A REGULATORY PERSPECTIVE ON ACCELERATED PRODUCT DEVELOPMENT PROGRAMS

Christopher Downey, PhD
FDA/CDER Office of Biotechnology Products
FDA Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Outline

1. Benefits and Risks of Accelerated CMC Development
2. Expedited Regulatory Pathways
3. Points to Consider and Lessons Learned
1. Benefits and Risks of Accelerated CMC Development
Bringing lifesaving products to patients is a shared goal of industry and FDA

- Industry interest in:
  - early development strategies that can speed getting to proof-of-concept and first-in-human studies to inform decisions on developability
  - later development strategies to achieve faster approval and commercialization

- Potential benefit to patients if promising products are identified early and resources are marshalled towards their speedy development and approval
Benefits of fast CMC development must be weighed against risks of incomplete product and process understanding

- Pay now or pay later decisions
- Delaying development activities early in development can risk problems or delays later in development and risk burdensome control strategies and PMCs upon commercialization
- Crafting a licensing application with limited manufacturing and clinical experience can be challenging
- Risk assessment and risk mitigation at each phase of development are critical
Examples of areas where decisions made to accelerate early development can impact later development

- CQA assessment and product characterization
- Formulation development
- Cell line cloning, master cell bank development and characterization
- Assay development (e.g. potency, host cell protein assay, immunogenicity assays)
  - Bridging early assays to commercial assays
  - Suitable assays in place for process performance qualification
  - Suitable assays in place for pivotal trials
- Timing of process scale-ups and site transfers
Case study: setting specifications with limited manufacturing and clinical experience

• Relatively few lots manufactured in expedited program

• Challenge in setting specs from few lots mitigated by:
  – Early identification of CQAs enabled targeted process characterization and development
  – Early development of assays maximized availability of high-quality data
  – Post-marketing commitment to reevaluate and adjust specifications after specified number of commercial lots
Case study: underdeveloped reference standard

- Reference standard stored as liquid solution
- Reference standard requalification program did not track potency against a separate standard or measure an absolute potency
- Significant drift in relative potency for lot release and stability data attributed to loss of reference standard potency on long-term storage
- **Lesson learned**: delaying reference standard development negatively impacted control strategy
Goal of any CMC development program is to ensure consistent production of a safe and effective commercial product

- The pace of development does not fundamentally change the content of BLA CMC sections
- “Flexibility” on the type and extent of the CMC information expected at the time of BLA submission vs what can be provided during BLA review or post-approval will depend on:
  - Risk-benefit of less CMC information vs. patient benefit
  - Product and process knowledge and strength of control strategy
2. Expedited Regulatory Pathways
Regulatory flexibility and risk tolerance are increased for life-threatening conditions and unmet medical needs

- 21 CFR 312.80 establishes procedures to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists.

- Physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses than they would from products that treat less serious illnesses.

- For such products, FDA will exercise the broadest flexibility in applying statutory standards, while preserving appropriate guarantees for safety and effectiveness.
Specific expedited programs for serious conditions

- Fast Track Designation
- Breakthrough Therapy Designation
- Accelerated Approval (approval from surrogate or intermediate clinical endpoint, with post-approval confirmatory studies)
- Priority Review (6 month BLA review clock instead of 10)

Refer to: *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*
Fast Track Designation

• Intended to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need:
  – More frequent meetings with FDA, e.g. pre-IND, end of phase 1, end of phase 2, additional meetings as needed to discuss content of filing or other critical issues)
  – Eligible for priority review or accelerated approval (if respective criteria are met)
  – Eligible for rolling review
Breakthrough therapy

• Designed to expedite development and review of drugs:
  – Intended to treat a serious condition
  – With *preliminary clinical evidence* that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)

• Breakthrough Therapy gets:
  – All features of Fast Track designation
  – Intensive guidance on an efficient drug development program, beginning as early as Phase 1
  – Organizational commitment involving senior managers and experienced review staff
  – “All hands on deck”
Fast track and Breakthrough are opportunity to discuss accelerated CMC development strategies early and (sometimes very) often

- Early and frequent communication between FDA and sponsors is encouraged throughout the development and review process.

- Frequency of communication assures that questions and issues are resolved quickly, (ideally) leading to earlier drug approval and access by patients

- Meetings (e.g. pIND, EOP2) available for standard track products are also opportunities to discuss novel development strategies to speed CMC development
Clear communication between stakeholders is essential for rapid development

- Accelerated CMC development programs are by their nature different from “standard” programs and pose unique challenges.
- Early communication and agreement on accelerated development approaches can prevent delays later in development.
- **Lesson learned**: provide enough detail in meeting briefing packages to spur a meaningful dialogue.
  - Scientific rationale that CMC development strategy will yield a well-characterized product and well-characterized and well-controlled manufacturing process.
Case study: Accelerated development of life-saving Breakthrough product

- Unique expression system, with multiple manufacturing sites each for protein expression, purification, and drug product fill/finish
- Meetings throughout development led to paths forward for qualifying expression system, establishing comparability among sites, planning inspections
- Meetings during BLA review cycle sped resolution of review issues and yielded agreements on activities that could be submitted post-approval
- Life-saving orphan product developed and approved on a rapid timescale
3. Points to Consider and Lessons Learned
Successful accelerated CMC development requires careful planning

- Align CMC development with clinical development
- Process capable of supplying market and all needed supporting data are available for the CMC submission
- Timing of process scale-ups and site transfers
- Timing of rolling submissions (if applicable)
  - Rolling sections, including CMC, should be complete
Some CMC development strategies cannot be compressed or delayed

- The timing of some development activities may be risk-based
- Some activities are inherently fixed in timing or duration (e.g., respectively, comparability studies, accruing of long term of stability data)
- Some review activities have fixed timing (e.g. pre-approval inspection)
Case Study: BLA review delayed by manufacturing schedule

- Pre-approval inspection must be when “the establishment is in operation and is manufacturing the complete product for which a biologics license is desired” (21 CFR §600.21)
- Drug Substance manufacture scheduled too late in BLA review cycle to accommodate an inspection within the priority review timeline
- Lesson learned: timing submissions and manufacturing schedule facilitates abbreviated review timelines and reduces risk of fileability issues
Case Study: no stability data available for commercial product

• Expiration dating is based on data from at least 3 lots representative of commercial process (general expectation is at least 6 months or 3 data points)
• Data from clinical-phase lots can be leveraged if comparability is demonstrated
• Scale-up and transfer to commercial manufacturing site performed very late in development. No stability data available for any commercial site/scale lots at the time of BLA submission; little data would be available by goal date
• Lessons learned: careful planning needed to ensure sufficient data are available for an fileable and approvable application; reach agreement on plans with FDA in advance
Getting the non-technical details right also accelerates approval

• Issues with “routine” aspects of commercializing a product can delay development or approval

• A solid CMC development program can be delayed by incomplete or unclear regulatory submissions
Case study: CGMP compliance issues delay approval

- For a product under an expedited review program, a pre-approval inspection identified significant CGMP issues at a multiproduct manufacturing/testing site.
- The issues identified were not specific to that product, but the unsatisfactory GMP status of the establishment delayed the review process.
- Lesson learned: importance of due diligence on manufacturing sites, test sites, CMOs.
Case study: missing information delays BLA review

- Initial CMC submission for product in expedited program under rolling review was missing key sections (e.g. analytical method validation, comparability studies)
- Most of the studies had been performed, but were not included in the dossier
- The incomplete CMC submission delayed the start of the PDUFA clock
- Lesson: accelerated product development includes accelerated dossier development
Summary

• Risk-based regulatory approach to accelerated development: benefits to patients vs potential risks of reduced product and process understanding (and mitigations thereof)

• Expedited programs provide greater regulatory flexibility and opportunities for more frequent communication

• Effective and detailed communication between sponsors and FDA throughout development facilitates better and more informed CMC development decisions

• Successful strategies plan for all information that will be required at the time of marketing application, during the review cycle, and post-approval