Inspection Challenges, Efficiencies, & Opportunities

Biosimilar BLA Perspective
Focus Communication

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50% of BLA CRLS are Inspection related

Quality related Observations, can we reduce percentage CRLs with communications?

❖Common Goal for FDA and Industry:

- Achieve a 1st cycle approval
- Ensure medications are safe, effective and of high quality.

❖CRL is not in the best interest of FDA, Applicant, Patients, Payers and Pharmacies;

- Biosimilars bring price competition: Delay to the market impacts affordable medicines for patients
- Payers, Hospitals frustrated as they have deliverables
  - Intensive work required to bring biosimilar to patients: Assumes approval, preparation for launch readiness at pharmacies and hospitals, insurer preparations, distribution centers
- Resources FDA and Applicant: 2nd submission and review
- If needed, reinspection is not overnight, often a year later
- Wasted shelf life: Likely loose a year of stability impact strong supply chain

❖Problem: 50% of BLA CRLS are Inspection related

- 2024 Duke-Margolis meeting: "*Continual Improvement of CDER BLA Submission, Assessment, and Facility Readiness/Inspection: CMC for Biologics & Biosimilars"*
  - Goal "Opportunities to improve communication between sponsors, contract manufacturing organizations, FDA"

Communication is Vital for first cycle approvals:

Inspections during BLA: Often PLI plus Surveillance

Challenges BLA review Timelines,

❖Recently surveillance inspection are combined with PLI: The bottle neck of a BLA.

- An NAI status is rare. Often there is an observation, and a Form 483 is received
- *If a form 483 is received an IR is sent to the applicant "During a recent inspection of (FEI 12345678) manufacturing facility for this BLA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this BLA may be approved."*
- Surveillance Inspection closeout to EIR status is 3 months

❖Timeline challenge for a 1st cycle approval for a BLA

- Month 5 Mid Cycle: Need for an inspection is often communicated
  - Advanced notice is required for an inspection: scheduled 30-45 days after mid cycle
  - Inspection now conduction around month 6-7 of review
  - EIR would then come month 10
  - PLI for a Biologic requires inspection of the manufacturing process for both the DS and the DP
  - Careful rescheduling of approved product manufacturing for PLI: not to interrupt supply chain
  - Even providing proposed inspection before mid cycle, never heard of an inspection
- Month 9 late cycle: Acceptance of data after late cycle is minimal
  - Often results in an extension or CRL
  - Time needed for legal sign off by multiple departments at FDA

BsUFA III Commitment letter

Recognizes the importance of communications between agency and applicant

Excerpts from BsUFA III Commitment Letter

- FDA and industry believe enhanced communication between review teams and industry on certain pre-license inspections can facilitate an efficient application review process.

- FDA's goal is to communicate its **intent to inspect a manufacturing facility at least 60 days in advance of the pre-license inspection and no later than mid-cycle**. FDA reserves the right to conduct manufacturing facility inspections at any time during the review cycle, whether or not FDA has communicated to the facility the intent to inspect
- Late-Cycle Meeting Discussion Topics inspectional findings identified to date
- FDA's goal is to complete all GCP, GLP, and GMP inspections ,,, within 10 months of the date of original receipt of the application. This will ***allow 2 months at the end of the review cycle to attempt*** to address any deficiencies identified by the inspections

- FDA **will focus on enhancing communications** during application review, including inspection communications, and advancing the development of combination and interchangeable products

How can we act on these commitments?

Post Inspection Communication with applicant: Enhanced communication between Inspectors & OPQ

What works Well during an Inspection

Recognizing Auditors have tight schedule, Communication is imperative

- 1st Day Opening meeting: Inspectors present their schedule
  - Agree for daily host meeting: Best time of day to discuss findings with inspectors and clarification
- Daily Host Meeting:
  - Inspector Summarize the findings for the day
    - Ensures manufacture knows findings before issue the 483
    - Transparency: When a observation refers back to CFR, clearly define what is expected and what is the non compliance.
  - Applicant allowed to ask questions
    - Present what is already self identified and planned in the system
    - Provide documentation (work order, new equipment, etc.)
    - Work each day to start addressing findings, agree on appropriate next steps
- Prior to Closeout Meeting: Sponsor allowed to present implemented CAPAs and effectiveness check so as not to be reflected in the Form 483
- Final closeout discussion: Only open observations will be reflected in the form 483

Daily communication could simplify process: Address daily events

Goal: More defined end of audit document: Clearly calls out issues that require further interventions (re validate, additional studies)

Challenges of an Inspection

Timing and communication

- ❖Foreign Inspections: Should have a collaborative approach
  - Individuals who appear to be fluent in English may not be
  - Individuals afraid of speaking and need more time to answer
- ❖Lack of Transparency:
  - Findings often don't refer back to CFR hence subjective and not clear what is expected
  - What is expected and what is the observation and what is the non compliance.
- ❖Closeout Inspectors move on to another inspection, report is sent to OPQ
- ❖No ability to request a post inspection meeting with OPQ:
  - To clarify questions from either side
  - Confirm CAPAs are in line with FDA expectations
  - Align Appropriate Effectiveness checks
  - What else needed for 1st cycle approval (additional testing etc.?)

Worst Result: Reinspection is required for Effectiveness check

Often wait a year, there are alternate ways to address effectiveness

Challenge Post inspection: Communications between FDA Offices

Form 483 is presented to the applicant as one issue to be resolved

- Manufactures perspective: Enhance communication between OII, OPQ and OTBB
  - OPQ's role: Integrate the assessments for a single quality assessment:
    - BLA review with the evaluation of manufacturing facilities,
  - However, OTBB PM does not have information regarding inspections
- Lack FDA Feedback: Form 483 CAPA proposals and monthly updates

"Satisfactory resolution of these deficiencies is required before this BLA may be approved "

  - No Transparency:
    - Which deficiencies are not resolved: based on proposed CAPAs
    - Which proposed effectiveness are not adequate
  - No Insight: What is needed for first cycle approval
    - Further testing, 3rd party oversight what does it take?
  - No Segregation of the 483 findings linked to BLA in the review vs. general GMP findings
- Post Inspection: No Process for Applicant /Manufacturer to request meeting OII & OPQ

Summary: Proposals to Consider

Especially when there is a combined PLI and Surveillance

- Start Inspection Process Earlier in BLA
  - Notify applicant if an inspection is required by day 60 rather than month 5 mid cycle
  - Recognize BLA proposed early inspection dates by Applicant
- During Inspection
  - Give time for daily discussion between manufacturer and Inspector
- Applicant Responses post Inspection:
  - Allow for clarification meeting with manufacturer before late cycle meeting.
  - FDA provide feedback proposed CAPAs & effectiveness check
  - If there is a CRO manufacture allow applicant to be involved with the proper legal consent
- Segregate the 483 findings linked to BLA in the review vs. general GMP findings
- Utilize Late cycle meeting: Applicant to obtain appropriate legal consent if CRO involved
- If needed, a meeting before the EIR to demonstrate effectiveness or additional requirements
- Post Approval Commitments:
  - Commitments and timelines for CAPAs contained in post approval letter to avoid CRL or extension