Breakthrough Therapy – CMC Challenges

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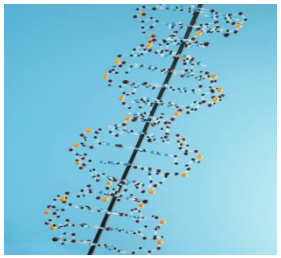
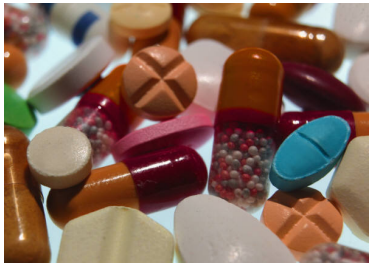
MERCK
Be well

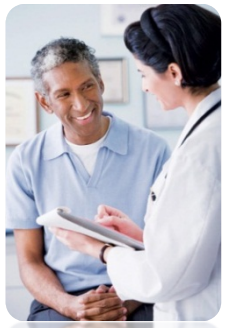
Topics

- Current state of Breakthrough Therapy Designation
- Merck's experience
- Closing thoughts

Drug Development Sequence







Discovery Collaboration → **Market Formulation / Device Development** → **Lifecycle Management and Product Creation** → **Clinical Supplies and Logistics**

The Molecule

The Patient

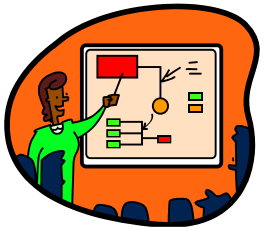
Key CMC Milestones - Traditional

Pre-Clinical	Phase I	Phase IIA	Phase IIB
Safety Assessment Formulation	Single Dose Formulation Phase I/IIA Formulation	Preliminary Market Formulation	

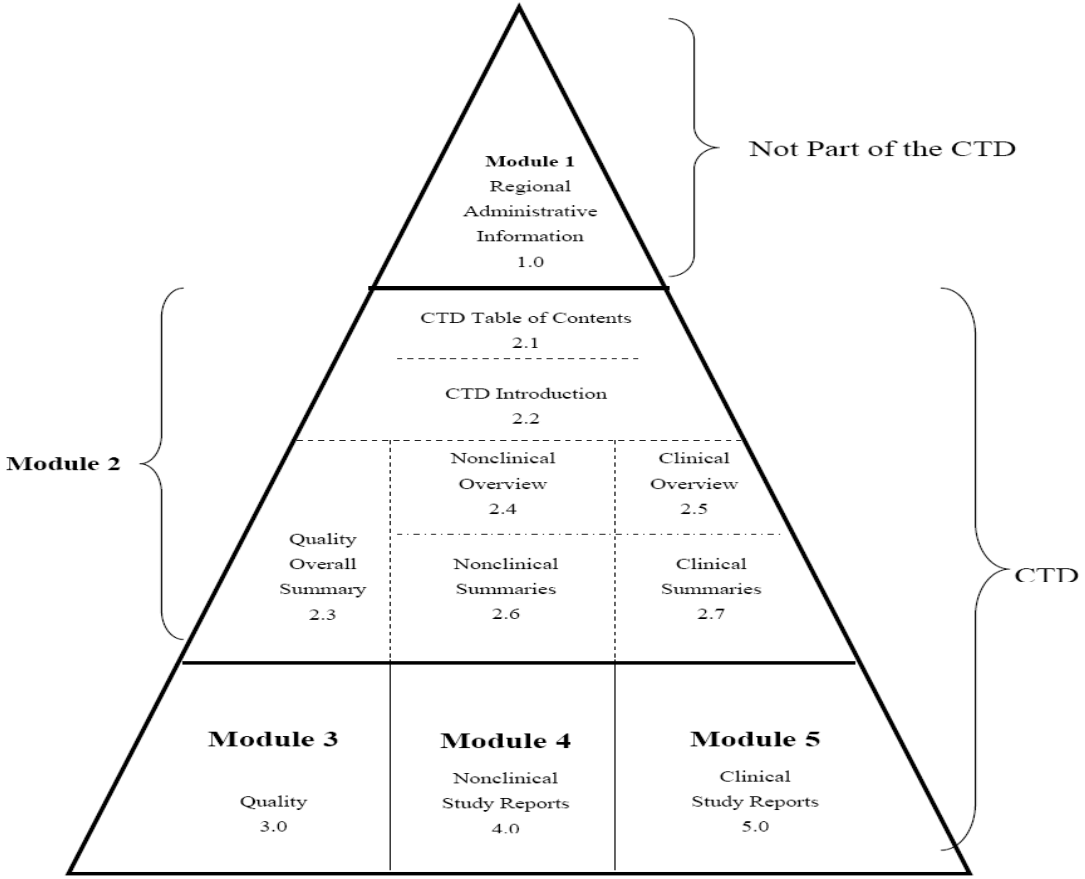
Analytical Methods Development and Application to Preformulation / Formulation / Clinical Supply Release

Clinical Supplies

CTD Structure



Diagrammatic Representation of the Organization of the CTD



Current state of BreakthroughTherapy

- Breakthrough Therapy Designation program was initiated in 2012 by the US FDA
  - to expedite development of treatments for serious or life threatening illness that demonstrate “substantial improvement” over existing therapies
- Sponsor and FDA collaborate in a dynamic process to ensure smooth progression towards supporting clinical trials
- The CMC teams have to expedite significantly to support the clinical development to ensure quality, safe supplies are developed and manufactured at a faster pace; no reduction in CMC requirements.

FDA Policy and Procedures

- **MAPP (Manual of Policies and Procedures) 6025.7**
  - Effective: March 9, 2015
  - Good review Practice: Review of marketing Applications for Breakthrough Therapy –Designated Drugs and Biologics that are receiving an expedited review

- Does not
  - address the specific content of scientific reviews
  - cover the review of breakthrough therapy designation requests
  - cover CDER actions from the time a breakthrough therapy designation has been granted until a marketing application has been submitted

Experience from the approval of BTD Biologics

KEYTRUDA® (pembrolizumab) for Injection 50 mg

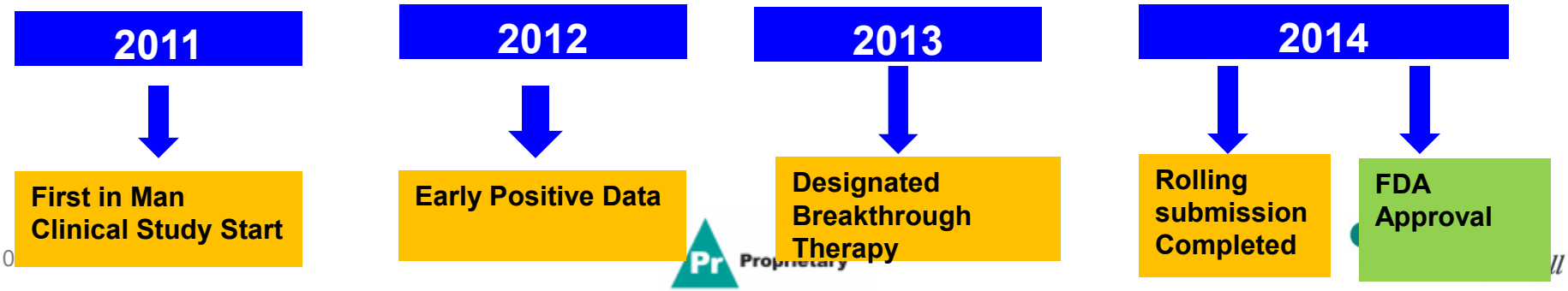
- Keytruda (Pembrolizumab) injection for 50 mg
- First anti-PD1 therapy to get FDA approval in September 2014
- Designated as Breakthrough Therapy by the FDA
- High Affinity, humanized monocloncal antibody IgG4 that binds to PD1 and prevents binding to PD-L1and PD-L2
- Data from a Phase 1 study supported accelerated FDA approval in September 2014

Three Major Transitions in Drug Supply

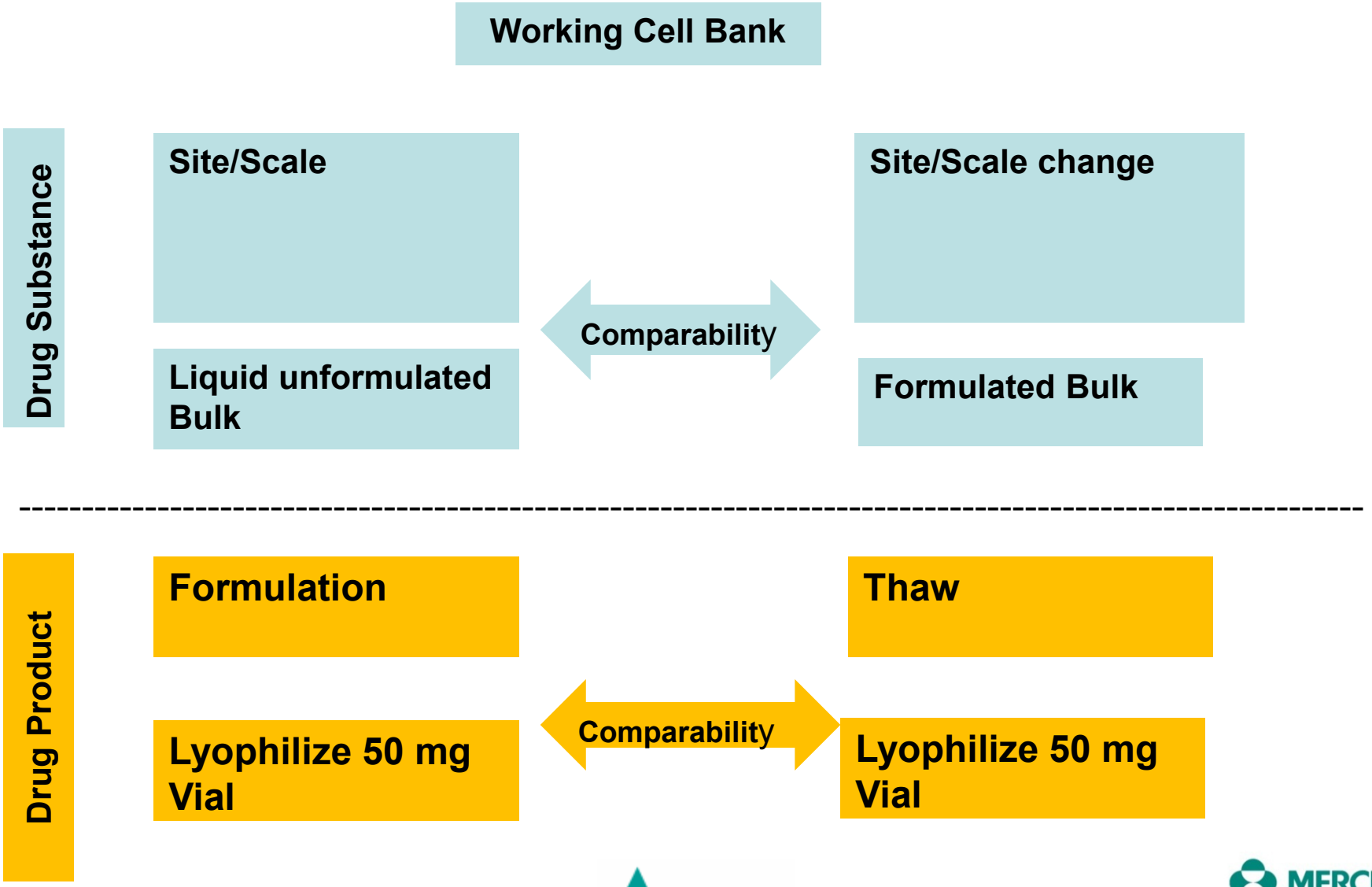
- **Material A** (support early development clinical studies)
  - Drug Substance prepared in clinical manufacturing facility
  - Drug Product lyophilized vial in a clinical manufacturing facility

- **Material B** (support late development clinical studies and launch)
  - Drug product (lyophilized) scaled up to commercial manufacturing facility

- **Material B-prime** (support late development clinical studies and launch)



Comparability Strategy



Merck's approach – strong science; successful bridging through development

- **Merck decided to prepare for commercial launch out of 2 sites**
  - Planned CMC activities for Keytruda were typical for biologics development
  - Scale up from pilot facility to commercial is expected as clinical development progresses
  - Submission strategy relied heavily on a comprehensive demonstration comparability as prescribed by ICHQ5E guideline

- Challenges unique to Keytruda were:
  - Pursuit of 2 commercial supply chains in parallel
  - Typical late stage CMC timelines of 24-36 months compressed to 12-18 months

Key to Success and Lessons Learned

- Strong Science and frequent interactions with FDA
  - Comprehensive analytical comparability package
- Working with the FDA
  - Establish Good lines of communication
    - Helped to resolve any issues quickly
    - Request all available PDUFA meetings (Application Orientation, mid-cycle, late cycle) to ensure alignment on content, and address any problems with datasets or other issues impeding review
      - Merck had formal CMC –focused meetings with the FDA routinely, every 2-3 months: 5 in total with informal meetings
- Commitment from both FDA and sponsor to deliver the product to patients as quickly as possible

PhRMA Vision of CMC review of BT Therapies

Establish

clear, consistent, predictable and transparent policies and processes,

developed with stakeholder input, that

align pharmaceutical development and commercial manufacturing programs to applicable regulatory pathways, especially for products designated as breakthrough Therapies

PhRMA WG Proposal on CMC Review of BTD submissions

CMC Review of BT – High Level thoughts of PhRMA WG

- For Breakthrough designated products,
  - **Create a step-wise, risk-based approach with stakeholder input for**
  - (1) submission, review and post-approval commitments for CMC data
  - (2) risk-based pre-approval inspections

Assessment by an independent contractor with expertise in assessing biopharmaceutical development and regulatory review

BT Experience with a small molecule product

- **Merck has an application that has been accepted under the Breakthrough Therapy designation – under review**

- **Will be able to share this experience at a later date**

Closing thoughts – Breakthrough Therapy Reviews and approvals

- **A great opportunity to set the stage for great collaboration between regulators and the industry sponsors**
  - Understanding the requirements
  - Evaluating areas for progressive and innovative ways to streamline dossier presentation, review process, response to Agency questions and approval
  - Enhanced engagement of regulators and industry throughout the development and review of the drugs and biologics

Availability of unmet medical needs expeditiously to patients

Patients WIN

Acknowledgements

- **Keytruda Project Team (Merck)**
- **BT PhRMA WG**

Question and Answers