A Potential Innovative CMC Solution: Responding To Public Health Needs With An Accelerated Clinical Pathway–A Vaccine Example

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It is an Internal Race to Bring Products to the Market
Meet the Drivers:

Clinical Product Development constitutes the progressive clinical research studies to demonstrate the product is safe and efficacious.

Chemistry, Manufacturing, and Controls (CMC) constitutes that part of pharmaceutical development that deals with the nature of the drug substance and drug product, the manner in which both are made, and the manner by which the manufacturing process is shown to be in control.
Clinical Development Takes the Lead with an **Accelerated Approval Pathway**

Per CODE OF FEDERAL REGULATIONS SEC 601.41

- FDA may grant marketing approval on the basis of clinical trials that establish the biological product has an **effect on a surrogate endpoint**
- Applicant to study the biological product further to verify the clinical benefit
- Post-marketing studies would usually be underway

**Accelerated Approvals Bring Products to Patients Faster**

**Accelerated FDA Approval of New Hib Vaccine Boosts Nationwide Supply**

Yael Waldbaum
August 20, 2000

August 20, 2009 — The US Food and Drug Administration (FDA) has granted accelerated approval for a tetanus, diphtheria, and pertussis vaccine (Hib vaccine pharyngeal).  A booster dose for children aged 15 months through 5 years.

**FDA Approves a Vaccine to Address a Critical Public Health Need — Trumenba® for Prevention of Serogroup B Meningococcal Disease**

Published on November 13, 2014 by FDA Voice

By: Kenneth B. Midthun, M.D.
Vaccine Case Study Background

The Mission: Develop a high quality vaccine for unmet medical need that can be launched expeditiously and available to patients all the time

Clinical - Go FAST!
- Vaccine target is recognized by health authorities as an unmet medical need
- Regulatory agencies provide early feedback they are open to considering an accelerated pathway (no commitment)

CMC – Can we keep up?
- Final manufacturing process is still under development
- Need a facility for Ph3 clinical manufacturing
CMC Strategy: Enable acceleration by leveraging CMC opportunities

1. Compress process and analytical development timeline
2. Supply Ph3 clinical consistency lots from an existing facility and tech transfer prior to initial licensure
3. Compress timelines for licensure facilities
Opportunity # 1: Compressing Process Development Timelines
Accelerated Pathway puts the Squeeze on CMC Window

Seek agency commitment to Accelerated Approval Pathway prior to start of Phase 3
Start the race together

Pre-Investment Increases CMC window

$$ and resources prior to Proof of Concept
What happens in the “CMC window”?

- Define raw materials, process operations, and parameter set-points.
- Complete Analytical method development

**Process Characterization** - Additional process experience to understand impact of raw material, components, and process parameters on critical quality attributes and process variability.

DS and DP process qualification lots are manufactured in commercial facility to demonstrate the process is capable of reproducibly meeting critical quality attributes.

Accumulate minimum of 6M of drug product accelerated and real-time stability data and prepare file for submission.
Strategy: Initiate CMC Activities Earlier and Overlap in Acceleration Model

- Process Definition & Analytical Development
  - Facility Design, Build, Qualification
  - Process Characterization
  - Analytical Validation
  - Process Qualification
- Stability Data
- Prepare to File
Benefits:

- Earlier process characterization work increases process understanding and opportunity to influence Final Manufacturing Process
- Early site engagement improves knowledge transfer and increases influence during process design needed for robust manufacturing procedures

Challenges:

- Facility design re-work if process changes identified during process characterization
- Rapid increase in resource demand to support characterization and facility design
- Cannot accelerate generation of stability data. Compress with agency alignment to use stability data from product development studies.
Opportunity #2: Supplying Phase 3 Consistency Lots from Existing Facility
Opportunity: Supply Clinical Consistency Lots From an Existing Facility (not Launch Facility)

Impact: File Ready milestone delayed by years if consistency lots must be supplied from commercial launch facility.
Strategy: Gain Regulatory Alignment to Allow Flexibility in Sourcing Clinical Consistency Lots

Proposal to Regulatory Agencies:
- Allow company to use **100% of clinical consistency lots from pilot plant or CMO facility**
- Demonstrate **analytical comparability** through deep and extended characterization between the consistency lots and PPQ lots from the commercial facility to ensure comparability of the clinical and commercial product
Benefits:

- Critical to enable accelerated pathway
- Faster patient access to vaccine to meet an unmet medical need
- Company can complete tech transfer in parallel to the Ph3 study

Challenges:

- Vaccines do not typically have the benefit of platform technologies (ex. Biologics)
- Minimizing process changes during tech transfer may propagate long-term process robustness and supply risks
- Scale-up may be required between pilot plant/CMO and commercial facilities
- Failure to meet comparability requirements may lead to additional process development and repeating qualification lots with impact to file timeline
Opportunity #3: Compress timelines for licensure facilities
**Opportunity:** Optimize facility plan based on project timing and resources

Facilities needed for each node:
- Drug Substance
- Drug Product
- Laboratory Operations

- Internal New Build (Cannot meet Accelerated Timeline)
- Internal Retro-fit of Existing Space
- External Partner
- External Contract Manufacturer
**Strategy:** Capital investment in facilities to support launch, Acceleration timeline, and defers spend required to increase capacity.
Benefits:

• Minimizes capital spend prior to approval
• Improves speed to market for unmet medical need
• Launch facility could be designed as product agnostic to repurpose for future pipeline opportunities

Challenges:

• Launch facility is not sized for market demand or cost effective (COGs)
• Post-approval filings required for capacity expansions.
CMC Strategies may Enable Clinical and CMC to Finish Together but Comes with Risk

- Compress process and analytical development timeline
  - **RISK:** Post-approval filings to improve process/analytical robustness. May result in high discard rates and product shortages impacting patient access and public trust

- Supply Ph3 clinical consistency lots from an existing facility that will not be used for commercial supply
  - **RISK:** If regulatory feedback does not support strategy, significant impact to speed to market and patient access

- File and launch from a commercial facility with limited capacity
  - **RISK:** Post approval filings required and risk of product shortages until larger facility is approved
Early Feedback of Possible Accelerated Approval Pathway is Not a Commitment

If Accelerated Approval pathway is not granted:

**Impact if company continues program:**
- Increased time to improve process and analytics
- Return on investment is delayed by multiple years
- Facility has prolonged idle period
- Staffing challenges to maintain experienced operators

**Impact if company discontinues product development:**
- Unmet medical need remains
- May influence other companies to discontinue programs given product development investment and clinical trial durations
- Sunk costs in facility and resources
- Factory must be repurposed
How Can Regulators Help CMC Support Acceleration and Ensure Robust Product Supply?

- Provide guidance and flexibility on expectations for clinical consistency lots if not manufactured in the commercial facility used for licensure.
- Flexibility to leverage stability data obtained during development (not PPQ/final facility) to support shelf-life.
- Guidance for change control requirements prior to BLA to support changes between manufacture of clinical supply lots and commercial facility qualification.
- Approve prospective comparability protocols to streamline post approval filings/reviews for scaling out of facilities (e.g. modular capacity expansions) based on sound science.
- Limit comparability requirements to only scope of transfer (ex. upstream, downstream, drug product).
THANK YOU