

Executive report

FDA COMPLETE RESPONSE LETTER ANALYSIS

# The gap between a nearly complete filing and a CRL is still usually the unfinished execution layer around the science.

This brief consolidates 291 unapproved FDA CRLs into a share-ready narrative, then connects that narrative to a curated 500-check operating file and the underlying raw exports.

**291**

unapproved CRLs

**1,748**

deficiency rows

**500**

ranked Top 500 checks

**77%**

major or critical findings

REPORT FRAME

**Share-first artifact**

Leadership should start with the executive report, not the raw CSVs. The ranked checklist only makes sense once the pattern and burden distribution are clear.

**Operating file**

The Top 500 checklist is ranked by distinct letter recurrence, total mentions, and dominant severity so teams can work recurring risk before submission.

**Evidence retained**

The full checklist and full deficiency exports remain in the package to preserve traceability back to the extracted dataset.

EXECUTIVE TAKEAWAYS

## What this report says in plain terms



**Execution gaps still dominate**

The recurring pattern is not just scientific disagreement. The letters repeatedly surface unfinished safety, labeling, translation, facility, and cross-module execution work.



**The working file must be curated**

2,802 unique extracted requirement statements were reduced into the 500 most recurring checks so a team can work the highest-signal items first.



### Recent years carry the heaviest load

The 2024-2025 slice alone contributes 168 letters and 3,078 extracted checklist actions in the current repository set.

#### PACKAGE ASSETS



##### Executive PDF

The share-first artifact for leadership, investors, quality heads, and regulatory leadership.

[Download PDF](#)



##### Top 500 checklist

The ranked operational file for pre-submission work allocation and internal review.

[Download CSV](#)



##### Full checklist export

All extracted checklist lines retained for QA, RA, and regulatory operations teams.

[Download CSV](#)



##### Full deficiency export

One row per deficiency with module, regulation, root-cause tags, and response action language.

[Download CSV](#)

#### REPEATED TRIGGERS

## The same avoidable patterns keep showing up

### 213

#### Safety update findings

Safety update wording still appears at a scale that should force earlier ownership and closer resubmission discipline.

### 163

#### Proprietary name findings

Proprietary name work is still treated as late-stage admin too often, even though it repeatedly triggers delay and rework.

### 110

#### Manufacturing facility findings

Facility readiness remains a hard gate. Once unresolved inspection issues enter the letter, document quality no longer offsets them.

### 70

#### Foreign labeling translation findings

Translation misses are low-complexity defects that should be eliminated by process, not discovered in review.



#### CATEGORY SPREAD

### Where the remediation burden actually lives

**Clinical** 753  
Clinical remains the largest category, but most of the recurring load is still packaging, completeness, interpretation, and documentation discipline.

**Labeling** 488  
Labeling is not a side stream. PI structure, carton/container text, translations, and proprietary name loops keep surfacing.

**Data Integrity** 342  
Cross-module mismatch continues to create late credibility problems that are expensive to remediate once FDA is already inside the file.

**Administrative** 338  
Administrative misses are still common enough to prove that process design, not just science, drives CRL risk.

**Manufacturing** 299  
Manufacturing pressure rises sharply in 505(b)(2) work and remains inseparable from facility readiness.

**Quality Systems** 294  
When quality-system defects appear in the letter, the remediation footprint usually expands beyond one isolated item.



#### CITED REGULATIONS

### Safety and labeling still dominate the citation surface

21 CFR 314.50(d)(5)(vi)(b) 199

21 CFR 314.50(l)(1)(i) 90

21 CFR 201.56(a) 37

21 CFR 201.56(d) 35

21 CFR 201.57 34

#### PATHWAY COMPARISON

## The burden moves by filing path

The average load changes meaningfully across NDA 505(b)(1), NDA 505(b)(2), and BLA work. The operating mistake is assuming a lighter clinical bridge also means a lighter execution burden.

### NDA 505(b)(1)

105 letters

**5.5**  
AVG FINDINGS

Standard NDAs still skew toward clinical packaging discipline, safety work, and cross-module consistency rather than one isolated science issue.

AVG CHECKLIST

**18.5**

PRIMARY MODULES

M5 (314), M1 (204), M2 (68)

TOP ISSUE CLUSTERS

Clinical (323), Labeling (171), Data Integrity (150)

**NDA 505(b)(2)**

106 letters

**6.2**

AVG FINDINGS

505(b)(2) work continues to underweight M3 and labeling burden relative to the clinical bridge assumptions many teams start with.

AVG CHECKLIST

**20.1**

PRIMARY MODULES

M1 (247), M3 (221), M5 (198)

TOP ISSUE CLUSTERS

Clinical (205), Labeling (183), Manufacturing (159)

**BLA**

76 letters

**6.6**

AVG FINDINGS

BLAs carry the heaviest average deficiency load in the set and show deeper data-integrity spillover when issues compound.

AVG CHECKLIST

**19.2**

PRIMARY MODULES

M5 (217), M1 (163), M3 (135)

TOP ISSUE CLUSTERS

Clinical (218), Labeling (130), Data Integrity (118)

## TOP 500 PREVIEW

**The ranked checklist starts with recurring requirements, not generic advice**

| RANK | REQUIREMENT   | LETTERS |
|------|---|---------|
| 1    | <div style="display: flex; align-items: center; gap: 5px;"> <span style="border: 1px solid gray; border-radius: 10px; padding: 2px 5px;">Major</span> <span style="border: 1px solid gray; border-radius: 10px; padding: 2px 5px;">M1</span> </div> Provide English translations of current approved foreign labeling not previously submitted.                   | 176     |
| 2    | <div style="display: flex; align-items: center; gap: 5px;"> <span style="border: 1px solid gray; border-radius: 10px; padding: 2px 5px;">Critical</span> <span style="border: 1px solid gray; border-radius: 10px; padding: 2px 5px;">M5</span> </div> Include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b) when responding to deficiencies.        | 98      |
| 3    | <div style="display: flex; align-items: center; gap: 5px;"> <span style="border: 1px solid gray; border-radius: 10px; padding: 2px 5px;">Major</span> <span style="border: 1px solid gray; border-radius: 10px; padding: 2px 5px;">M5</span> </div> Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time). | 89      |
| 4    | <div style="display: flex; align-items: center; gap: 5px;"> <span style="border: 1px solid gray; border-radius: 10px; padding: 2px 5px;">Major</span> <span style="border: 1px solid gray; border-radius: 10px; padding: 2px 5px;">M5</span> </div>   | 72      |

| RANK | REQUIREMENT  | LETTERS |
|------|--|---------|
|      | Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data. |         |
| 5    | <p>Major M5</p> <p>For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.</p>           | 71      |
| 6    | <p>Critical M5</p> <p>Present new safety data from studies/clinical trials for the proposed indication using the same format as in the original submission.</p>                  | 70      |
| 7    | <p>Major M5</p> <p>Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies.</p> <p>Critical M5</p>                | 66      |



#### SEVERITY MIX

##### Most findings are not advisory cleanup

|               |            |
|---------------|------------|
| Major         | 1036 (59%) |
| Critical      | 310 (18%)  |
| Minor         | 282 (16%)  |
| Informational | 120 (7%)   |



#### METHODOLOGY NOTES

##### The report and downloads share one source of truth

Source letters: data-letters/letters/unapproved\_CRLs

Requirement extraction field: metadata\_overlay.summary.key\_requirements\_detail

Finding extraction field: findings.items

Curated ranking order: Distinct letter recurrence -> Total extracted mentions -> Dominant severity -> Requirement type priority -> Requirement text

#### INTERPRETATION NOTES

## What to do with this report

Use the executive report to align leadership on where the actual CRL exposure concentrates. Use the ranked Top 500 checklist to assign operational ownership. Use the raw exports to validate, challenge, or extend any finding back to the extracted evidence.

The numbers here are generated from the same dataset and summary file that feed the landing page and the downloads. The intent is to reduce packaging risk without losing traceability.

#### Primary share route

Send the PDF when the recipient needs a compact, executive-ready artifact. Send the web report when they are likely to browse the methodology and downloads directly.

#### Recommended operating sequence

1. Review the executive pattern. 2. Work the ranked Top 500. 3. Escalate into the raw checklist and deficiency exports only where the evidence needs a closer read.



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GLOBAL REGULATIONS

BIOPHARMA

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21 USC  
FDA Letters

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ICH SOON  
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NDA  
BLA  
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De Novo  
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