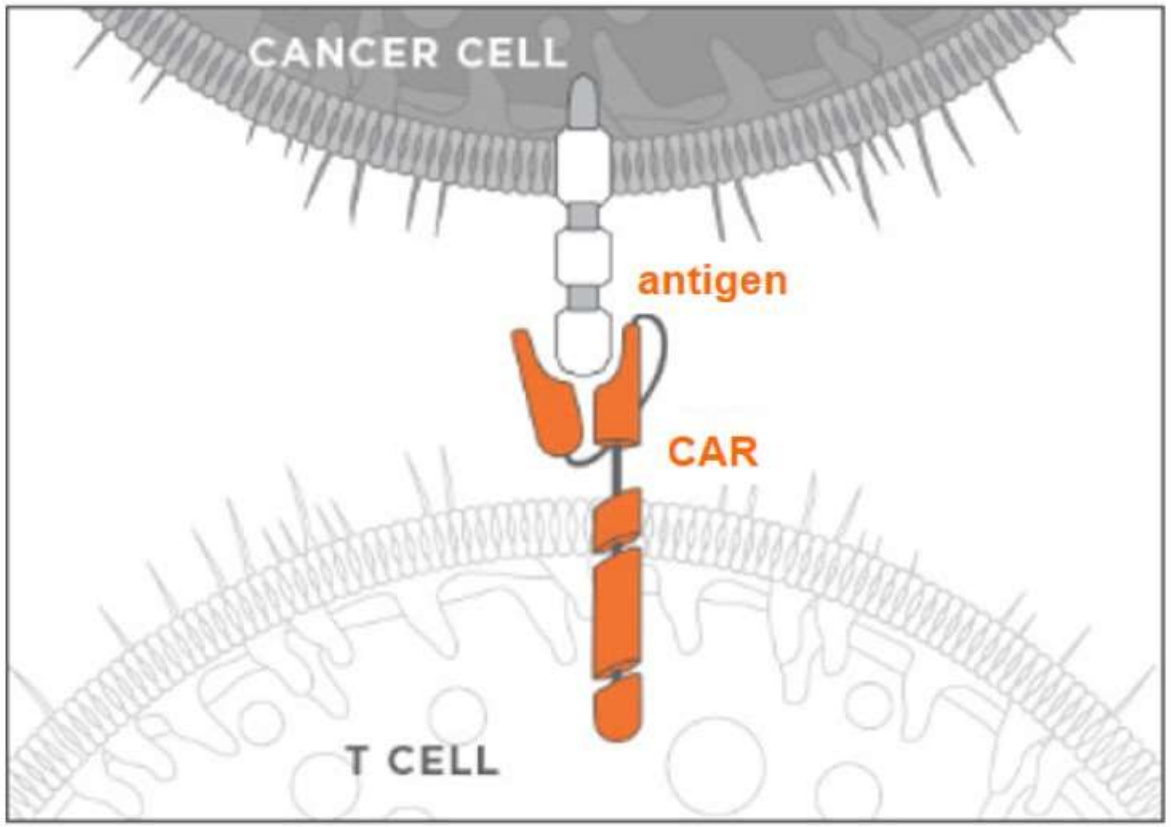
CAR T cell therapy



- 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
  - Up until August 2018, NIH had reporting requirements under Appendix M of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules
  - Apr 2019: Removal of these reporting requirements with NIH finalized
- 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

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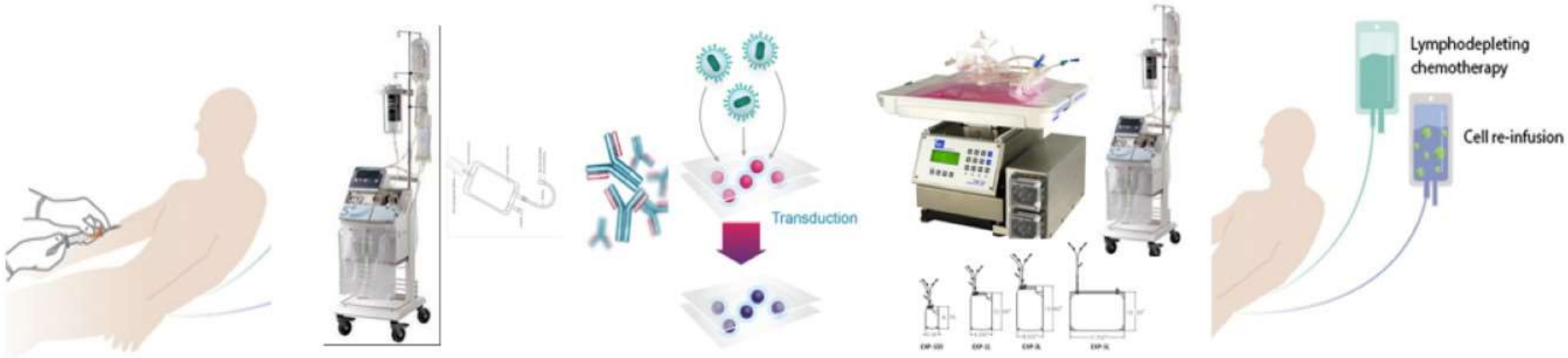
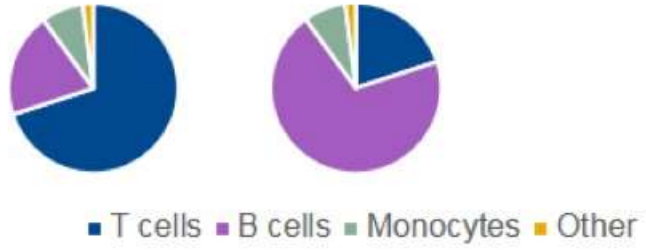
Autologous CAR T cell manufacturing



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

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
- Setting drug product specifications can be difficult since mechanism of action is not straightforward
- Limited platform and/or industry knowledge



Significant CMC changes may be required prior to, during, and after pivotal trial

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
  - BTD and RMAT designation allow for timely interactions with the FDA
  - PRIME designated products have an early CHMP Rapporteur appointment and an EMA quality specialist
  - During clinical development of regenerative medicine products, CMC information is mainly communicated through preliminary meetings and consultations with the PMDA, which is different from other product categories in Japan

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Case study: site addition for an ATMP

- Change: Manufacturing site addition for an autologous CAR T
  - Vector or drug product for the pivotal trial manufactured at site A
  - Commercial vector or drug product to be manufactured at site B
- Context
  - Rapid development often requires manufacturing to start in site A
  - Understanding of the manufacturing process is evolving
- Considerations
  - Demonstration of analytical comparability is key
  - Clinical manufacturing experience at site B prior to commercial manufacturing is desirable
- Approaches
  - Separate formal Agency meetings
  - Frequent interactions with an Agency

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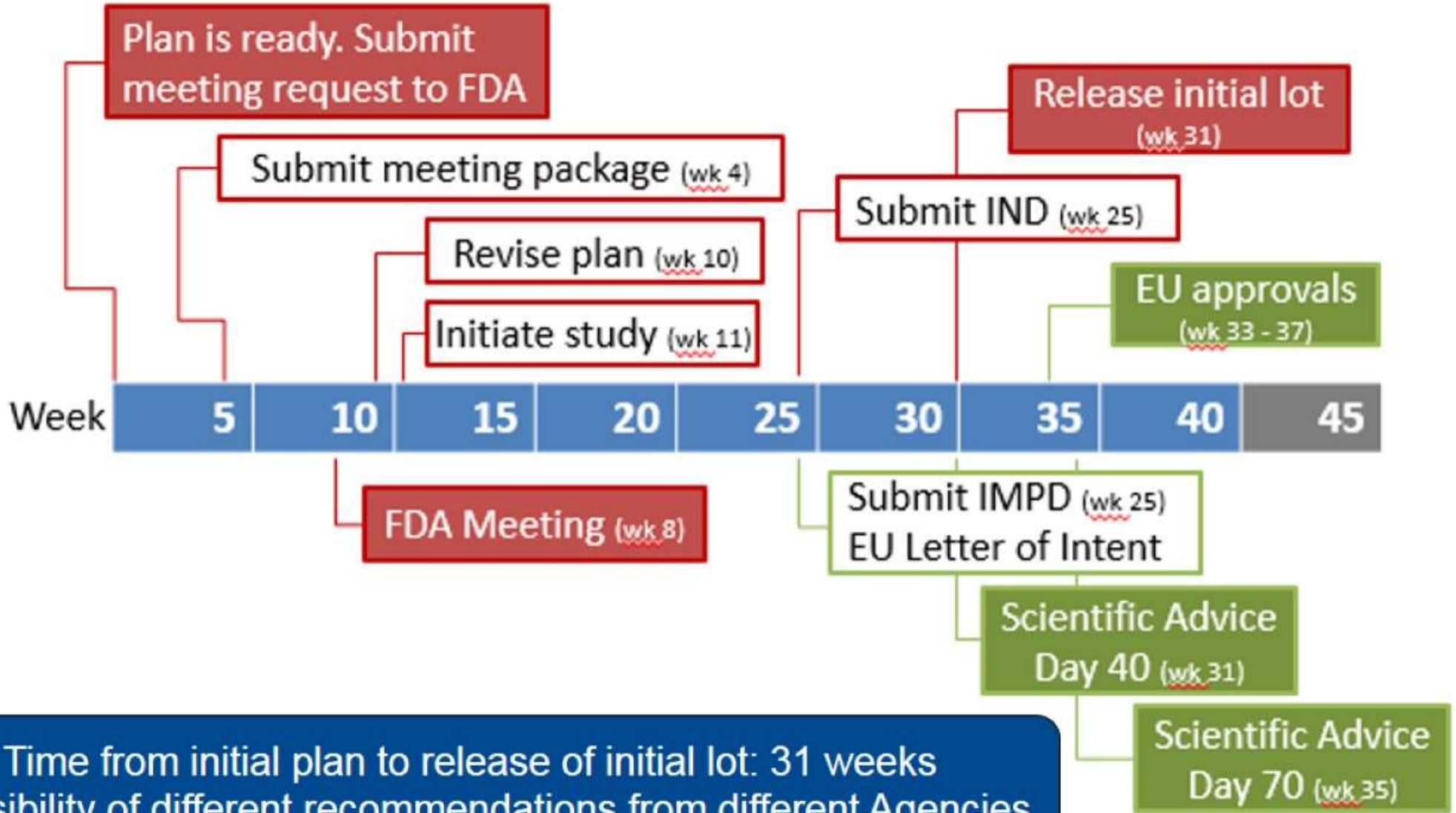
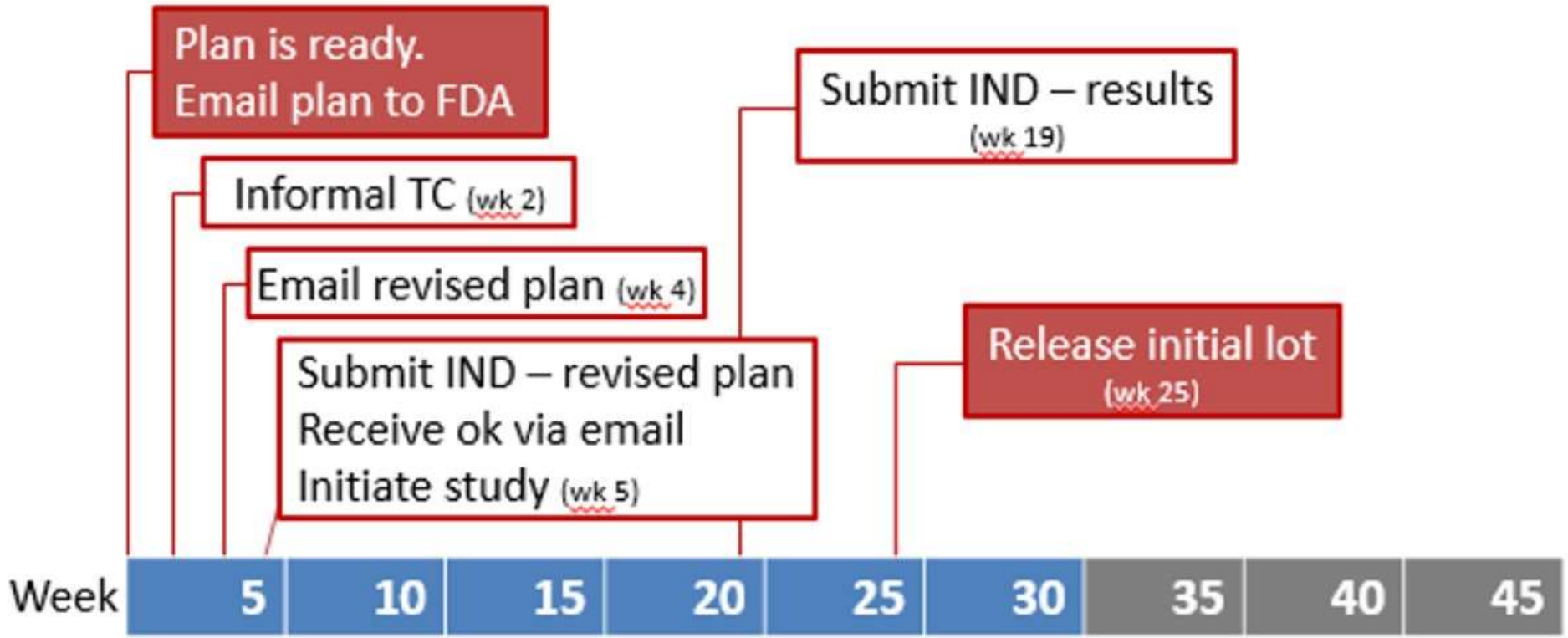
Typical interaction during development: formal meetings



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

- Regulatory tools to enable fast-to-market cell and gene therapy products
  - BTD, RMAT, PRIME designations help enable rapid development
  - Mechanism to confirm the best approach for asking questions is also helpful
- Additional efforts which could help expedite development
  - Standardization of analytical methods
  - Certification scheme for critical raw materials in the EU
  - Consultative advice