CMC/GMP Considerations for Accelerated Development and Launch of Breakthrough Therapy Products

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Outline

• Advancing Breakthrough Therapies for Patients Act
  – Benefits and Challenges

• Breakthrough CMC/GMP Strategy for Large and Small Molecule Products
  – Process and Formulation Development
  – Process Validation Considerations
  – Analytical Development & Control Strategy
  – Manufacturing Scale and Launch Site
  – Pharmaceutical Quality Systems Considerations

• Potential Opportunities for Flexibility in CMC Development Activities for Breakthrough Therapy Products
## FDA’s Existing Expedited Pathways

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<th>Accelerated Approval</th>
<th>Fast-track Designation</th>
<th>Priority Review</th>
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<td><strong>When Appropriate</strong></td>
<td>Drugs with the potential to fill an unmet need for serious or life-threatening diseases, and whose activity can be assessed using a qualified surrogate endpoint</td>
<td>Drugs intended to fill an unmet need for serious diseases</td>
<td>Drugs with potential to provide major advance over existing therapies</td>
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<td><strong>How it Helps</strong></td>
<td>Makes potentially useful new agents rapidly available to patients</td>
<td>Enables more efficient development through frequent communication between FDA and sponsor</td>
<td>Shortens FDA review time by 4 months</td>
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<td><strong>Limitations</strong></td>
<td>Requires additional randomization of patients in confirmatory trials</td>
<td>Does not condense or abbreviate clinical development</td>
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The Advancing Breakthrough Therapies for Patients Act—July 2012

• New abbreviated Development Pathway
  – Legislation included as part of the 2012 PDUFA V re-authorization to expedite development of new, potential “breakthrough” therapies
  – Specifies that a new drug may be designated as a Breakthrough Therapy if it is intended to treat a serious or life-threatening disease, and preliminary clinical evidence suggests that it provides a substantial improvement over existing therapies
  – Benefits of the Fast-Track designation (i.e. rolling submissions) and Accelerated Approval (i.e. use of surrogate endpoints) and Priority Review are all available in the Breakthrough Therapy Program

• Sponsors can request Breakthrough designation at any time during review of an IND, and FDA has sixty days to respond to the request

• FDA developing guidance on criteria for designation, and processes to make a designation and expedite the development and review of a potential breakthrough product
Benefits and Challenges of Breakthrough Therapy Designation

• FDA and sponsor collaborate in a dynamic, multi-disciplinary process to determine most efficient path forward—"all hands on deck approach"
  - Senior manager and experienced review staff involved
  - More frequent and interactive communications

• Expedited development and review so that clinical trials are as efficient as possible and number of patients exposed to a potentially less efficacious treatment is minimized
  - Clinical development timelines potentially reduced from 7-10 years to 3-5 years

• Shorter clinical development programs will have significant impact on product and process development timelines requiring sponsor to undertake “all hands on deck approach”
  - Requires collaborative cross functional approach between development, commercial and regulatory operations
  - Resource intensive; will need to be selective
  - Will need effective interface with clinical to identify potential candidates early
Accelerated clinical timelines for products designated breakthrough therapies will necessitate new approaches to product & process development, commercial readiness, launch and regulatory filings.

- Does not mean you can do less, will need to start some activities sooner
  - Focus on reliable supply of quality product at launch, not process optimization
  - Front-load critical product and process characterization activities earlier

- Develop manufacturing readiness plan to address timeline for development of the manufacturing capabilities with goals aligned to clinical development program
  - Manufacturing sites
  - Validation approach for process and methods
  - Stability studies

- Perform risk assessment regarding availability of less CMC information at the time of filing and product launch versus patient benefit; discuss mitigation approaches with FDA early
Key Considerations for Accelerated CMC/GMP Development Programs

• Intended product quality must not compromise patient safety or assurance of commercial supply
  – Use of initial product supply from clinical manufacturing process/site
  – Delay certain process validation requirements not directly related to patient safety
  – Leverage prior knowledge, platform data, and use of comparability protocols
  – Leverage use of stability data from representative pilot scale lots
  – Consider broader product quality acceptance ranges for non-critical quality attributes until further manufacturing experience is gained post-approval
Design of Expedited CMC Development Programs for Large and Small Molecule Products

- Cross functional technical team from Genentech-Roche modeled accelerated timelines for large and small molecule products

- Assumptions for timeline creation:
  - Breakthrough designation obtained shortly after phase I studies, with pivotal study becoming expanded phase Ib or II
  - Typical clinical development program would be 5 years from initiation of phase I to launch
    - 1-2 years to generate sufficient preliminary clinical information to qualify for breakthrough therapy designation
    - 2-3 years to complete the pivotal study, file an application and launch the product

- Under this scenario some phase III activities will need to be accelerated pre-approval or deferred post-approval

- This is a model and each breakthrough development programs will vary depending on: complexity of the product; timing of designation; how soon accelerated CMC development activities begin; availability of platform technology and relevant prior knowledge
Breakthrough CMC/GMP Strategy for Large and Small Molecule Products
Breakthrough CMC Timeline Considerations

*Process and Formulation Development*

- Prioritize development efforts on process reliability over yield and cost of goods
  - Small molecule drugs focus on:
    - API attributes impacting formulation and DP manufacturability
    - DP process impacting PK and patient safety
    - Lock clinical formulation to avoid BE studies prior to launch
  - Large molecule drugs focus on:
    - Cell line lock at phase 1
    - DP formulation lock at phase 1
- Propose reduced real time stability for commercial material
  - Leverage stability from early development when formulation remains unchanged
  - Commit to provide more real time confirmatory data during review and post-approval
Breakthrough CMC Timeline Considerations

Process Validation Considerations

• Likely to have limited manufacturing experience at commercial scale

• Leverage life-cycle validation principles, “continued verification”
  – Inclusion of development experience/smaller scale batches in PPQ strategy
  – Some PC/PV studies could be deferred, such as linkage studies

• Consider concurrent validation with product distribution concurrent with release (or approval for release) of each conformance batch

• Cleaning verification demonstrating process capabilities vs cleaning validation
  – Cleaning validation accomplished by concurrent validation and deferred to post-filing

• PC/PV studies impacting patient safety must be complete prior to filing
Analytical Development & Control Strategy

- Analytical method development
  - Front-load analytical understanding to offset more limited process robustness and support future comparability exercises.
  - Test qualification lots before final assay validation is completed; presents a business risk and must be completed before release.
  - Launch from clinical site with QC release, and transfer to commercial site QC release post-launch.

- Control strategy based on limited manufacturing experience
  - Gain flexibility to modify the control strategy, specs, or key process parameters post-launch after more manufacturing experience and completion of process validation.
  - File with more tests and then justify dropping some when more data become available.
  - File with provisional specifications and IPC’s and update post-approval.
  - Manage second generation processes through a life-cycle approach in post-approval lifecycle management plan.
Breakthrough CMC Timeline
Considerations

Manufacturing Scale and Launch Site

• Clinical vs commercial launch site
  – Determine as soon as possible launch sites for DS and DP
  – Consider dedicated launch sites

• Expectation is that the clinical manufacturing facilities used for launch would need to meet the same quality expectations as commercial manufacturing facilities.

• Key differences for consideration are
  – Cleaning verification versus cleaning validation
  – Multi-product manufacturing, including investigational compounds with limited safety data
PQS Alignment with Breakthrough Product Development

• Assess PQS and build in appropriate flexibility to accommodate accelerated activities for BT products

• Identify documents covering potential patient safety related activities and classify into three categories:
  – Must comply fully to address patient safety need
  – May be delayed post filing but completed prior to launch
  – May need to be deferred until post-approval

• Prepare internal assessment addressing need for flexibility in PQS and how to resolve
  – Obtain Quality unit approval
  – Discuss and reach agreement with FDA prior to application submission
Opportunities for Flexibility in CMC Development Activities for Breakthrough Therapy Product
FDA Standards for Marketing Approval of Breakthrough Therapy Drugs

• FDA expectation for pharmaceutical quality is the same for all drugs
  – Approval standards require demonstration of substantial evidence of effectiveness, safety and product quality

• The streamlined development programs for breakthrough therapies, and potentially smaller patient populations for which they are being developed will create significant challenges to develop and launch these products

• FDA regulations for rare diseases allow for flexibility and scientific judgment in:
  – Applying approval standards, and
  – The kind and quantity of data required for a particular drug to meet the statutory standards

• Need to balance risk of less data at time of filing with benefit to patients through use of:
  – PMCs & PMRs
  – Post-approval life cycle management plan in marketing application
  – Well designed comparability protocols
Opportunities for Flexibility in CMC Development
Activities for Breakthrough Products (1/3)

• Manufacturing Scale and Launch site
  - Scale-up phase 3 clinical lots to commercial scale for launch with bridging comparability study
  - Launch from clinical site with clinical QC release, and transfer to commercial site with commercial QC release post-approval

• Control System
  - Launch with provisional control system that ensures consistent product, and upgrade the control system post-approval after more manufacturing experience and completion of process validation, i.e.
    • Filing with more tests initially, and justifying elimination of some post-approval
    • Filing with broader IPC and product specification acceptance criteria at launch and tightening post-approval for specifications that demonstrate process consistency
Opportunities for Flexibility in CMC Development
Activities for Breakthrough Product (2/3)

• Process and Formulation Development
  – Launch commercial process with limited experience and optimize post-approval with comparability protocol and in vitro in vivo correlation model as a biomarker for making changes to a small molecule drug post-approval
  – Launch with phase 1-2 formulation and optimize post-approval with comparability protocol and in vitro in vivo correlation model as a biomarker for making changes to a small molecule drug post-approval
  – Leverage life-cycle validation principles “continued verification” to release batches concurrent with manufacture of initial conformance batches

• Stability Data
  – Launch with reduced real time stability for commercial material and leverage stability from development lots and predictive modeling for small molecule degradation profiles
Potential Opportunities for Flexibility in CMC Development Activities for Breakthrough Product (3/3)

• Discuss with FDA risk of less CMC information at the time of filing and product launch vs patient benefit; and mitigation approach
  – Include post-approval lifecycle management plan (PALM) as part of the filing to support completion of deferred CMC activities post-approval
  – Provide detailed timelines, deliverables, and types of regulatory filings to complete activities

• Discuss with FDA appropriate phase-specific flexibility of the Pharmaceutical Quality System to accommodate accelerated manufacturing development activities for a breakthrough product
Summary

- Breakthrough Therapies offer significant patient benefits, but also introduce CMC challenges during the product development lifecycle.

- CMC activities may define the Critical Path, and lead to truncated Phase III development cycles. In some cases, Process Characterization/Validation activities may need to be accelerated or delayed post-approval.

- Key aspects of the Phase I process (cell line, DS process, formulation) will be maintained for commercial product launch. Post-launch process changes may be needed to ensure continuous supply.

- Some elements of PAI Readiness, Control Strategy and PQS may need to be adapted for Breakthrough Therapies.
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