FDA Complete Response Letter Database: A Classified Dataset

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Executive Summary

FDA's public **Complete Response Letter (CRL)** database at open.fda.gov contains letters associated with approved and unapproved New Drug Applications (NDAs) and Biologics License Applications (BLAs) (open.fda.gov). A complete response letter is the formal regulatory instrument FDA sends when it will not approve a **New Drug Application (NDA)**, **Biologics License Application (BLA)**, or **Abbreviated New Drug Application (ANDA)** in its current form, as defined in 21 CFR 314.110 and 21 CFR 601.3 (ecfr.gov) (ecfr.gov). The CRL mechanism itself dates to August 11, 2008, when a Federal Register final rule replaced the older "approvable" and "not approvable" letter system to implement Prescription Drug User Fee Act (PDUFA) III review-timing commitments (govinfo.gov) (fda.gov).

On **July 10, 2025**, FDA made an initial public batch of more than **200** complete response letters available; that batch was associated with since-approved applications, while FDA had historically refrained from publishing CRLs for pending applications (fda.gov). Two months later, on **September 4, 2025**, FDA released a further **89** previously

unpublished letters and committed to real-time disclosure going forward, with company names retained rather than anonymized (fda.gov) (fda.gov). As of August 13, 2026, FDA's own application programming interface reported **458** total CRL records (api.fda.gov), though the policy was not linear: FDA paused real-time publication in April 2026 after a citizen petition and resumed on July 10, 2026 with 14 additional letters, while a formal rulemaking (RIN 0910-AJ16) targets an October 2026 proposed rule to clarify and expand the FDA Commissioner's discretion regarding public release of complete response letters (fiercebiotech.com) (reginfo.gov).

This report classifies the released letter corpus against three independent schemas: FDA's own statutory grounds for non-approval under 21 CFR 314.125, a peer-reviewed academic taxonomy from a 2014 JAMA study of 151 first-cycle review failures finding efficacy deficiencies in 32%, safety deficiencies in 26%, both in 27%, and chemistry-manufacturing-and-controls (CMC) or labeling problems in 15% (nature.com), and an independent third-party coding of the newly released batch that instead found facility and manufacturing-quality issues most prevalent, detailed in the classification schema below. A CRL reflects FDA's determination that it will not approve an application in its current form (open.fda.gov).

Introduction and Background

This report examines what a CRL legally is, what FDA's public database contains, how the deficiencies in the letters can be classified using a documented schema, and what happens procedurally after a sponsor receives one.

The trigger for this analysis is a genuine policy discontinuity. FDA's July 2025 and September 2025 releases, followed by a rulemaking now moving through the Unified Agenda, represent the first sustained effort to make CRL content systematically public since the letter type was created in 2008 (fda.gov). That makes the database a genuinely new category of open regulatory data, comparable in kind (though not yet in maturity) to the European Medicines Agency's (EMA) long-standing legal requirement to publish refusal assessment reports for rejected marketing authorizations (ema.europa.eu).

This report is organized as a data-classification exercise rather than a narrative history. It states the method used to classify deficiencies, cites the primary regulatory text underlying every procedural claim, and separates FDA's own statements from independent, third-party analysis of the released letters wherever the two diverge. As of **September 5, 2026**, the database, the classification schemas, and the disclosure policy itself are all still being actively revised by FDA, so every volatile figure below carries the date on which it was observed.

What Is a Complete Response Letter? Statutory and Regulatory Definition

A complete response letter is the formal written decision FDA issues when its review of a marketing application concludes that the application, as submitted, cannot be approved. For drugs regulated under the Federal Food, Drug, and Cosmetic Act, the controlling regulation is 21 CFR 314.110, which states that "FDA will send the applicant a complete response letter if the agency determines that we will not approve" the NDA or ANDA in its present form (ecfr.gov). For biologics, the parallel provision at 21 CFR 601.3 obligates FDA to "send the biologics license applicant or supplement applicant a complete response letter" under equivalent circumstances (ecfr.gov).

By regulation, the letter must do two things. First, it "will describe all of the specific deficiencies that the agency has identified" in the application (ecfr.gov). Second, "when possible," it "will recommend actions that the applicant might take to place the application" in a condition FDA could approve (ecfr.gov). Notably, the regulation does not require FDA to complete every element of review before issuing a CRL: the agency "might issue a complete response letter without first conducting required inspections" of manufacturing facilities, reserving those inspections for a later review cycle (ecfr.gov).

History

The complete response letter did not always exist under that name. Before August 11, 2008, FDA used two separate instruments, an "approvable letter" and a "not approvable letter," both of which were eliminated by a Federal Register final rule effective that date. The rule's stated purpose was to consolidate the two prior letter types to implement Prescription Drug User Fee Act (PDUFA) III review-timing commitments, and the Federal Register text confirms that "previous §314.110 (21 CFR 314.110) set forth provisions on the issuance of and response to approvable letters," a section now repurposed entirely for complete response letters (govinfo.gov).

What happens next

After receiving a CRL, the regulation requires the applicant to take one of a small set of defined actions. For an NDA or ANDA, the required actions are (ecfr.gov):

- **Resubmission**, addressing the deficiencies FDA identified.
- **Withdrawal** of the application.
- **A request for a hearing** on whether the application may be approved.

For biologics under 21 CFR 601.3, the applicant "must take either of the following actions," resubmission or withdrawal, without an explicit hearing-request pathway in that section (ecfr.gov). If a sponsor takes none of these actions, FDA "may consider an applicant's failure to take any of such actions within 1 year after issuance of a complete response letter" as an implicit request to withdraw the application, subject to extension on request (ecfr.gov).

A CRL is distinct from a "Refuse to File" decision, which occurs earlier in the process when FDA declines to accept an application for review at all rather than reviewing it and finding it deficient; that earlier-stage mechanism is governed by a separate section of 21 CFR 314 and is outside the scope of the CRL database discussed here.

Inside FDA's Public CRL Database: Scope, Access, and Disclosure Timeline

The database that answers "FDA complete response letter database" as a search query lives at open.fda.gov, FDA's open-data platform. Its scope statement covers both drugs that eventually reached the market after a CRL and applications that never did, associated with both New Drug Applications (NDAs) and Biologics License Applications (BLAs) (open.fda.gov). FDA's own "Key Facts" panel for the dataset states a coverage window of 2020 through 2024 and describes the "Frequency of API updates" as "Infrequently" (open.fda.gov), a cadence markedly slower than openFDA's adverse-event or recall feeds, which update daily or weekly.

Public access takes two forms. A search interface at open.fda.gov's CRL table lets users query "By Company Name," filter by "Status: All, Approved, Unapproved," and filter "By Year" (open.fda.gov). Separately, FDA distributes the underlying letters as bulk archives, describing the option to "Download Approved Complete Response Letters in PDF format" as a single compressed file rather than as individually indexed records (open.fda.gov). A structured, queryable programming interface also exists at api.fda.gov; as of August 13, 2026, a query against it returned a stated total of 458 CRL records, the most current machine-readable count identified during this research.

Legal basis and redaction

FDA situates the database's legal authority in the Freedom of Information Act framework and the agency's own disclosure regulations, stating that letter content is "redacted prior to public disclosure under the Trade Secrets Act 18 U.S.C. 1905" (open.fda.gov), the statute that criminalizes unauthorized federal disclosure of confidential business information. This is the mechanism that reconciles broad public release with the confidentiality protections sponsors otherwise retain over proprietary manufacturing and formulation detail.

The 2025 to 2026 disclosure timeline

Table 1 below summarizes the sequence of policy actions that built the current database, drawn from FDA's own announcements, a formal rulemaking record, and independent trade-press confirmation.

Date	Action	Scale or Detail	Source
2008-08-11	Complete response letter created, replacing approvable/not-approvable letters	Federal Register final rule, effective date	(govinfo.gov)
2025-07-10	First public release of CRLs ("radical transparency")	More than 200 letters, applications submitted 2020 to 2024	(thefdalawblog.com)
2025-09-04	Second batch and real-time policy announced	89 additional letters; future CRLs to include company names	(raps.org)
2026 (proposed)	Notice of Proposed Rulemaking targeted, RIN 0910-AJ16	Would eliminate presumption that an application's existence is confidential	(reginfo.gov)
2026-04 (approx.)	Real-time release temporarily paused	Paused after a citizen petition; agency working to "formalize policy"	(fiercebiotech.com)
2026-07-10	Release resumed	14 new letters published	(fiercebiotech.com)
2026-08-13	Live database count observed	458 total CRL records via application programming interface	(api.fda.gov)

The pattern this table shows is a policy still in motion rather than a settled dataset. FDA committed to real-time release tied to a federal scientific-transparency executive order, then paused that commitment within roughly seven months, then resumed it, and is simultaneously pursuing a proposed rule to clarify and expand the FDA Commissioner's discretion regarding public release of complete response letters, aiming to "eliminate the

longstanding presumption that the mere existence of a marketing application constitutes confidential commercial information" (reginfo.gov). A researcher citing a specific record count from this database should record the observation date rather than treating any figure as fixed.

A Documented Deficiency Classification Schema

Answering "what are the common reasons for FDA complete response letters" requires a schema, not a list, because three legitimate but different sources classify CRL deficiencies in three different ways. This report presents all three side by side rather than collapsing them into a single number, since each measures a different population of letters over a different period using a different unit of analysis.

Schema 1: NDA refusal grounds

Under 21 CFR 314.125, FDA may refuse to approve an NDA for enumerated reasons, including inadequate manufacturing methods, facilities, or controls; inadequate safety or effectiveness evidence; false or misleading labeling; and specified compliance or application-content deficiencies. This NDA-specific provision is not an all-application taxonomy and does not establish that these grounds exhaust every potential basis for non-approval across NDAs, ANDAs, and BLAs.

Schema 2: Peer-reviewed academic taxonomy (2000 to 2012 NME cohort)

The most rigorous published quantification comes from an FDA-authored study appearing in JAMA in 2014, which examined 151 first-cycle review failures among new molecular entity (NME) applications. As summarized in Nature Reviews Drug Discovery's coverage of that work, CRLs in the cohort were classified as citing "efficacy deficiencies (32%), safety deficiencies (26%), efficacy and safety deficiencies (27%), or chemistry, manufacturing and controls (CMC) and/or labelling problems (15%)" (nature.com). The same analysis found that "theoretical risks related to drug mechanisms of action, structure or class were noted in 7% of first-round complete response letters" (nature.com), a comparatively rare but distinct category. The original JAMA analysis further breaks first-cycle failure into granular subcategories, including an "uncertainty/disagreement about appropriate dose" item cited in a meaningful share of efficacy-related letters (jamanetwork.com), and the same dataset shows first-cycle approval rates varying sharply by medical specialty, with oncology applications succeeding at a notably higher rate ("Oncology ... 61 ... 44 (72)") than several other therapeutic areas in the same cohort (jamanetwork.com).

Schema 3: Independent coding of the 2025 released batch

A third-party analytics project built a public dashboard directly from the openFDA release, reporting "202 Documents in FDA CRL Dataset, 294 Letters within the 202 documents, 284 Complete Response Letters" after excluding a small number of non-CRL documents bundled into the archive (prvwatch.com). That project's manual coding, tagging each letter with every issue it raises (so categories overlap and totals exceed 100%), found facility-inspection concerns in "166" letters, or 58% (prvwatch.com), product-quality concerns in "123" letters, or 43% (prvwatch.com), and clinical concerns in "79" letters, or 28% (prvwatch.com). A separate, independently authored compliance-industry analysis of the same July 2025 batch reported that "manufacturing-related issues appeared in nearly three-quarters of all CRLs" in the release, with "roughly half of the CRLs" also citing clinical evidence concerns (auriacompliance.com).

Table 2 places these three schemas side by side.

Schema	Source Type	Population	Top Category	Notable Figure
NDA refusal grounds	Primary regulation, 21 CFR 314.125	NDAs	Not separately quantified	Enumerates NDA refusal grounds; not an all-application taxonomy
Academic taxonomy	Peer-reviewed, JAMA 2014 (jamanetwork.com)	151 first-cycle NME failures, 2000 to 2012	Efficacy deficiencies, 32%	CMC/labeling problems, 15%; theoretical risk, 7%
Independent coding	Third-party dashboard of 2025 release (prvwatch.com)	284 letters, applications 2020 to 2024	Facility inspection, 58%	Product quality, 43%; clinical, 28%

Reading these three rows together, and not in isolation, is the point. The peer-reviewed academic sample (Schema 2) measures only NME applications from an older era (2000 to 2012) and finds clinical (efficacy and safety) issues dominant. The independent coding of the 2025 release (Schema 3) covers a more recent and broader population, including generic and established-company applications, and finds facility and manufacturing issues dominant instead. The gap between the two is a genuine finding about how the population and period sampled change the answer to "what causes a CRL," not a contradiction to be resolved in favor of one number.

A separate FDA presentation on generic-drug quality deficiencies under GDUFA (the Generic Drug User Fee Amendments) confirms that this manufacturing emphasis is deliberate agency practice for ANDAs specifically: major quality themes are organized by discipline, spanning drug substance, drug product, manufacturing-facility, microbiology, and biopharmaceutics review, and the agency states plainly that "Major Quality deficiencies will be sent in CRLs, including facility deficiencies," while lesser quality issues are communicated earlier through a separate mid-cycle Discipline Review Letter (fda.gov).

The Resubmission and Response Process After a CRL

Receiving a CRL is not the end of an application's regulatory life. FDA maintains a defined, multi-track process for what happens next, governed by regulation, agency manuals, and topic-specific guidance documents.

Resubmission classification

FDA's GDUFA III guidance states that ANDA amendments are classified as major or minor and receive a goal date based on factors including whether a preapproval inspection is needed. As noted above, a sponsor that takes no action for a full year risks FDA treating the application as implicitly withdrawn.

Clarification teleconferences (generic drugs)

For ANDAs specifically, FDA publishes guidance on post-CRL clarification calls under GDUFA (the current generic-drug user-fee agreement). Under GDUFA III, FDA commits to "providing a scheduled date for 90 percent of post-CRL clarification teleconferences within 14 calendar days" of a properly filed request (fda.gov), and the calls

themselves are deliberately narrow, functioning as a clarification mechanism rather than a substantive re-negotiation of the review.

Meetings for novel drugs

For NDAs and BLAs, FDA provides formal Type A meetings. FDA's meeting-management guidance defines this category as covering "post-action meetings requested within 3 months after receipt of an FDA regulatory action other than an approval (e.g., issuance of a complete response letter)" (fda.gov), with FDA required to respond and schedule promptly under PDUFA-era timelines.

Table 3 consolidates the applicant-facing timelines described above.

Pathway	Applies To	Trigger Window	FDA Timeline Commitment	Basis
ANDA amendment	ANDA	Under GDUFA III	Major/minor classification; goal date depends on priority and preapproval inspection	(FDA guidance)
Post-CRL clarification teleconference	ANDA (generic drugs) only	Request within 10 days of CRL (per guidance)	90% scheduled within 14 days; 30-minute call limit	(fda.gov)
Type A meeting	NDA, BLA	Request within 3 months of CRL	Prompt FDA scheduling response under PDUFA goals	(fda.gov)
Deemed withdrawal	All application types	No sponsor action for 1 year	Written notice, then 30 days to respond	(ecfr.gov)

Two features of this process matter for interpreting the public CRL database. First, a letter's presence in the database does not indicate the application's outcome, since the letter is a snapshot at one point in a multi-cycle process that can still end in approval after one or more resubmissions. Second, FDA's GDUFA III ANDA Meeting Program includes both post-CRL clarification teleconferences and post-CRL scientific meetings.

Data Analysis and Evidence

Methodology note

A peer-reviewed, FDA-authored cross-sectional study published in BMJ in 2015 examined complete response letters initially issued by FDA's Center for Drug Evaluation and Research.

Volume observed over time

The scale of what FDA has actually released grew across three distinct events. The July 2025 release covered "more than 200 decision letters" tied to applications submitted between 2020 and 2024 (fda.gov). The September 2025 release added "89 previously unpublished CRLs issued from 2024 to the present associated with pending or withdrawn applications" (fda.gov). By August 13, 2026, the live database total stood at 458 records, roughly double the initial 200-plus release, consistent with ongoing archival additions rather than a single static drop.

Sponsor size

Independent analysis of the July 2025 batch found that "approximately 70% of CRLs in the dataset were issued to small or mid-sized sponsors" (auriacompliance.com), a figure that, if representative, suggests the visibility gain from public disclosure disproportionately affects companies whose regulatory setbacks previously received the least independent scrutiny, since large sponsors' CRLs are more likely to already be covered by financial press and securities disclosure obligations regardless of FDA's own release policy.

Approval outcomes for context

To situate CRL frequency against overall approval activity, CDER's own annual reporting provides a first-cycle baseline: in 2023, "CDER approved 46 of the 55 novel drugs of 2023 (84%) on the 'first cycle' of review" (fda.gov), implying that roughly 16% of that year's eventually-approved novel drugs experienced at least one CRL or equivalent delay before approval. This figure describes only successful applications; it does not capture applications that received a CRL and were later withdrawn rather than resubmitted, which do not appear in a novel-approvals report at all.

Analysis of Key Segments: Therapeutic Areas and Sponsor Type

Segmenting CRLs by therapeutic area is harder to do rigorously than segmenting them by deficiency category, because no FDA report or peer-reviewed study identified during this research publishes a comprehensive, current therapeutic-area breakdown of the newly released letters. The most rigorous therapeutic-area data available remains the older JAMA cohort, which found first-cycle approval rates varying by specialty, with oncology applications succeeding at a distinctly higher rate than several other areas in the same 2000 to 2012 sample (jamanetwork.com). Whether that pattern still holds for the 2020 to 2024 population now in the public database is an open question this report cannot answer from available sources; it is flagged here as a genuine gap rather than papered over with an inferred figure.

Rare disease and generic-drug context

Trade-press coverage published after the September 2025 release described a broader pattern in which several rare-disease drug applications relying on confirmatory or real-world evidence generated under accelerated approval pathways received CRLs, a development independent analysts characterized as reflecting reduced regulatory flexibility for evidence packages built around post-market confirmatory data rather than traditional randomized controlled trials. That reporting remained behind a subscription paywall beyond its headline during this research and its underlying statistics could not be independently verified, so it is noted here as a directional trend rather than a quantified one. Separately, on the generic-drug side, FDA's own GDUFA III presentation organizes major quality deficiencies (the dominant CRL category for ANDAs) into five discipline areas: Drug Substance, Drug Product, Manufacturing, Microbiology, and Biopharmaceutics, a taxonomy specific to generics and distinct from the NME-focused academic schema discussed above.

Recent-year volume

CDER's own annual reporting for 2025 provides the most current official count identified: according to that report, "during 2025, the Center issued 19 complete response letters for 18 novel drugs" (FDA's 2025 New Drug Therapy Approvals report), against a backdrop in which the same report described 46 novel drug approvals that year, of which "twenty-three novel drugs received Orphan Drug Designation, supporting the treatment, diagnosis, or prevention of rare diseases" (FDA's 2025 New Drug Therapy Approvals report). Read together, these figures suggest that a substantial share of 2025's novel-drug approval pipeline involved orphan and rare-disease products, precisely the population trade press flagged as increasingly subject to CRLs over evidence-quality concerns, though this report cannot quantify the overlap between the 19 letters and the 23 orphan approvals from the sources available.

International comparison

The United States is not alone in moving toward CRL-equivalent transparency, though its approach remains less formalized than the European Union's. Under EU procedure, EMA guidance states plainly that "information about all refusals and the reasons for them shall be made publicly accessible" (ema.europa.eu), a legal requirement rather than a discretionary policy. EMA also commits to a fixed publication timeline, stating that "the refusal assessment report will be published within four weeks of a European Commission decision" (ema.europa.eu). By contrast, FDA's own dataset documentation describes update frequency only as infrequent, as noted above, and the actual 2026 record shows an unplanned multi-month pause in the middle of the policy's first year. FDA's pending rulemaking (RIN 0910-AJ16) is proposed to clarify and expand the FDA Commissioner's discretion regarding public release of complete response letters (reginfo.gov).

Implications and Future Directions

The database makes the released CRL text available for readers who wish to examine the deficiencies identified in those letters.

Organizations using the database for recurring analysis can document their methodology and the specific CRL text underlying any derived statistic.

Conclusion

FDA's complete response letter database contains CRLs associated with approved and unapproved NDAs and BLAs.

The public CRL corpus can support research into the deficiencies FDA identifies during its review of an application.

Frequently Asked Questions (FAQs)

What is a complete response letter from the FDA?

A complete response letter is the formal decision FDA sends when it will not approve a drug or biologic application in its current form. It must describe the specific deficiencies FDA identified and, when possible, recommend how the applicant might resolve them.

Where are FDA complete response letters published?

The primary public source is open.fda.gov's CRL database, searchable by company name, approval status, and year, with bulk PDF downloads and a structured application programming interface also available.

Are all FDA complete response letters public?

FDA states that it will continue to add CRLs to the database as CRLs are issued to sponsors (open.fda.gov).

What are the most common reasons FDA issues a complete response letter?

It depends on the population studied. A peer-reviewed 2000 to 2012 cohort found efficacy and safety concerns dominant (nature.com), while independent coding of the 2020 to 2024 released batch found facility and manufacturing issues more prevalent.

What happens after a company receives a CRL?

For an NDA or ANDA, the applicant must resubmit the application, withdraw it, or request a hearing under 21 CFR 314.110. For ANDAs, GDUFA III amendments are classified as major or minor, with assessment goals based on factors including priority and whether a preapproval inspection is needed.

Does FDA name the company in a public complete response letter?

As of the September 2025 policy change, yes: FDA stated that future letters will contain company names alongside redaction of trade secrets and personal information, as detailed above.

How many complete response letters has FDA published?

As of August 13, 2026, FDA's own application programming interface reported 458 total records, up from an initial batch of more than 200 in July 2025 plus a September 2025 addition of 89 more, as detailed above. This total changes over time and should be re-verified before citation.
