Challenges and Opportunities for Commercial Manufacturing Readiness and Launch of Large Molecule Breakthrough Therapy Products

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Outline

• Potential scenarios and accompanying challenges
  – Considerations for accelerated CMC/GMP development
  – CMC activities that may become part of the critical path to filing

• Balancing risk of less CMC data at time of filing vs. patient benefit
  – Increased post-launch activities to mitigate risks
    • streamline path to post-launch process optimization & site transfers
    • launch with provisional control strategy and update later
    • defer design space claims
  – Opportunities in pre-launch workflows to enable rapid timelines
    • use clinical sites and material for launch
    • enable reasonable shelf-life with reduced real-time stability data
    • complete certain activities during filing review
    • delay or waive PAI inspection

• Summary
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*

• FDA and sponsor collaborate in a dynamic, multi-disciplinary process to determine most efficient path forward—”all hands on deck approach”

• 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
CMC Activities May Become Critical Path

- Accelerated clinical timelines for products designated breakthrough therapies will necessitate new approaches to product & process development, commercial readiness, launch and regulatory filings

- The context for a given project (timing of BT designation, length of clinical studies, etc.) will lead to different needs for different cases

- Key considerations for Large Molecule CMC development
  - Focus on reliable supply of quality product at launch, not process optimization
  - Front-load critical product and process characterization activities where possible
  - Perform risk assessments regarding availability of less CMC information at the time of filing and product launch versus patient benefit
  - Negotiate with FDA on the CMC/GMP activities that can be deferred post-approval without compromising patient safety
A Scenario Where Breakthrough Therapy Designation Would Compress CMC Timelines

Breakthrough Designation

CMC on Critical Path to Launch

Compress CMC Ph 3 Activities

0 1 2 3 4 5 6

Clinical Timeline

R&D Non-Clinical Phase 1 Phase 2 Phase 3

Non-clinical Studies

Clinical Studies

Define TPP pCQAs Establish Analytical Profile & Methods

Product Release w Qualified Methods Commercial Method Transfer & Validation Product Release w Validated Methods

Cell Line Selection

Mfg at Clinical Site Commercial Process Development Process Characterization & Validation

Mfg at Commercial Site

DS/DP Qual Lots

Stability studies

File Approve Life Cycle Management

Interim Data

Interim Data
Increasing Post-Launch Activities to Mitigate Risks

• Launch commercial process with limited experience and optimize post-approval
  – Process optimization work (increased titer/yield) will be truncated
  – Focus on reliability of cell line, process and formulation and address only critical issues
  – In some cases, post-approval changes may be needed to ensure adequate supply
  – For complex products, reduced development can be a significant risk (should be easier for antibodies)

• Full package of studies to support design space claims unlikely to be available at time of launch
  – Certain PC/PV studies could be deferred, such as linkage studies
  – Focus on completing PC/PV studies with patient safety implications

• Streamlined path to process modifications and site transfers post-launch could be important to ensure long-term supply
Developing a Control Strategy with Limited Process & Manufacturing Experience

• Front-load analytical understanding to offset more limited process robustness and support future comparability exercises

• Leverage life-cycle validation principles and “continued verification” post-launch
  – Consider concurrent validation – could provide validation protocol and at least one executed batch record at time of filing and leverage robust Quality systems & demonstration of manufacturing of consistent clinical material

• Launch with provisional control system focused on ensuring consistent product

• Request flexibility to upgrade the control strategy, specifications, or CPPs post-launch with additional manufacturing experience & completed process validation
  – File with more tests initially, and justify elimination of some post-launch
  – File with broader IPC and product specifications at launch and tighten post-approval for attributes based on demonstration of process consistency

• Include Post-Approval Lifecycle Management plan in filing to support completion of deferred CMC activities post-launch
Manufacturing Scale and Launch Site Considerations

- Pivotal studies may be performed with material from different scale and/or site than is intended for long term commercial production.

  *studies originally expected to be Phase 2 studies could be used as pivotal studies*

- Scale-up to commercial scale for launch with bridging comparability study
  - With compressed timelines, may be desirable to launch from clinical site and transfer to commercial site subsequently
  - Ongoing clinical studies may provide opportunities to bridge materials

- Clinical manufacturing facilities used for launch would need to meet quality expectations of commercial manufacturing facilities
  - Key differences for consideration include:
    - cleaning verification versus cleaning validation
    - multi-product manufacturing, including investigational compounds with limited safety data
Enabling Reasonable Shelf Life with Reduced Real-Time Stability Data

- Accelerated development timelines may limit availability of real-time stability data from commercial DP site

- Launch with reduced real-time stability for commercial material
  - Leverage stability from early development when formulation remains unchanged and product comparability demonstrated
  - Provide stability protocol for commercial material
  - Commit to provide more real-time confirmatory data during review and post-approval

The need for an alternative path to enable an acceptable shelf-life for long term supply may be a fairly common issue for Breakthrough Therapies
Summary

• Breakthrough Therapies offer significant patient benefits, but the reduced timelines introduce significant CMC challenges for large molecule development.

• Each case will have different risks and constraints so the specific CMC approaches will vary by product.

• Key areas of opportunity include:
  – Increased post-launch activities including control system updates, process optimization where needed and streamlined site transfers.
  – Use of clinical sites & materials for launch and enabling reasonable shelf-life with reduced stability data.

Effective collaboration with the FDA is critical to enable getting these important new medicines to patients.
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Doing now what patients need next