Quality Challenges for Breakthrough Designated Products

EMA/FDA Workshop
November 26, 2018

Ramesh K. Sood, Ph.D.
Senior Scientific Advisor
Office of New Drug Products
OPQ/CDER/FDA

Outline

- Background
  - FDASIA/21st Century Cures Act – Breakthrough therapies (BT)/RMAT
- Expedited programs for serious conditions
  - Final guidance
- Quality expectations and risk considerations
- CMC challenges for expedited submissions

FDASIA (2012)

- Section 901– Fast Track Drug Products
  - Facilitate development and expedite the review of drugs for the treatment of a serious or life-threatening disease or condition that demonstrates the potential to address unmet medical need
- Section 902 –Breakthrough Therapy Drugs
  - Expedite the development and review of a drug for serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies
    - Provide timely advice and interactive communication with the sponsor regarding the development of the drug
    - Provide a collaborative cross disciplinary review utilizing senior managers and experienced review staff, as appropriate

Regenerative Medicine Advanced Therapy (RMAT)

- 21st Century Cures Act (2016): Established a new expedited program for Regenerative Medicine Advanced Therapies (RMAT)
  - Like Breakthrough, RMAT products are for serious or life-threatening diseases or conditions, and there must be preliminary clinical evidence
- RMAT products have the potential to address unmet medical needs for disease or condition
- RMAT designation confers the same benefits as Breakthrough
- As of August 30, 2018: 74 RMAT requests, 26 granted (35%)
- 2017 Draft Guidance: Expedited programs for regenerative medicine therapies for serious conditions

Comparison of FDA's Expedited Programs

	Breakthrough	Fast Track	Accelerated Approval	Priority Review
Qualifying criteria	• Treat serious condition. • Preliminary clinical evidence indicates drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies	• Treat serious condition. • Non-clinical or clinical data demonstrate the potential to address unmet medical need • OR • Drug designated as Qualified infectious disease product	• Treats serious condition. • Provides meaningful advantage over available therapies • Demonstrates an effect on surrogate end point that is likely to predict clinical benefit	• Application for drug that treats serious condition. • If approved, will provide significant improvement in safety or effectiveness • Drug qualified infectious disease product.
When to submit request	With IND or after Ideally no later than EOP2 meeting	With IND or after Ideally no later than the pre-NDA or pre-BLA meeting	Discuss with review division	With original BLA, NDA or efficacy supplement
Features	• Intensive guidance on drug development. • Organizational commitment • Rolling review • Other actions to expedite review (e.g. priority review)	• Actions to expedite development and review • Rolling review	• Approval based on effect on surrogate endpoint	Shorter review clock

Guidance for Industry

- Expedited Programs for Serious Conditions – Drugs and Biologics (2014)
  - Typically involve a rapid manufacturing development program to accommodate the accelerated pace of the clinical program
  - Communication is critical
  - Importance of early communication to ensure that the manufacturing development programs and timing of submissions meet the Agency's expectations for licensure or marketing approval
  - Proposal of a commercial manufacturing program that will ensure availability of quality product at the time of approval

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

BT Submissions (FY12-18)

	Received	Granted	Denied	Withdrawn	Approved
CDER	630	242 (38%)	294 (46%)	81 (13%)	120 (NDA, BLA, Efficacy supplements
CBER	127	40 (31%)	79 (62%)	7 (6%)	6 BLAs

Quality Expectations

- Are safe, efficacious, performs consistently over shelf-life and available
- Quality expectations not based on the approval process (accelerated vs standard)
- Willing to accept inherent potential risk as long as benefit outweighs the inherent risk
- US Prescribing Information has no section to include quality related risk
- Shared responsibility to meet these expectations

Regulators Challenges for Expedited Development and Assessment

- Accelerated manufacturing development likely to have less information than typically available
  - Challenging to establish/evaluate control strategy
  - Setting product specifications
  - Setting commercially viable expiration period
- Makes it challenging to do a risk-benefit assessment regarding risk of less CMC information vs. patient benefit
- Require innovative risk-mitigation strategies to ensure product quality and reduce quality related product risk to an acceptable level

Regulators Challenges for Expedited Development and Assessment

- Lack of sufficient data from
  - Commercial manufacturing site
  - Stability data to support long shelf-life
  - Data to bridge clinical and commercial materials
  - Commercial supply/availability considerations
- Procedural/Assessment challenges
  - Increased communication during pre-submission and assessment period
  - Usually have priority status with shortened time line
  - Needs to manage with existing high workload
  - Assessment timing constraints for inspections

Conclusions

- FDASIA (2012) and 21st century Cures Act (2016) provide for expedited development and assessment of a drug for serious or life-threatening disease
- Challenges in meeting patient expectation for the quality and performance of drug
- Accelerated approval process can result in misalignment of clinical and CMC development
- This poses challenges for applicants and the Agency
- Need to overcome these challenges for the greater benefit of patients

Thank you!