

COLLABORATION SESSION

The Future of Quality and Supply: Site Transfers and Manufacturing Resilience

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Building Redundancy That Works: FDA's Critical Path for Site Transfers

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Site Transfers and Supply Resilience

- Manufacturing redundancy depends on successful site transfers. Approval delays can postpone access to additional capacity.
- Facility compliance and submission quality both matter. Deficiencies in either can delay approval.
- FDA's complete response analysis highlights recurring obstacles. These findings offer lessons for preparing site transfer submissions and facilities.

A Complete Response Letter (CR) Doesn't Just Delay Approval — It Delays Supply

- Typical first-cycle PAS review goals (site transfers)
  - ANDA (generic drugs): 4–10 months
  - NDA and BLA (biologics/biosimilars): 4 months
- A CR adds significant time on top
  - Sponsors typically take ~6 months or more to respond to a CR
  - FDA review of the resubmission adds another 3-10 months
  - A single CR can add a year or more to the timeline — and CRs can happen more than once

FDA Study of Facility-Related Complete Response Letters

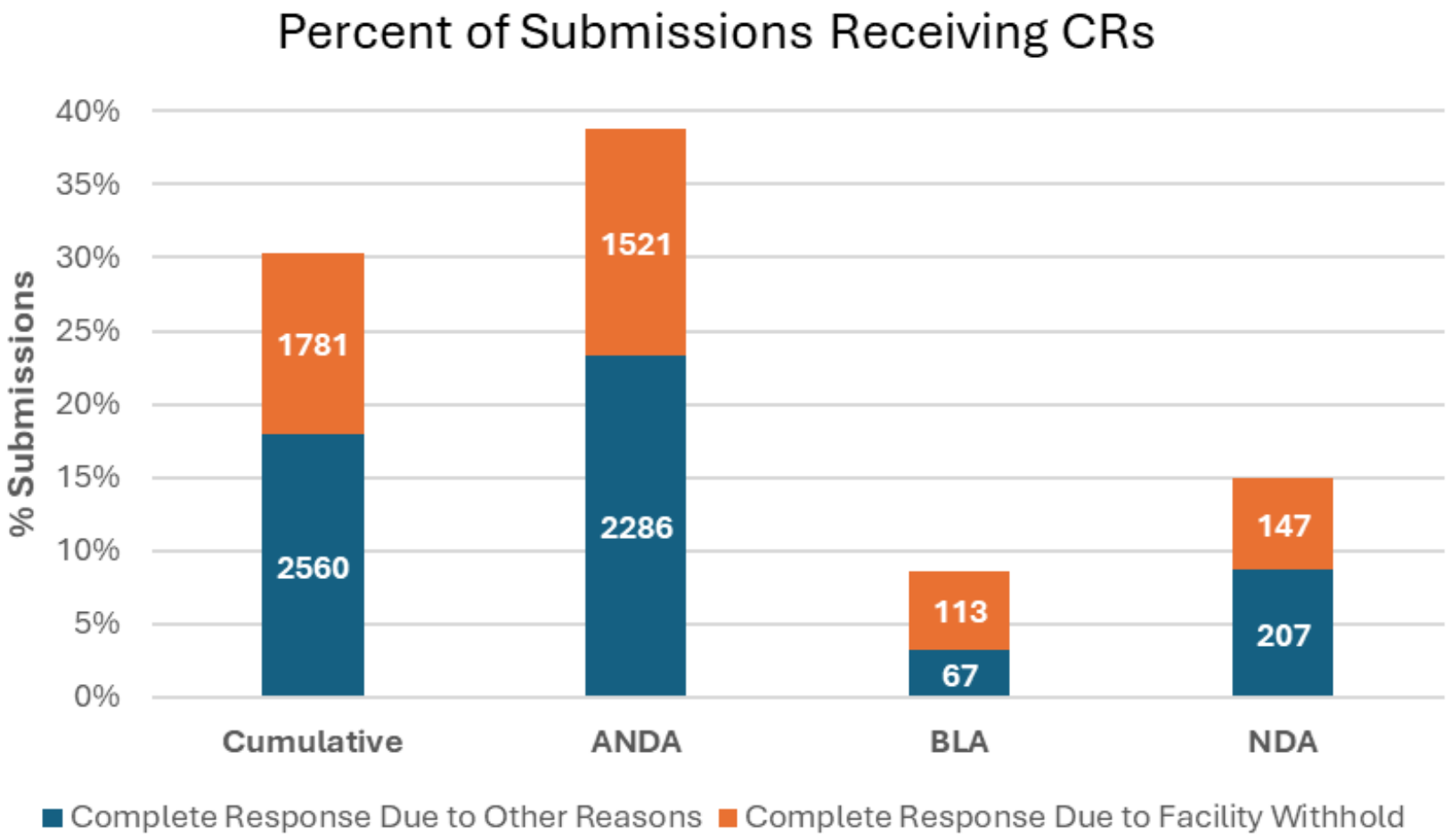
Every CDER drug submission that received a facility evaluation as part of its review

14,302	30,281	1,781	3 Years
Drug Submissions	Facility Evaluations	Submissions with a Facility Withhold CR	FY2023 – FY2025

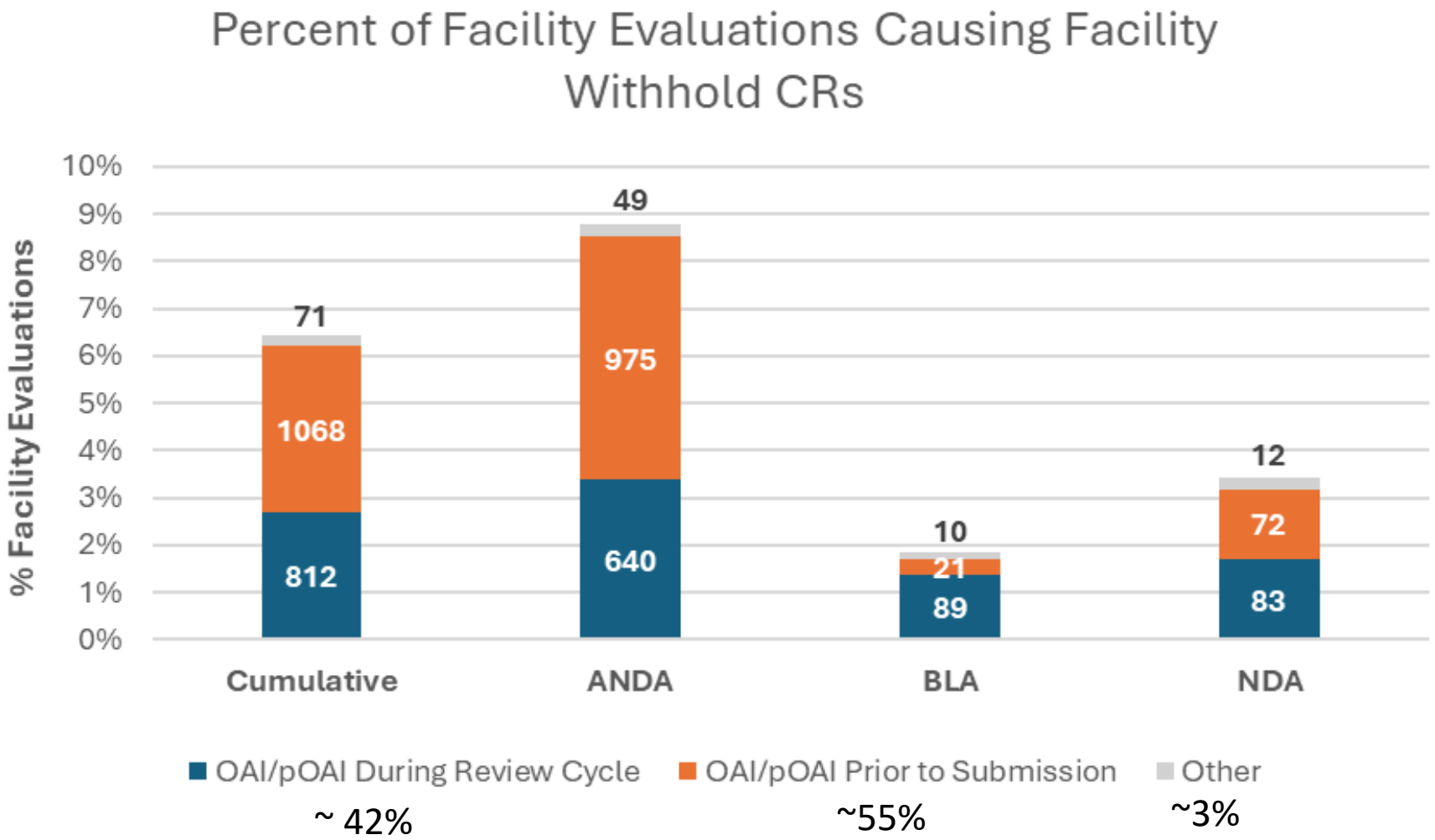
SCOPE:

- All CDER-regulated applications: ANDAs, NDAs, and BLAs
- Original applications, amendments to CR'ed applications, and supplements to approved applications
- *Includes impacts from both CGMP surveillance inspection and PAI/PLI findings*
- "Facility evaluation": unique submission and facility FEI pairing

41% of CRs Were Due to Facility Recommendation
59% of CRs Did Not Include a Facility Deficiency



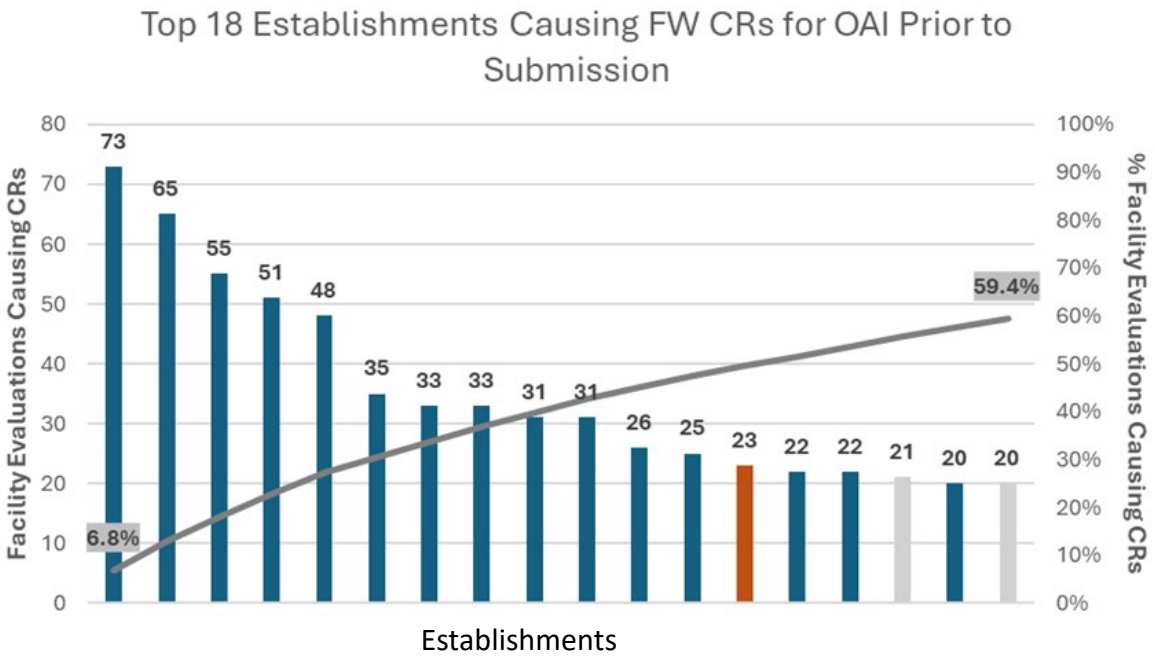
55% of facility-related CRs due to OAI prior to submission

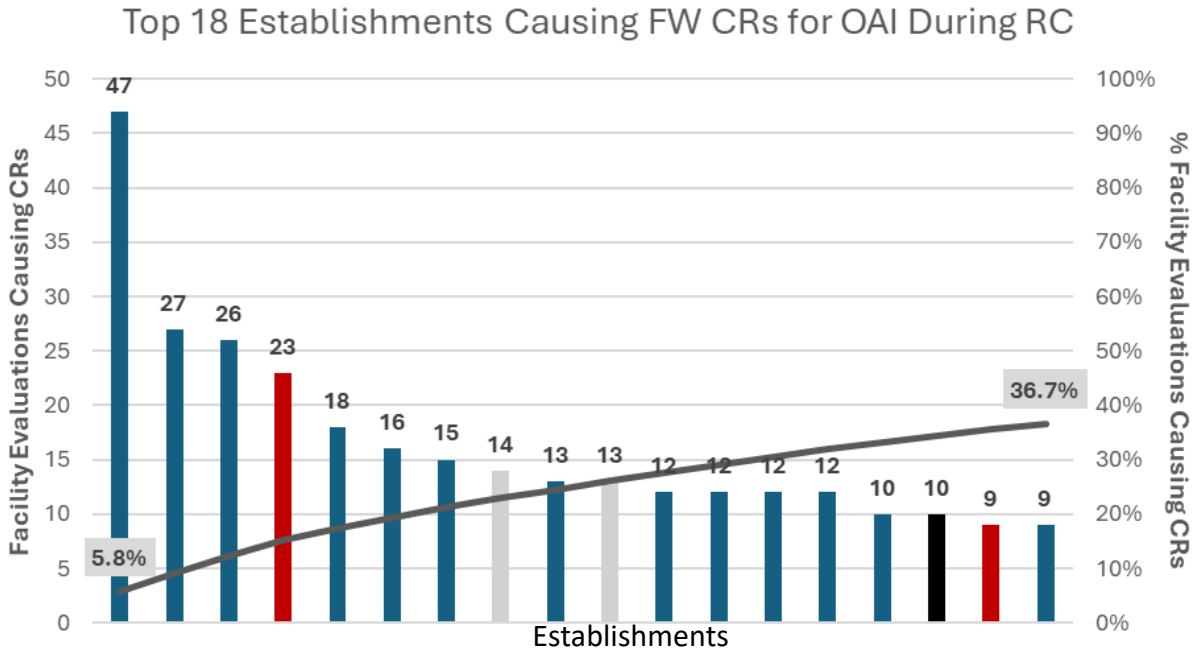


A Small Number of Facilities Drive Facility-Related CRs

350 facilities accounted for 1,880 facility evaluations causing facility withhold (FW) CRs

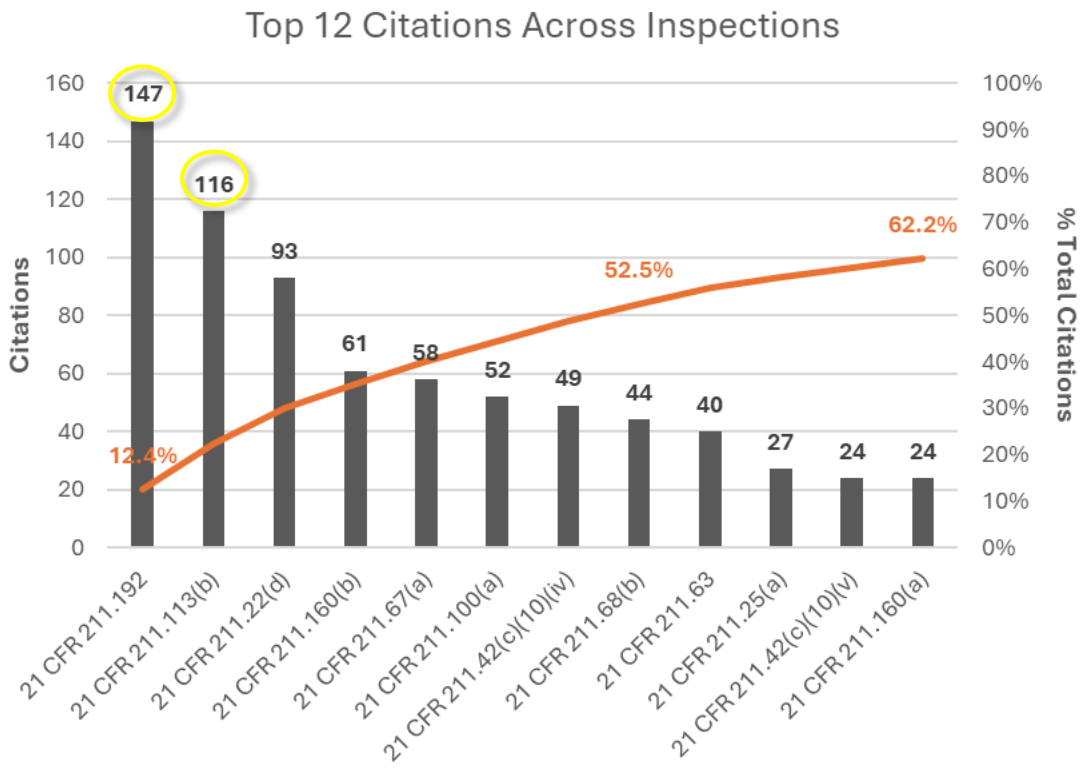
Blue = India
Red = China
Grey = USA
Black = Canada





Recurring Citations Drive Most Facility Withhold CRs

Eight inspection citation categories account for **52.5%** of citations linked to facility-related CRs
Top 2 categories alone account for >20%.



#1 | 12.4% of all citations

21 CFR 211.192
Production Record Review

Incomplete batch records, uninvestigated discrepancies, batch failures without written conclusions

#2 | 9.8% of all citations

21 CFR 211.113(b)
Microbial Contamination Control

18.2% of BLA PLI/PAI citations. Most CDER biologics are sterile injections

Lessons learned from CR Study–Facility Evaluation

- ~55% of facility evaluations that led to CRs were due to OAI inspections occurred prior to submission— Use FDA's publicly available Inspection Classification Database to verify the compliance status of every facility before submitting.
- ~42% of facility evaluations that led to a CR are due to OAI/pOAI during the review cycle — Ensure facilities are always inspection-ready
- ~3% involve other reasons, including remote regulatory assessments — Maintain complete, readily retrievable records, respond promptly to FDA requests, and address identified deficiencies.
- Eight inspection citation categories account for 52.5% of citations linked to facility-related CRs — Focus improvements on areas of known risk, including production record review and microbial contamination control.

Lessons learned from CR Study – Submission Review

- 59% of CRs are not facility-related. High-quality submissions help reduce avoidable review deficiencies and support timely approval.
  - Submit a complete, scientifically justified, and internally consistent CMC package.
  - Ensure the application accurately reflects manufacturing practices at the proposed site.
  - Confirm that referenced DMFs are complete and current, as applicable.
  - Include risk assessments and supporting data that address potential product quality risks.

Common CMC Deficiencies in Site Transfer Submissions

- **Generic Drugs (ANDAs)**
  - Incomplete nitrosamine risk assessments
  - Inadequate impurity control — missing qualification data
  - Incomplete Drug Master File (DMF) for API supplier at new site
  - Insufficient polymorphic characterization of drug substance
  - Manufacturing process descriptions missing batch parameters or yields
- **Biosimilars (BLAs)**
  - Insufficient commercial-scale process validation data at the new site
  - Weak analytical characterization — inadequate higher-order structure data
  - Inadequate specification justification — limits not grounded in science
  - Unexplained batch-to-batch variability in comparability data
  - Misalignment between CMC package and inspection findings

Summary

- **Reliable site transfers support supply resilience.** A single CR can delay approval by a year or more.
- **Facility readiness starts before submission.** Verify compliance status and maintain inspection readiness throughout review.
- **Address recurring deficiencies.** Focus on known risks, including production record review and microbial contamination control.
- **Submission quality matters.** Provide a complete CMC package that aligns with actual manufacturing practices.
- **Sustained CGMP compliance and high-quality submissions support first-cycle approval and reliable supply**

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Thank You

Questions & Discussion

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DISCLAIMER: The views expressed are those of the presenter and do not necessarily represent official FDA policy.