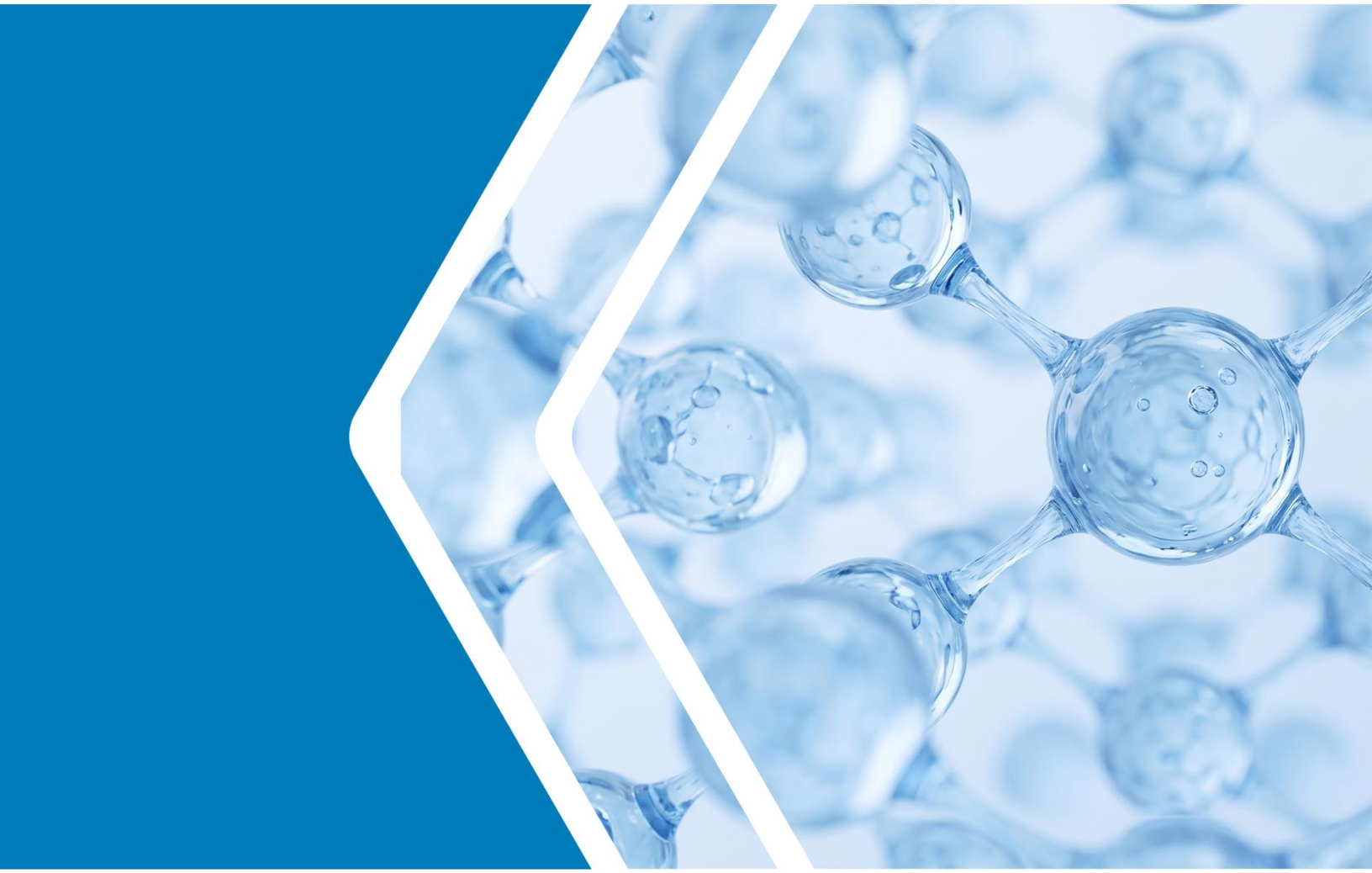
First-Cycle Complete Response Rates for CDER NDA and BLA Applications:

A Longitudinal Analysis



FY 2008–2024

First-Cycle Complete Response Rates for CDER NDA and BLA Applications: A Longitudinal Analysis, FY 2008–2024

1. Introduction

Over the last year, the rates of drugs that have received approval (AP) or complete response (CR) decisions at the conclusion of the first cycle of FDA's regulatory review have received attention from industry, Congress, and the media. The analysis in this paper aims to share accurate data about historical first-cycle CR decisions of original new drug applications (NDA) and biologic license applications (BLA) and serves to establish a common factual foundation for future discussion. External reports and analyses on FDA regulatory review actions may vary in their definitions and methodologies, and without clear documentation of data sources and inclusion/exclusion criteria, cross-study comparisons may be unreliable. Our analysis includes CDER NDA and BLA original applications and efficacy supplements and uses CDER's internal Document Archiving Reporting and Regulatory Tracking System (DARRTS) and follows the same rules used for regulatory tracking in congressional reporting[1]. This analysis accounts for historical filings and regulatory actions at the submission level, where each regulatory action is counted as a distinct observation[2].

2. Background

Recent reports in the media[3,4] have suggested that first-cycle complete response (CR) rates have increased over time. However, the underlying methodological parameters in these analyses are often not fully specified. Replicating estimates in some of these reports can be challenging due to insufficient documentation of data sources, analytical units, inclusion/exclusion criteria, and methodological approaches. Investigating and analyzing first-cycle CR and approval rates require some familiarity with nuances in FDA's regulatory data and reports[5] as well as the business rules applied in various publicly available reports. Furthermore, publicly available data may be limited in some cases. For example, some applications in the CR dataset are not yet publicly available therefore, an accurate and comprehensive analysis based on public data alone may not be possible.

Consider, for example, FDA's Novel Drug Therapy Approvals report and the annual Prescription Drug User Fee Act (PDUFA) Performance Report to Congress. The Novel Drug Therapy Approvals report tracks approvals at the product level on a calendar-year basis, counting a single distinct approval per new active

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[1] The only exception is the case of application resubmission after withdrawal, which PDUFA performance report considers as an application for first review cycle.

[2] Please note, data on regulatory submissions and actions are potentially subject to change as a result of application cohorts maturing over time, data corrections and other factors. Hence some of the data presented here (retrieved as of 6/1/2026) may have slight differences with publicly available data released historically.

3 US FDA's Rising First-Cycle Complete Response Rate Draws Congress' Attention, Jun 11, 2025, https://insights.citeline.com/pink-sheet/product-reviews/complete-response-letters/us-fdas-rising-first-cycle-complete-response-rate-draws-congress-attention-RZM2AHQ3IZBBBAQTEPX4NRPKDI/#:~:text=Congressional%20Directives,rate%20was%205%25%20in%202015.

4 Podium Finish: US FDA's 61 Novel Approvals In 2024 Fall Short Of 2023 Peak but Exceed Average, Jan 01, 2025, https://insights.citeline.com/pink-sheet/pink-sheet-perspectives/podium-finish-us-fdas-61-novel-approvals-in-2024-fall-short-of-2023-peak-but-exceed-average-7C7X5A6I4RF6RCZSOQ25UOYZJA/

5 For instance, the Novel Drug Approvals report, published after the conclusion of each calendar year, reports solely on the approved New Molecular Entity NDA's and Original BLAs at Product Level unit of analysis, where it combines all approved product submissions (dosage forms and Indication) into one consolidated approval record, even if the drug has received different actions for other indications and dosage forms. PDUFA performance report on the other hand, reports, among other things, the NDAs and BLAs filed and acted upon in a given fiscal year, at the submission level where all individual submissions are distinctly observed and stem from products with multiple indications, dosage forms and/or fix dose combinations.

ingredient. As a result, all approved indications and dosage forms for a given product are consolidated into one record. The PDUFA Performance Report, by contrast, operates at a more granular level of analysis, tracking individual regulatory submissions within each fiscal year. Under this framework, a single active ingredient may have more than one submission reflecting different formulations or indications. These distinctions are significant when calculating rates of regulatory actions, to select appropriate numerators and denominators from data with same unit of analysis (e.g. product level data versus submission level data) and within the same time frame (i.e. fiscal year or calendar year).

Each application the agency receives is unique with distinct set of characteristics, potentially leading to different regulatory review scenarios that may change expected timelines. To accurately evaluate CR and approval rates, it requires data that capture a full picture of each application's complete life cycle from receipt (and filing) to regulatory review action, and whether there are subsequent resubmissions and review cycles/actions in case of CRs. Building a panel dataset that follows application history from receipt to first action can be challenging from PDUFA performance and other public reports alone, due to the nature and purpose of those reports.

3. Methodology and Data

We define first-cycle CR rate for a given fiscal year, FY20XX, as the percentage of original new drug applications that received a CR in the first review cycle out of all original new drug applications (NDAs) and biologics license applications (BLAs) filed[6] in FY20XX.Given the type of submission, subsequent goal times of those submissions for a regulatory review action under PDUFA, submissions received in a given analysis fiscal year-typically referred to as a "Receipt Cohort"- can "mature" across up to 3 fiscal years[7]. In other words, it can take up to three fiscal years for all (or almost all) of those submissions to have a first-cycle regulatory review decision. However, generally most applications received and filed in a given fiscal year will have a first-cycle review action by the end of next fiscal year. With that in mind, for this analysis, a panel dataset has been built for Fiscal years 2008-2024 (i.e. since PDUFA IV)[8,9].

[6] Includes filed original NDAs, BLAs, including withdrawn after filing. Applications with following status are excluded from this analysis: Refused to File (RTF), Withdrawn before filing, pending. For the FY2008-FY2024 cohorts in this study, as of 6/1/2026 there were only two pending original applications and one pending efficacy supplement from FY 2024 cohort.

[7] As an example, consider a scenario where an NME application received near the end of a fiscal year (e.g. FY20XX), subject to a 12-month review goal date. If a major amendment is submitted during the first review cycle, the review goal date is extended by three months. As a result, the first review action for that application would fall not in the immediately following fiscal year (FY 20XX+1), but in the fiscal year thereafter (FY20XX+2).

[8] Data as of 6/1/2026.

[9] FY2025 has been excluded from this analysis, because as of 6/1/2026 CDER has 31 submissions pending within goal (~ 25% of original NDA/BLA submissions in FY2025), still without a regulatory decision. Calculating CR rate with those many pending decisions will not render a reliable CR rate estimate for FY2025.

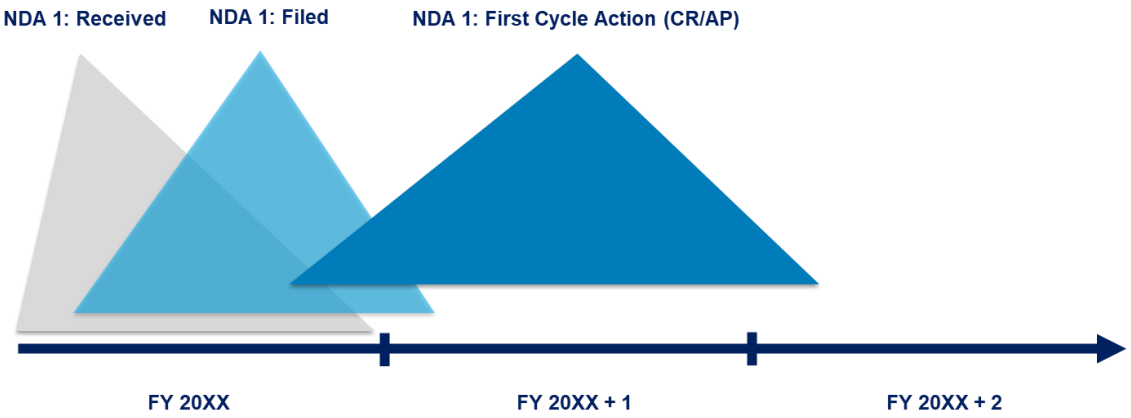

Figure 1: Building a data panel to follow application history from receipt to first action, can involve covering 3 fiscal years.

4. Analysis and Findings

4.1. CR/AP Trends

A comprehensive examination of all original CDER NDA/BLA filings for each fiscal year and their subsequent review decisions in the first-cycle review since the start of PDUFA IV, suggests that overall, the long term first-cycle CR rates for original NDAs and BLAs show a downward trend from 47% CR rate for FY2008 cohort to approximately 27% in FY2024. From FY2008 to FY2024, the first-cycle CR rate averaged 33.7%, with a standard deviation of 7.8 -percentage-points and a range of 22% to 50%. Year-to-year changes averaged about 5.9-percentage-points in absolute value, but the data indicate an overall decreasing trend over a 16-year period (FY2008-FY2024).

As seen in the graph below, The NDA/BLA complete response rate was notably higher in FY2008–FY2010, ranging from 47–50%, before dropping to a lower range of approximately 25–35% starting in FY2011 — a visually detectable change also confirmed by statistical testing[10]. After that drop, the rate fluctuated from year to year but overall plateaued and remained remarkably stable through FY2024 with median and average rates of 29% and 30.3%, respectively.

[10] Ordinary Least Square (OLS) regression over FY 2008–2024 yields a statistically significant negative slope of −0.83 percentage points per year (p = 0.0265). However, the Mann-Kendall test does not detect a significant monotonic trend (Tau = −0.26, p = 0.174), indicating the negative OLS slope may not be driven by a consistent year-over-year decline. Additionally, Bai-Perron structural break analysis with RSS-based corrected BIC (BICc – suitable for small sample size) suggests a likely structural break in CR rate in 2011 (BICc = 60.75 for one break vs. 69.69 for no break, p=0.0015; ΔBICc=8.94), meaning that 2011 represents the estimated year after which CR rates shifted to a persistently lower level — dropping from a pre-break mean of 47.7% (2008–2010) to a post-break mean of 30.6% (2011–2024) . However, given that pre-break area comprises only three observations (2008, 2009 and 2010 CR rates) the exact timing of this shift cannot be established with confidence with these data, and the finding should be considered indicative rather than conclusive warranting corroboration from contextual knowledge of regulatory, methodological, or submission-related changes that may have occurred in prior years. Overall, the OLS regression and Mann-Kendall test results, together with the structural-break analysis, may be an indication of a one-time downward level shift around FY 2011 rather than a sustained year to year long-term decline.

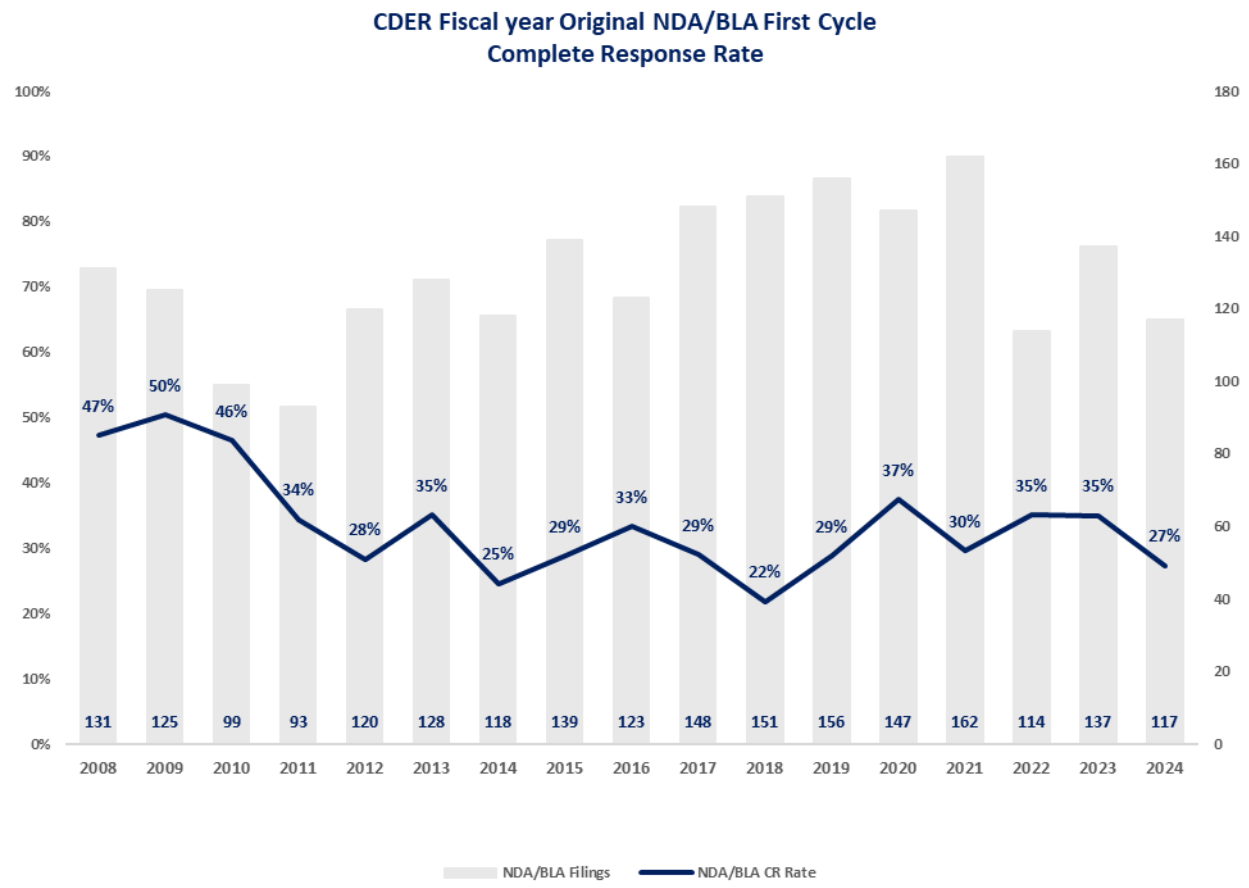

Figure 2: CDER Fiscal year Original NDA/BLA First Cycle Complete Response Rate.

In more recent years, since FY2018, some increase in first-cycle CR rate can be observed but that increase appears to have plateaued and subsequently reversed more recently, but not significantly for year-to-year trends ($p = 0.355$). FY2018 application cohort had a first-cycle CR rate of 22%, which climbed to 37% for FY2020 cohort but has since declined to 28% for FY2024 application cohort. A range of factors could have contributed to these observed variations, potentially including inability or limited ability to conduct inspections in years impacted by the COVID-19 pandemic. Further analysis may be needed to identify root causes.

Given that the long-term signal is an overall declining CR rate, the FY2018-FY2020 period seems to represent a temporary perturbation and not a trend reversal. The three-year moving average, which mitigates the impacts of year-to-year fluctuations in first-cycle CR rates, further corroborates the observation that overall CR rates have generally trended downward.

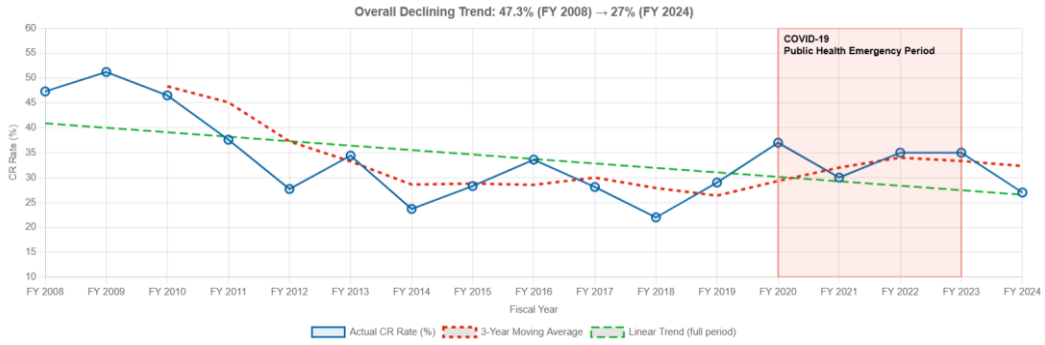

Figure 3: The three-year moving average of CR rates.

4.2. New Molecular Entities (NME) and New Therapeutic Biologics under Biologics License Applications (BLAs)

The long-term declining trends generally hold true for NMEs and new therapeutic BLAs as well, showing a 24-percentage-point decline from 50% CR rate in FY2008 to 26% in FY2024. Similarly, non-NME applications show a 17-percentage-point decline for the same period. The exception to these trends are CDER BLAs, which have seen the sharpest increase in CR rates in recent years (see section 4.3 below).

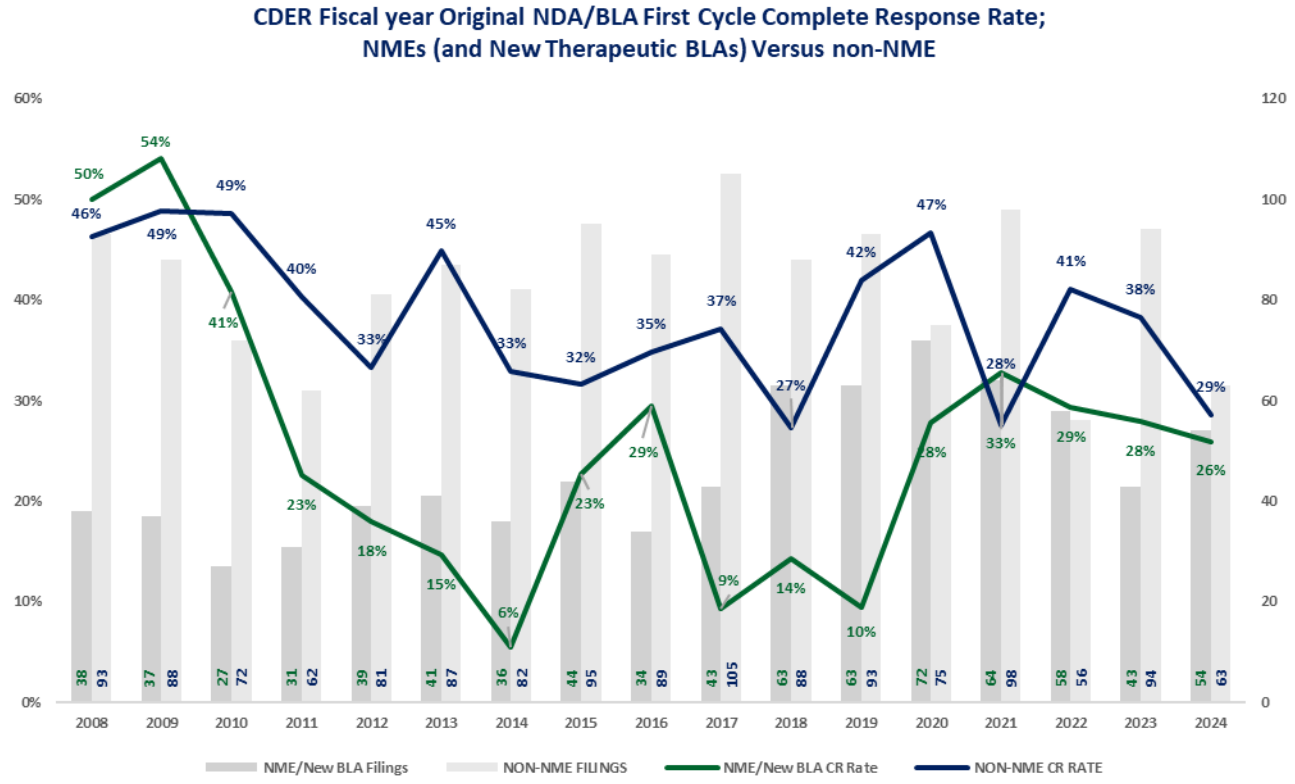

Figure 4: CDER Fiscal year Original NDA/BLA First Cycle Complete Response Rate; NMEs (and New Therapeutic BLAs) Versus non-NME.

4.3. NDA Versus BLA

Of note is the increase in CR rates of CDER's original BLAs since FY2019. This increase is more pronounced for new BLAs (Original BLAs containing new active ingredients).

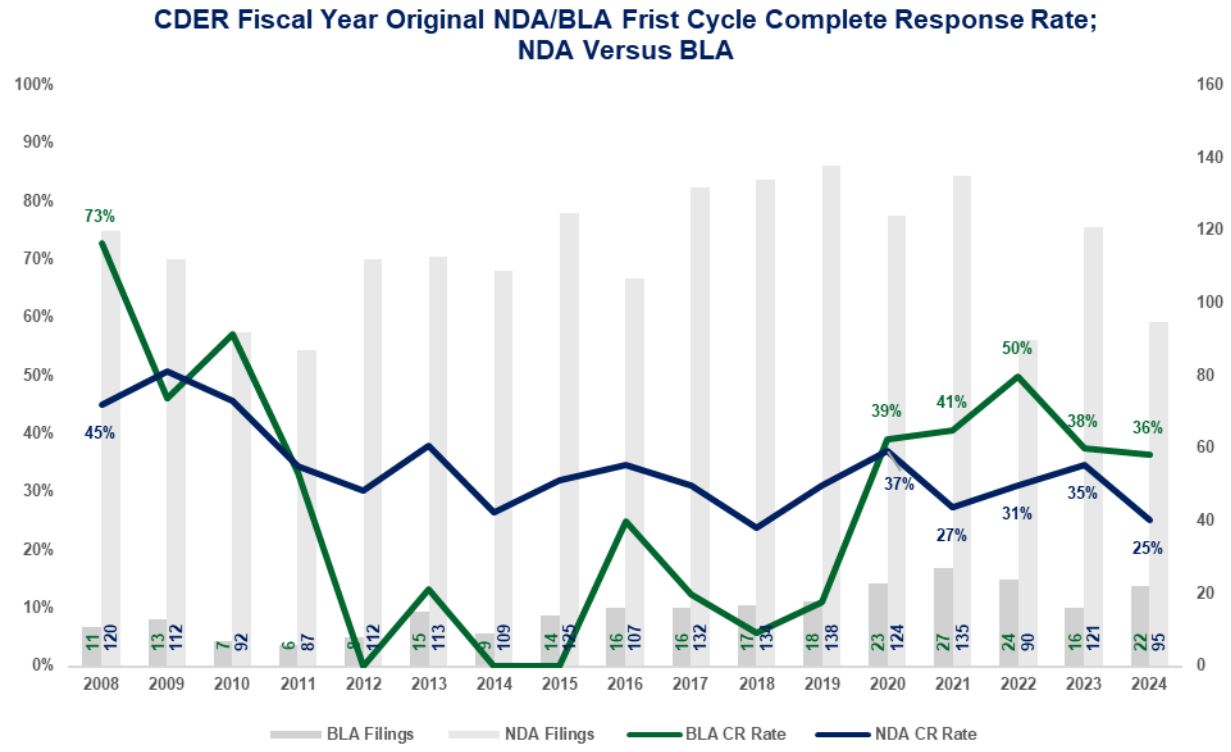

Figure 5: CDER Fiscal Year Original NDA/BLA Frist Cycle Complete Response Rate; NDA Versus BLA.

CDER's NME NDAs and new BLAs' CR rates, show the same pattern as all NDAs and BLAs, in that some increase in rates of CR can be seen clearly since FY2019. It should be noted that NDAs, on average, account for 88% of CDER's original submissions compared to an average of 12% for BLAs, however the number of BLA filings has consistently grown over the years, from an average of 9 BLA filings under PDUFA IV (FY2008-FY2012), to 14 under PDUFA V(FY2013-FY2017) and 22 under PDUFA VI (FY2018-FY2022).

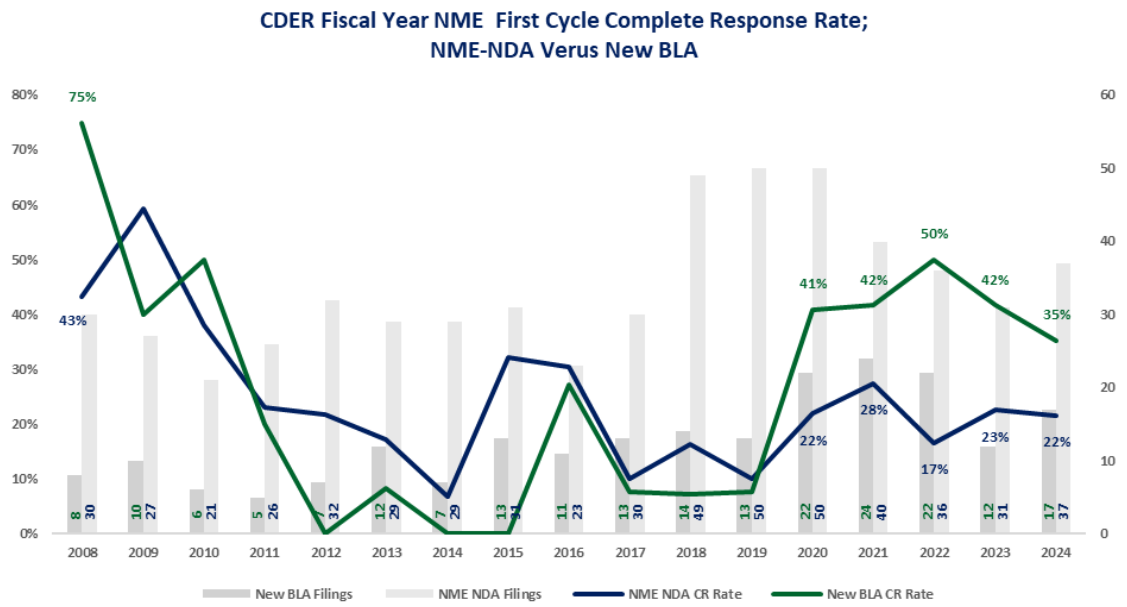

Figure 6: CDER Fiscal Year NME First Cycle Complete Response Rate; NME-NDA Verus New BLA.

4.4. Efficacy Supplements

The first-cycle CR rate for NDA/BLA efficacy supplements has consistently and substantially declined since FY2008, approximately from 30% in FY2008 to 7% in FY2024, despite submission volume nearly doubling in the same period.

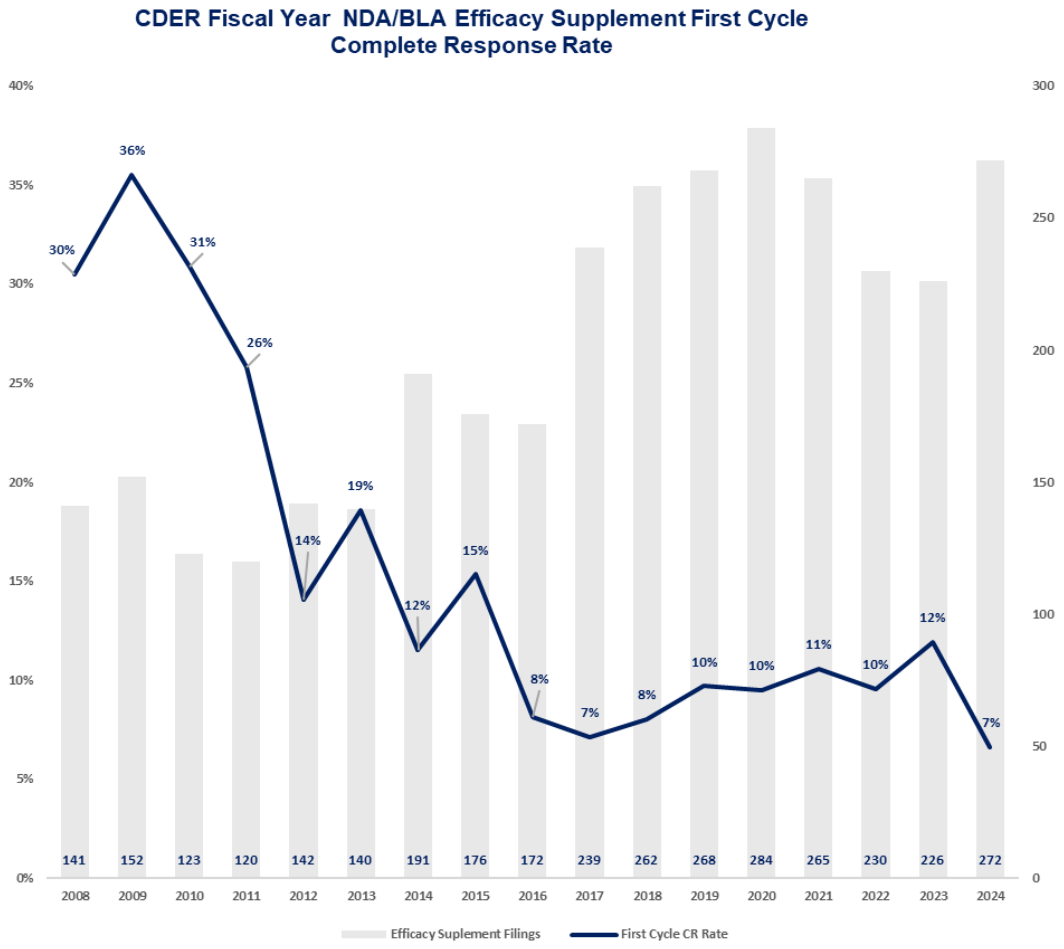

Figure 7: CDER Fiscal Year NDA/BLA Efficacy Supplement First Cycle Complete Response Rate.

4.5. First-Cycle Approval Rates Versus Current Approval Rates[11]

Often, original applications that receive a CR in the first-cycle review, successfully address application deficiencies in subsequent resubmissions to receive approval. This means patients will gain access to these innovative therapies once their safety, efficacy and quality have been deemed acceptable according to scientific and regulatory standards. Overall, the median of current approval rates for NDAs/BLAs, inclusive of subsequent review cycles, for fiscal years 2008-2024 is approximately 77%, which shows a 13-

[11] Current approval rates, of all applications submitted each year, what percentage are currently in approved status as of today. This will capture approvals that were obtained after second or more review cycles and represents the "current state" of applications in approved status. In calculating current state approval rates, applications that had received approval at some point and were subsequently withdrawn have been excluded.

percentage point increase compared to the median of first-cycle approval rates of approximately 64% for the same period. In other words, of all original NDA/BLA applications submitted to the FDA for review between fiscal years 2008-2024, about 77% are currently in approved status and available to patients.

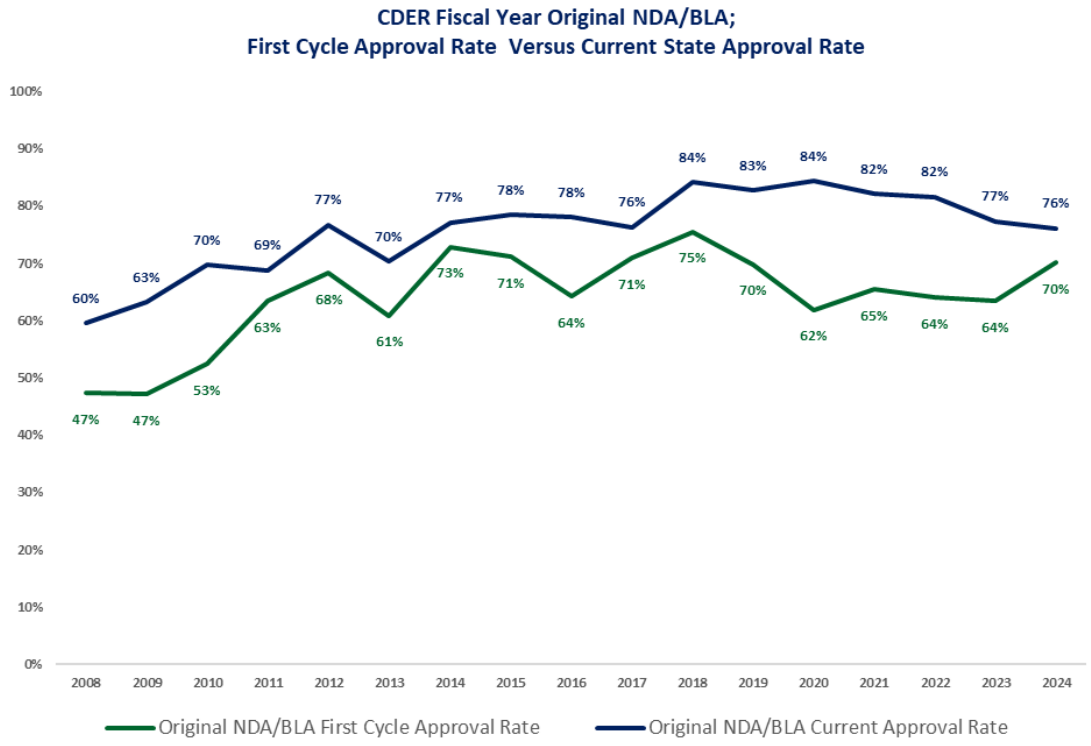

Figure 8: CDER Fiscal Year Original NDA/BLA; First Cycle Approval Rate Versus Current State Approval Rate.

5. Conclusion and Discussion

The data presented in this analysis provide important context for the ongoing public debate surrounding FDA's first-cycle complete response (CR) rates. External reports have characterized recent CR rates as rising and potentially problematic; however, a comprehensive, longitudinal examination of CDER's internal DARRTS regulatory tracking data across 16 years (FY2008–FY2024) paints a more nuanced picture, and counters the narrative of rising CR rates.

Over this period, the overall trend in first-cycle CR rates has been one of decline — from 47% for the FY2008 receipt cohort to approximately 27% for the FY2024 cohort —with an average of 33.7% across the full study period. The increase observed between FY2018 and FY2020 — from 22% to 37% — appears to reflect a temporary perturbation and may not be a structural reversal of the prevailing downward (2008-2024) - or plateaued (2012-2024)- trajectory. This transient uptick may help explain industry and media perceptions of rising CR rates driven by a focus on more recent data points, even though rates subsequently declined back to approximately 27% by FY2024. Importantly, year-to-year variation in CR rates is not unusual and has not been statistically significant over the study period. These patterns hold across both application types — NDAs and BLAs — as well as for novel designations (NMEs and new

therapeutic BLAs), though BLAs exhibited the largest CR rate increase during the FY2018–FY2020 window.

Taken together, these findings indicate that CDER's first-cycle approval and CR rates trended downward over the long term, and that characterizations of a sustained, structurally rising CR rate are not supported by a comprehensive reading of the available data. Continued monitoring of CR rates by product type — particularly for BLAs — and further investigation into the drivers, of observed variation remain warranted.

The expeditious availability of safe and effective novel therapies to U.S. patients is an objective shared by both FDA and the pharmaceutical industry. Meeting that objective requires a clear division of responsibility. FDA is accountable for providing transparent statutory and regulatory expectations. Industry, in turn, is responsible for leveraging FDA guidance, pre-NDA and pre-BLA meeting feedback, and publicly available information to construct high-quality submissions. Establishing a shared methodological foundation, as this analysis aims to provide, will be essential for ensuring that future policy discussions are grounded in accurate and comparable data.

There is perhaps value in a more in-depth analysis of complete responses to determine if there are additional activities that FDA, industry, or both could undertake to further facilitate positive outcomes on a first review cycle.

To that end, FDA continues to engage in many activities that may reduce the likelihood of complete responses, such as:

- Publishing guidance documents that provide advice on product development topics to help sponsors identify, avoid, and resolve common issues.
- Conducting external engagement meetings with stakeholders to discuss relevant information on product development topics[12].
- Providing public webinars and training on best practices within regulatory topics[13] .
- Providing product-specific advice directly to sponsors throughout their product development programs[14].
- Identifying potential issues for sponsors as early in the development program as possible[15].

Notes/ Glossary

Submissions:

- Inclusions: Filed original NDAs, BLAs
- Exclusions: Refused to File (RTF), Withdrawn before filing, pending (for this set, only one is pending from FY2024)

[12] In 2024, FDA partnered with Duke-Margolis to convene a public meeting to explore the root causes of CRs related to quality and facility issues for CDER regulated original and biosimilar BLAs. See Continual Improvement of CDER BLA Submission, Assessment, and Facility Readiness/Inspection: CMC for Biologics & Biosimilars (2024) (accessed at: https://healthpolicy.duke.edu/events/cderBLAsubmission)

[13] Each year FDA's Small Business and Industry Association (SBIA) hosts webinars featuring FDA experts discussing regulatory topics to engage and educate the public, small business, and industry stakeholders.

[14] One of the many avenues for advice is through meetings between FDA and sponsors, which may be held at various stages of product development.

[15] For example, FDA recently launched Chemistry, Manufacturing, and Controls Development and Readiness Pilot (CDRP) Program and the Support for clinical Trials Advancing Rare Disease Therapeutics (START) Pilot Program within the Center for Biologics Evaluation and Research (CBER).

Actions:

- Approval, Tentative Approval, Complete Response, Withdrawn (after filing)

New Molecular Entity (NME):

- NDA – New Molecular Entity (active ingredient containing no previously approved active moiety under section 505 of the Federal Food, Drug, and Cosmetic Act), AND
- Original BLA containing a novel active ingredient

First-Cycle Action Rate:

First-Cycle CR Rate = (First Cycle CRs) / (First Cycle Approvals + First Cycle Tentative Approvals + First Cycle CRs + First Cycle Withdrawn)

First-Cycle Approval Rate = (First Cycle Approvals+ First Cycle tentative Approvals) / (First Cycle Approvals +First Cycle Tentative Approvals + First Cycle CRs + First Cycle Withdrawn)