

**Minaris**  
Advanced Therapies

# The Evolving Landscape of FDA Complete Response Letters



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# Complete Response Letter

## What is the Purpose?

- Indicates the NDA / BLA is not ready for approval in current form
- Details specific deficiencies (i.e. safety, efficacy, manufacturing)
- May include suggested actions the sponsor can take



## Historical Context

- Replaced prior “approvable” vs “non approvable letters (2008) to communicate marketing application issues [FDA Final Rule](#)
- Traditionally confidential
- Sponsors disclosed minimal details
- Limited industry benchmarking / investor uncertainty

# FDA 2025 Transparency Shift



The screenshot shows the FDA OpenFDA website. The header includes the FDA logo and 'U.S. FOOD & DRUG ADMINISTRATION' on the left, and 'U.S. Department of Health and Human Services Food and Drug Administration' on the right. The navigation menu includes 'Home', 'About', 'APIs', 'Data', 'Community', and 'Disclaimer'. The main content area is titled 'Complete Response Letters' and contains the text: 'This database contains Complete Response Letters (CRLs) associated with approved and unapproved New Drug Applications (NDAs) and Biologics License Applications (BLAs). Currently, the database includes CRLs issued to sponsors as recently as 2025. FDA will continue to add to this database as CRLs are issued to sponsors, providing the public with significant insight into the agency's decisions. Additionally, FDA may publish in this database batches of CRLs from its archives associated with withdrawn and approved applications.'

## US FDA Complete Response Letters Offer 'Path Forward' To Approval

Recently released CRLs for unapproved products contain recommendations for new studies, including design element details and advice to consider in different submission pathways.



### FDA Announces Real-Time Release of Complete Response Letters ...

Sep 4, 2025 — The U.S. Food and Drug Administration today announced that it will release future complete...

FDA U.S. Food and Drug Administration (.gov)

### FDA Announces Prompt Disclosure of Complete Response Letters ...

Sep 9, 2025 — The U.S. Food and Drug Administration (FDA) on Sept. 4, 2025, announced the release of 89...

Holland & Knight

### FDA Publishes Complete Response Letters for Unapprove...

Sep 8, 2025 — FDA Publishes Complete Response Letters for...

LW Latham & Watkins LLP



# Legal &/or Ethical Considerations

- Break from confidentiality norms
- Concerns over proprietary data & competitive exposure
  - ✓ Can reveal Sponsor's drug development process to competitor's
- Transparency vs. trade secrets
  - ✓ CRLs can contain detailed technical assessment / experimental details



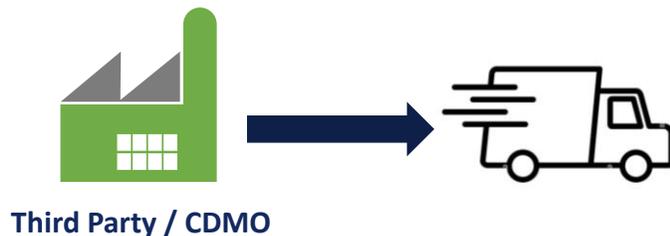
## Complete Response Letters: Will Industry Fight US FDA's Disclosure Plans?

The FDA's release of CRLs for unapproved products could bring a court challenge, but for now, sponsors should expect all past and future letters will be made public, experts said.



# What Are We Learning?

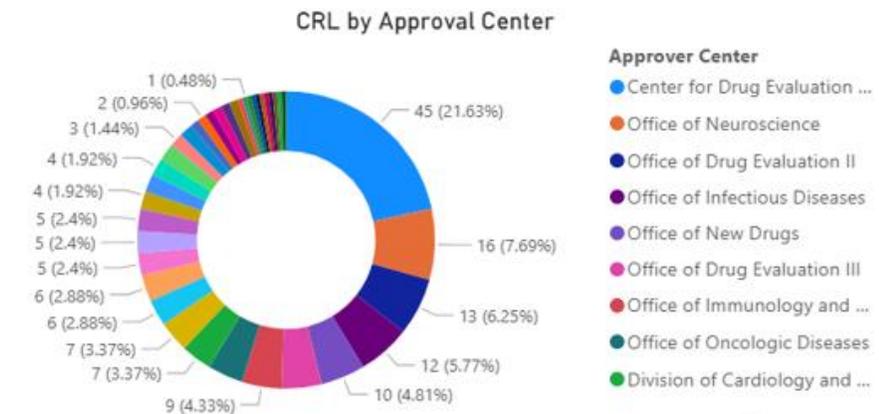
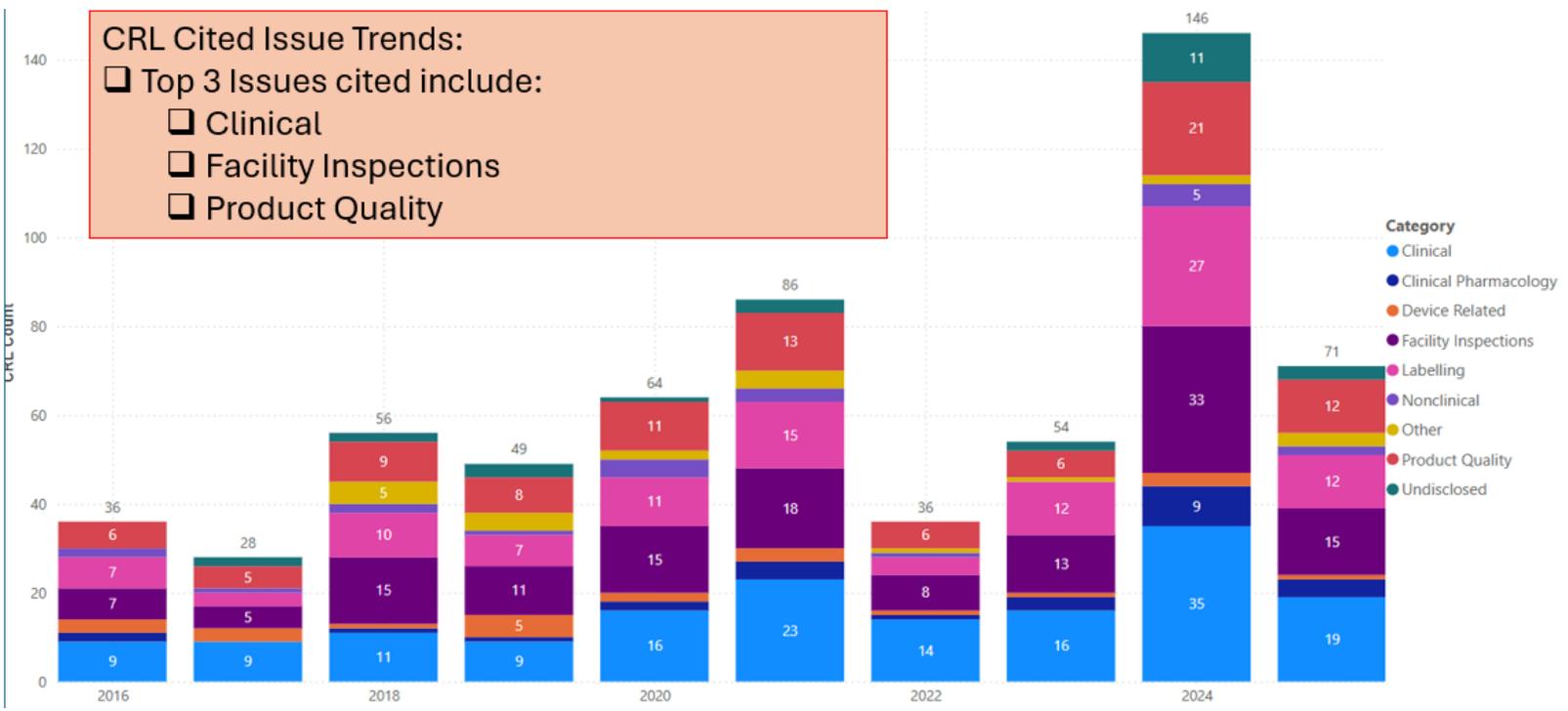
- Various consortiums industry is knowledge sharing.
  - Current challenges
  - Inspection best practices &/or outcomes → *Where can we be proactive?*
- Supply Chain demands / capacity constraints / business continuity



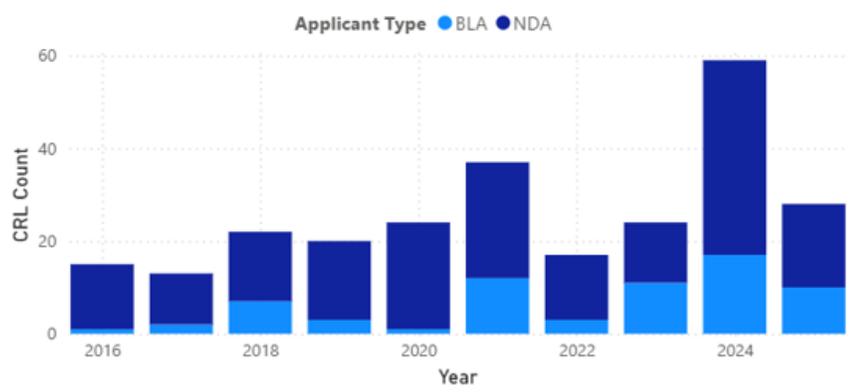
- ✓ Evolving demands require flexible capacity
- ✓ Rise in personalized medicines / complex biologics
- ✓ Accelerated development timelines / fast track designations

# CRL Categories Overview

**CRL Cited Issue Trends:**  
 □ Top 3 Issues cited include:  
 □ Clinical  
 □ Facility Inspections  
 □ Product Quality



CRL By Applicant Type



• What themes are we seeing?

# CRL Cited Themes:

- ❑ **Clinical Issues:** sample size and safety
  - ❑ FDA request for additional clinical trials with a confirmatory portion for the drug
  
- ❑ **Product Quality Issues:** manufacturing processes or chemical, manufacturing and controls (CMC)
  - ❑ Contamination with glass particles. / inadequate visual inspection programs
  
- ❑ **Facility Inspections:** quality system failures, inadequate investigations, CAPA, inadequate oversight, data Integrity, aseptic processing, contamination, validation of aseptic processes, process control, facilities and equipment, materials control and laboratory controls

***Facility Inspection issues at CDMOs are resulting in Complete Response Letter issuance to Sponsor – hence application is not able to be approved due to unresolved manufacturing issues at a third-party manufacturer:***

## Key Considerations

- ❑ ***FDA Expectations:*** Even when the drug itself meets safety and efficacy standards, the **Sponsor** is ultimately responsible for ensuring that all manufacturing partners are compliant with current Good Manufacturing Practices (cGMP).
  
- ❑ ***Approval Delay:*** Failure by a third-party manufacturer to meet FDA standards can directly halt the approval of a drug, even if the drug shows promise in clinical trials.
  
- ❑ ***Risk to Sponsors:*** This situation creates a significant risk for drug developers who rely on CMOs to meet commercialization timelines.

# Citations Noted...

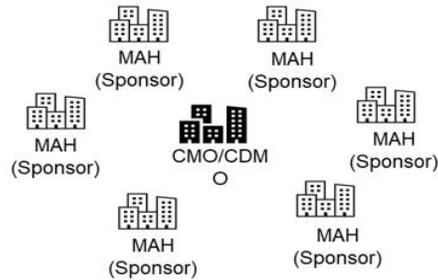
2. During inspection of the [REDACTED] (b) (4) manufacturing facility from [REDACTED] (b) (4), the FDA field investigation team conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Because of the above OOS results, we do not agree that the current in-house [REDACTED] (b) (4) [REDACTED] has been qualified appropriately.

## 4. Analytical methods

In section "Additional information related to Module 3", you revised the potency method (STM-0118) based on the change control CC-20-036. However, the summary information you provided to justify the changes made to the potency assay was inadequate because no supporting data were provided to allow assessment of the appropriateness of the proposed change. To ensure that the proposed change has no impact on the potency assay method validation and test article data, provide adequate information to support the proposed change.

# Collaboration & Transparency



- › Transfer of Knowledge
- › Product quality lifecycle management / CMCs
- › Comprehensive process analytics



- › GMP Transparency
- › Inspection profile vs Inspection trends
- › Quality Agreement with clear roles, responsibilities, and communication requirements

**Collaborate to Drive Operational Readiness**

## Key Points:

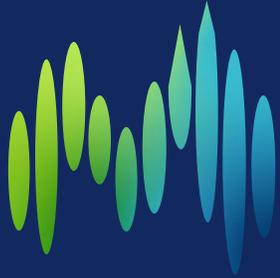
- Establish collaborative inspection strategy to address any known facility deficiencies
- Leverage previous 483s & CRLs to assess NDA/BLA to proactively identify risks in the CMO /Sponsor oversight model

# Conclusion -



## Industry Benefits:

- The evolving landscape of CRLs give industry opportunity insight to regulatory decision making
- Access = Predictability
- Enable more effective relationships for external sourcing and manufacturing partners
- Strengthen best practices & build more robust regulatory compliance strategies



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