Breakthrough Therapies - FDA Perspective

Olen Stephens, Ph.D.
Office of New Drug Products

Office of Pharmaceutical Quality
Outline

• Expedited programs for serious conditions
• BTD and risk/benefit analyses
• Quality expectations
• CDER approaches for Breakthrough (BT) applications
• Quality challenges for expedited submissions
• Case studies and personal observations
• Considerations moving forward for BT products
• Conclusions
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

- **Section 905 – Risk Benefit Framework**
  - Implement a structured risk-benefit assessment framework in the new drug approval process and regulatory decision making
The Risk/Benefit Balance…

Availability to patients

Risks to Quality

BTD is not granted for the benefit of Industry or the FDA; rather it is for the benefit of the American Public.
Expectations for Quality

• Patients and caregivers assume that their drugs:
  – Are safe and efficacious
  – Deliver the same performance as described in the label
  – Perform consistently over their shelf life
  – Are made in a manner that ensures quality
  – Will be available when needed

• Quality expectations not based on the approval process (accelerated vs. regular)
What is Pharmaceutical Quality?

• The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as identity, strength and purity (ICH Q6A)

• The degree to which a set of inherent properties of a product, system or process fulfills requirements (ICH Q9)

Office of Pharmaceutical Quality
MaPPs and Guidance

• MAPP 6025.6 describes CDER’s actions during the IND stage
• MAPP 6025.7 describes CDER’s actions during the NDA/BLA stage
• Guidance: Expedited Programs for Serious Conditions – Drugs and Biologics (2014)
  – Manufacturing development program that accommodates the accelerated pace of the clinical program
  – 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

Guidance for Industry

• BT will receive fast track features as well as:
  – Intensive guidance and communication regarding efficient drug development
  – Involvement of senior managers and experienced review staff (as appropriate) in a collaborative, cross-disciplinary review
  – An assigned cross-disciplinary project lead from FDA to facilitate efficient review and development
    • Within OPQ, a review team is assembled early in the clinical development to address all CMC facets
CDER Approach for BT Applications

• Early discussion of NDA submission strategy with the applicants
• Early assembly of appropriate review resources
• Anticipate problem areas and address issues during development stage
  – Risk identification and assessment
  – Discuss potential risk mitigation strategies
  – New technologies (continuous manufacturing)
  – Novel approaches (Q12)
  – Significant QbD aspects
  – Proposed regulatory flexibility
CDER Approach for BT Applications

- Some novel approaches used for BT applications
  - Accepting less stability data at submission
  - Additional amendments during review cycle
  - Reliance on supporting stability data
  - Early submission of some information (facilities)
  - Proactive communication between review and inspection staff
  - Increased use of PMCs/PMRs to cover residual risk
  - Treatment protocols/expanded access submissions
  - Open to novel risk mitigation strategies
Communications

• Communication is the key
• IND stage
  – preIND, EOP1, EOP2, preNDA
  – Additional meetings upon request
  – CMC-specific meetings are an option
  – Formal written feedback to information requests
• NDA stage
  – Application Orientation Meetings
  – Regular PDUFA V interactions (e.g. LCM)
  – Teleconferences during review clock, as needed
  – Formal information requests
Anticipated Areas of Concern

- Inadequate characterization (drug substance)
- Lack of stability data to support viable retest period (drug substance) or expiration period (drug product)
- Lack of nonclinical data to qualify identified impurities
- Poor understanding of formulation (drug product)
- Lack of understanding of critical quality attributes
- Inadequate analytical procedures
Anticipated Areas of Concern

• Commercial manufacturing process
  – Significant differences between manufacturing process for clinical and commercial product
  – Degree of commercial process development and understanding
  – Manufacturing sites readiness for inspection
  – Commercial process readiness for implementation in conformance with CGMP
  – Commercial manufacturing process readiness to meet launch requirements
Challenges for Expedited Quality Assessment

• Accelerated manufacturing development likely to have less information than typically available
  – Poses challenge for both applicant and regulatory bodies
  – Typically warrants a risk-benefit assessment
    • Risk of less quality information vs. patient benefit
  – May create gaps in manufacturing process development, analytical method development, or facility qualification and readiness
  – May require innovative risk-mitigation strategies to ensure product safety and reduce quality related product risk to an acceptable level
Challenges for Expedited Quality Assessment

• Limited data available and/or submitted
  – Commercial site manufacturing batch data
  – Stability data to support long shelf-life
  – Data to bridge clinical and commercial materials

• Review timing constraints

• Frequent communication needed during review

• Commercial supply/availability considerations
Quality Considerations: IND Stage

• Starts at IND/Pre-NDA stage
  – Start thinking about accelerated product development strategies at IND stage
  – Focus on clinical/commercial product comparability
    • Discuss strategy and data required with FDA
  – Stability data package to be submitted
    • Need for proposed stability amendments
    • Available supporting stability data
  – Commercial manufacturing sites information
    • Will sites be ready for inspection
  – Plans for treatment protocols/expanded access submissions
Quality Considerations: NDA Stage

• Discuss NDA submission strategy/timing as soon as possible
  – Early assignment of Quality review team
  – Proactive communication between review and inspection staff
  – Early submission of manufacturing site information
    • Submit with expanded access submission, if applicable
    • Submit with first piece of rolling review, if granted

• Unique application specific aspects
  – New technologies (continuous manufacturing)
  – Novel approaches
  – Significant QbD aspects
  – Proposed regulatory flexibility
Quality Considerations: During Review

• Stay engaged
• Quick turn around time for any information requests
  – Information requests may be staggered
• Availability for quick teleconference
  – Agency or applicant initiated
• Early discussion CMC labeling
• Discussion of residual product quality risk and appropriate mitigation strategies
  – Possible PMC/PMRs
• Discussion of launch challenges, if any
Quality Considerations: Manufacturing

- Plan for rapid development with and between manufacturing facilities
- Early decisions regarding dosage form
- Early methods validation
- Ensure facilities are capable and adequately qualified
- Provide transparent design evolution and rationale for the commercial manufacturing process and controls
Case Studies of BTD Products
Case Study #1
Communication of Early Problems

- SODF for Cancer
- Applicant made final decisions on dosage form, manufacturing process and controls in anticipation of BTT designation
- Issue with finished manufacturing process affecting specifications
- Proactively met early to discuss issues before filing
- Applicant discussed the failure, investigation and corrective actions
- Involved multiple agency review disciplines to evaluate and provide feedback
- Applicant discussed path forward, and impact to CMC data
- Facilitated review and provided FDA with clearer understanding during review process
Case Study #2
Ineffective Communication Between Sponsor and Manufacturers

• Small volume parenteral for cancer
• Applicant employed 2 API intermediate manufacturers and 1 final API manufacturer
• Final API manufacturer observed particulates in material received from 1 of the 2 intermediate sites and notified the sponsor
• Applicant did not convey findings to the implicated intermediate facility OR the sister facility
Case Study #3
Limited Batch Data at Time of Filing

• Single clinical batch for Orphan BTD product
• Minimal developmental data to correlate impact of physical properties of product on dissolution
• Process validation batches demonstrated segregation and impacted dissolution
• Clinical impact of segregation and variable dissolution weighed against the lack of alternative therapies
• Multiple PMC’s issued
Case Study #4
Minimal Stability Data and Batch Data

• Degradant observed on stability that was not qualified in development
• Data demonstrates the product is efficacious, but no data available on the risk imparted by new impurity
• Firm advised during development to qualify impurity
• Significant internal communication and with the applicant
• Several options considered:
  – Restrict shelf life
  – PMR’s/PMC’s
  – CR
Case Study #5
Enhanced Regulatory Approaches Proposed for BTD Product

- Applicant proposed enhanced control strategy using established conditions in initial NDA filing
- Enhanced control strategy was not discussed in IND phase
- Accelerated review did not allow time to properly discuss control strategy
- Approval for the BTD product was critical for American Public; development regulatory science (enhanced regulatory approaches) is of secondary concern
Overall Lesson From Case Studies

• Keep patient in mind while considering quality risk
• Delineate identified risks and potential unidentified risks to quality at IND stage and in NDA submission
  – Propose and discuss risk mitigation strategies as soon as possible with FDA
• Proactive and transparent discussions are more effective than retroactive or reactive steps
  – Save time during review
Potential Synergy with Continuous Manufacturing

• Process Development and Quality Advantages
  – Allows rapid & automated testing of process conditions
    • Quality by Design approach and increased process knowledge
  – Development at commercial scale
    • Minimize scale-up issues
  – Potential for improved product quality

• Manufacturing Advantages
  – Smaller equipment and facilities
    • Lower capital and operational costs
  – More flexible operation to meet demand – ↑ or ↓ run time
  – Reduced solvent use and wastes
  – Amenable to Real Time Release Testing approaches
Conclusions

• The BT route provides expedited availability of drugs for life-threatening diseases

• The expedited development of BT drugs provides opportunities as well as challenges

• FDA has been exploring and adopting novel strategies to assess the quality of BT therapies

• Active communication between FDA and pharmaceutical industry is necessary to facilitate timely approval of BT drugs
Weighing the Risks

• There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.

Donald Rumsfeld February 2012
Thank you!