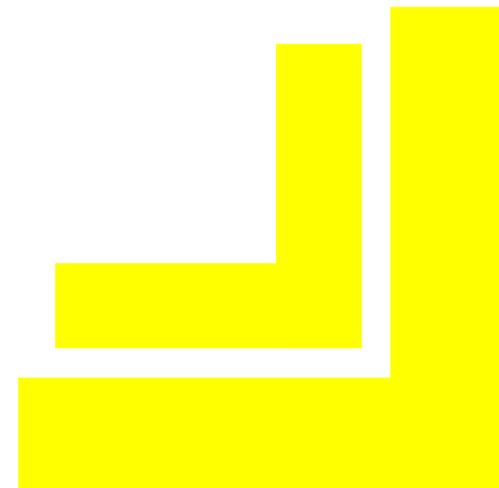


A Noble Mission Share by Both Regulators and Industry

- Protecting the public health by ensuring the safety, efficacy, and security of human drug products
- Advancing the public health by speeding innovations that:
 - Provides new products for unmet or undertreated medical conditions
 - Make products more effective, safer, available, and more affordable
- Doing all this while keeping the patient at the center of all we do

What is an FDA Complete Response Letter (CRL)

An FDA Complete Response Letter (CRL) is a letter sent by the U.S. Food and Drug Administration (FDA) to a drug sponsor when their application is not approved in its current form. The CRL details the deficiencies in the application and outlines the actions the sponsor needs to take to make the product approvable.



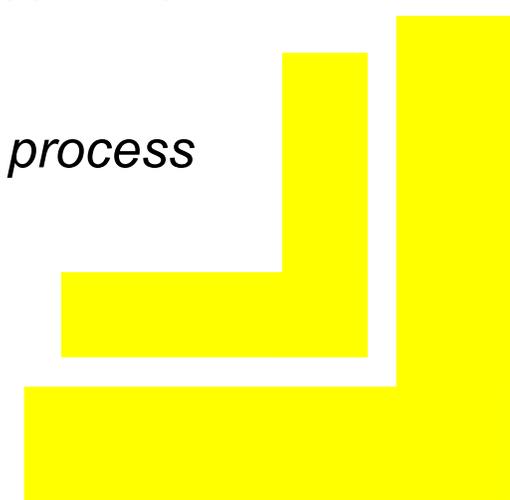
CRLs continue to be a challenge for industry

- Number of CRLs continues to be elevated
- Facility issues continue to be a significant portion of CRL issues across all CDER BLA submissions*
- New product introduction are being impacted
- Financial and perception impact on companies receiving / involved
- CRL's have in the past not been available to industry

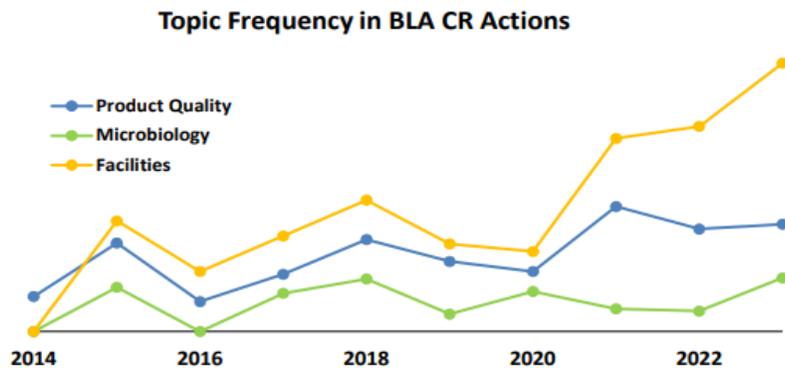
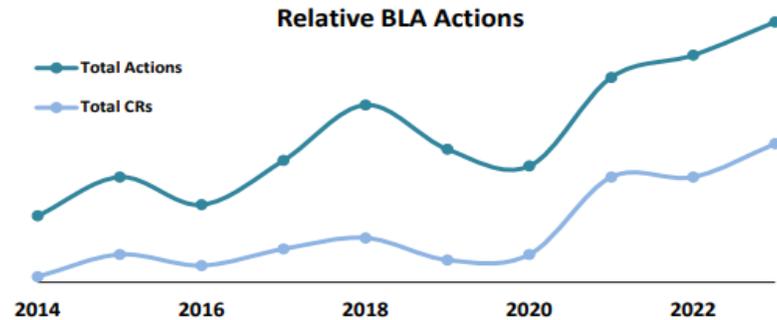
FDA's recent decision to release CRL's and their commitment to move to real time release is greatly appreciated.

This is not to say that CRLs, when needed, are not appropriate. Their use in the process is an important part of ensuring public health.

* From BLA Submission, Assessment, and Facility Readiness/Inspection: CMC for Biologics & Biosimilars (<https://healthpolicy.duke.edu/events/cderBLAsubmission>)



Action and Topic Trends

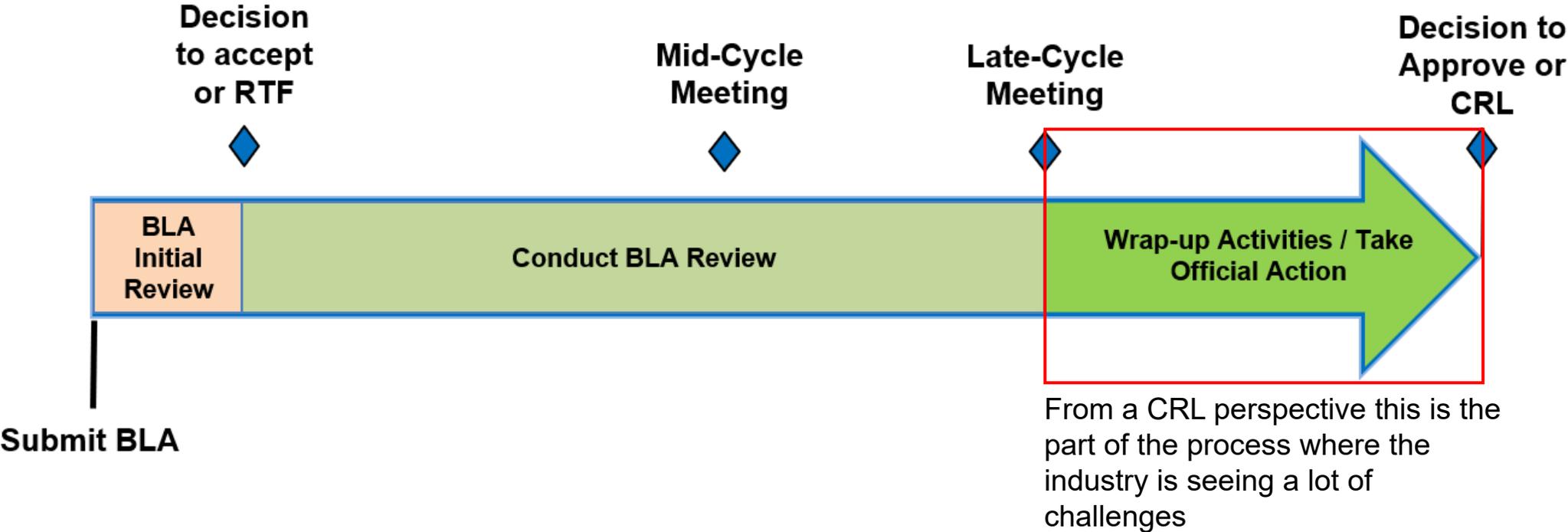


- Total Actions on BLAs have been increasing recently, with a concurrent increase in CRs for all reasons
- Frequency analysis identified consistent trends in CR rates, with the greatest increase in facilities deficiencies
- Increase in facilities trend
 - Impact of regulatory pathway
 - Impact of multi-product considerations

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* Slide from FDA Presentation 20 Aug 2024 at the Duke-Margolis Institute for Public Health meeting: Continual Improvement of CDER BLA Submission, Assessment, and Facility Readiness/Inspection: CMC for Biologics & Biosimilars (<https://healthpolicy.duke.edu/events/cderBLAsubmission>)

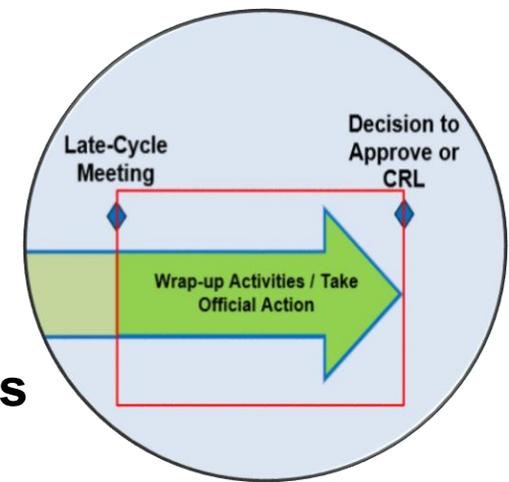
High Level FDA Review and Approval Timeline



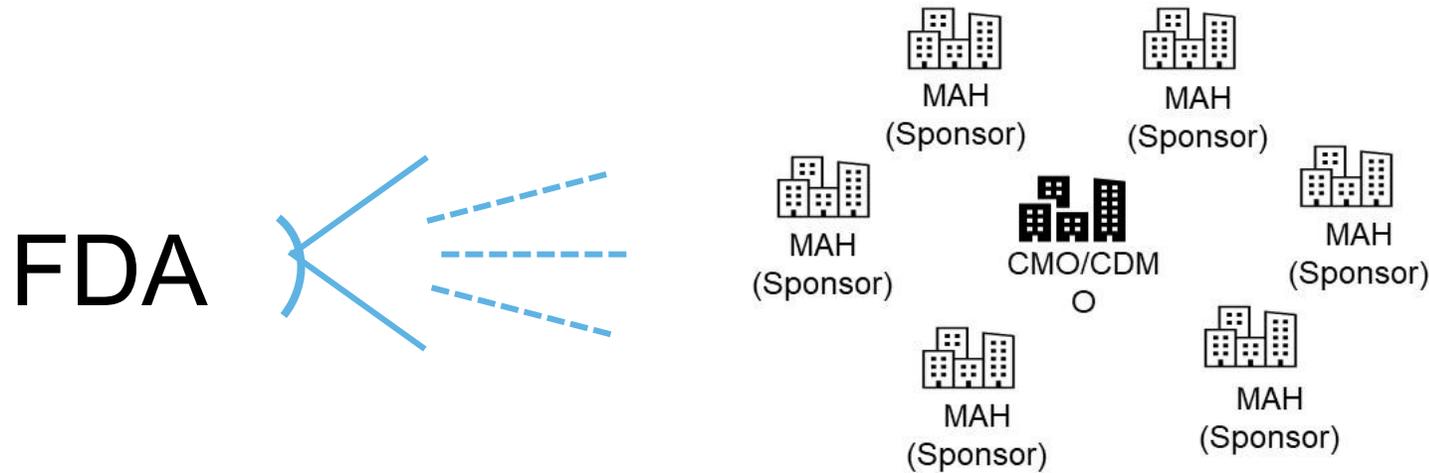
The FDA is expected to meet the PDUFA (Prescription Drug User Fee Act) timeline and action date for a decision (to approve the application or issue a CRL)

What are we hearing from industry?

- **Timing of Pre Approval Inspection (PAI)**
Timing of the PAI is in some cases occurring very late in review cycle, insufficient time to resolve any issues or concerns prior to action date
 - **Late in Review Cycle - New Request for Documents / Additional Questions**
Arriving after Late Cycle Meeting and too close to the action date – insufficient time to resolve any issues or concerns prior to action date
 - **Increasing GMP Expectations from Inspectors**
Inspectors are challenging what had long been settled science in the pharma industry, for example requiring significant equipment modifications to existing equipment sets and changes in process validation approaches. Is the PAI the correct place to be setting new industry expectations?
 - **Lack of Industry Visibility of Manufacturing Related CRL Issues**
FDA has been the only group that can see across all CRLs and provide trends of concern to industry (recently announced changes to release of CRL's welcomed)
 - **The CDMO CRL Dilemma**
Nearly half of CRs with facility deficiencies are for BLAs (CDER) with manufacturing proposed at CDMOs/CMOs*
- * From 20 Aug 2024 FDA Presentation at the Duke-Margolis Institute for Public Health meeting: Continual Improvement of CDER BLA Submission, Assessment, and Facility Readiness/Inspection: CMC for Biologics & Biosimilars (<https://healthpolicy.duke.edu/events/cderBLAsubmission>)

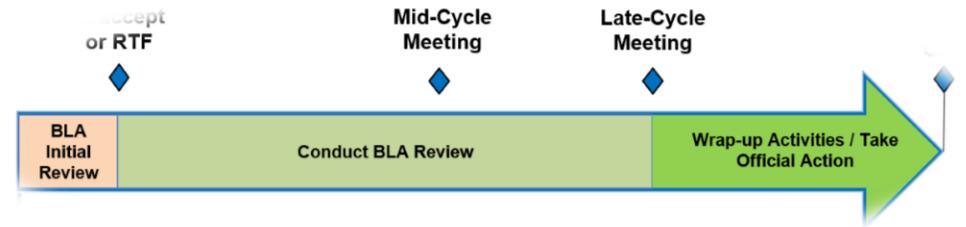


The CDMO CRL Dilemma



- MAH (Sponsor) receives a CRL related to a BLA for activities at a CMO/CDMO.
- Other MAHs (Sponsors) that have pending BLAs and also use the CMO/CDMO but are not aware there is a concern (based on inspection timing 483 not available)
- CMO/CDMO is not sharing based on contractual obligations
- How can the other MAHs (sponsors) know if the issues impact their BLA and if they will receive a CRL based on it? (Directionally the added transparency discussed by US FDA on CRLs may provide some help)

Final Thoughts



- CRLs will always be part of the process but should not be a surprise to the sponsor with issues being identified early for resolution if possible
- Any major concerns or issues with the submission and PAI that may impact its approval needs to be communicated no later than the Late-Cycle Meeting
- To be effective there must be FDA resources with the right expertise/training/experience and oversight for both the submission review and PAI
- In regard to the submission approval, is the expectation that FDA needs to meet the PDUFA target adding to this challenge?
- PDA is continuing to gather information on the current challenge industry is facing with CRLs and will continue to work with the industry's CQOs to raise the visibility of these challenges