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# ADUFA V Third-Party Assessment

## Final Assessment Report

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unconventional consulting

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# Executive Summary

During the negotiations for the reauthorization of the Animal Drug User Fee Act (ADUFA) in 2023, stakeholders from the animal drug industry and the Center for Veterinary Medicine (CVM) agreed to an independent assessment of 30 new animal drug applications (NADAs). Conducted by Eagle Hill Consulting (Eagle Hill), this evaluation assessed the effectiveness of the ADUFA program, including the review process, the tools used to improve efficiency, and the allocation of available resources.

This assessment is informed by the analysis of data from three primary sources: stakeholder interviews, system records, and process documentation. This comprehensive dataset includes:

- **112** stakeholder interviews, including with CVM leadership, CVM review teams,[1] and participants from the animal drug industry
- **1,600+** Investigational New Animal Drug (INAD) submissions making up **30** NADAs approved between ADUFA II – IV
- **110,000+** resource hours across **309** CVM personnel
- **200+** process documents detailing **14** processes making up the new animal drug review process

These data were evaluated against the objectives of the assessment to determine CVM's progress in expediting the animal drug review process. A log of challenges faced by both CVM and Industry was maintained throughout the assessment, along with a list of successes from CVM and the ADUFA program. In total, 126 distinct challenges were identified, highlighting key issues with processes, IT systems, and communication. Key findings, including both challenges and successes, from the analysis of the collected data were divided into 8 thematic groupings. By evaluating the challenges and successes within each of the thematic groupings, this assessment provides a balanced view of the program's effectiveness and areas for improvement. The categories of findings included in this report are detailed in Figure 1 below:

1. As of October 2024, CVM teams were restructured into branches. This change in CVM terminology will not be reflected throughout this report as the ONADE team structure was still in place while the analyses were conducted.

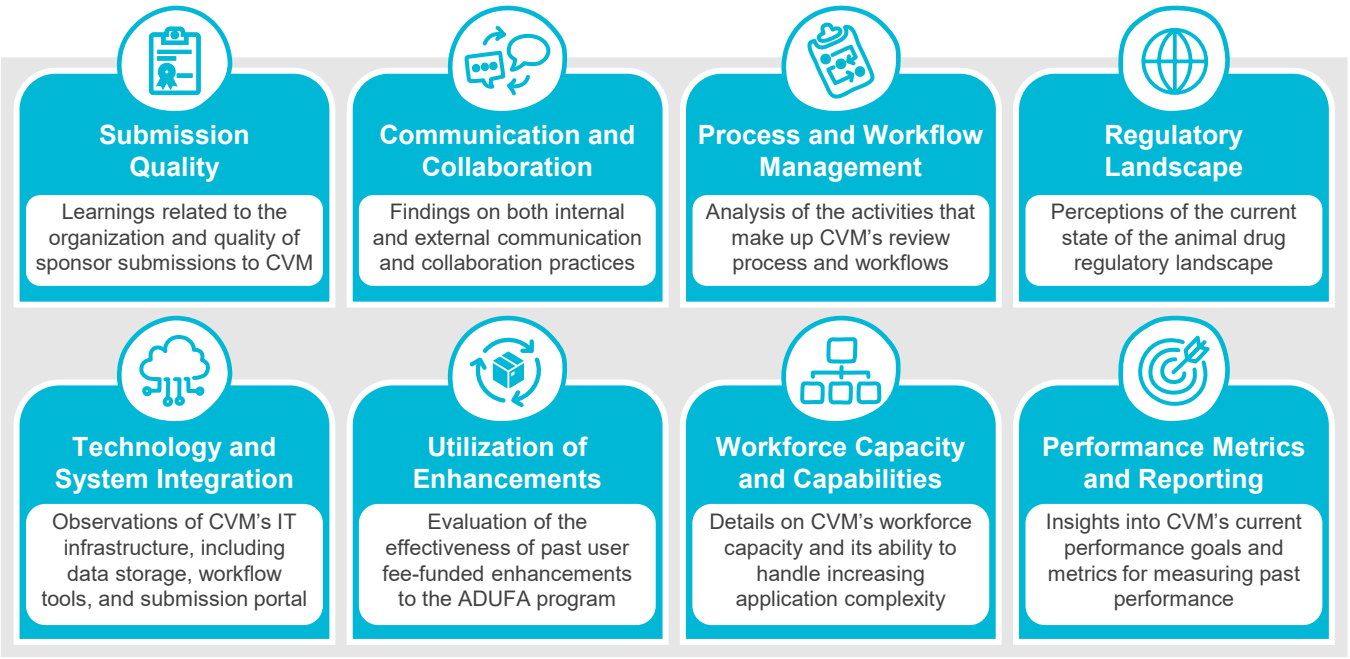



**Figure 1.** Key findings were classified into eight categories, each reflecting thematic similarities.

Following the analysis of the primary data sources, a Root Cause Analysis (RCA) was conducted to identify the fundamental causes behind challenges, aiming to prevent recurring issues. The analysis used both quantitative and qualitative data, applying Lean Six Sigma methods like Five Whys and hypothesis testing. Each challenge was tagged with root causes to identify patterns and provide evidence for addressing recurring issues, enabling long-term sustainability and success for CVM and its stakeholders. In total, 15 underlying root causes were identified as needing to be addressed to prevent the recurrence of common challenges.

To mitigate these issues, this report includes 10 recommendations, including 22 unique activities, to reduce the negative impact of these root causes. This report also includes recommendations for additional reporting metrics and a detailed list of actions to improve upon previously implemented program enhancements. Each recommendation detailed in this report includes a current state analysis, recommended activities, action items and outputs for implementation, and potential risks and benefits. The proposed level of effort for these recommendations does not currently account for potential resource and budget constraints that may arise due to any incoming legislative changes. We acknowledge that changes in the CVM's operating environment will affect the financial and staffing resources necessary for implementation. These recommendations are based on current conditions and assumptions, which should be adjusted to reflect any significant organizational or fiscal changes. These recommendations are detailed in Table 1 below:

**Table 1.** Overview of recommendations from the ADUFA V Assessment.

| Recommendations | Description |
|---|---|
| **Integrate the Project Management Team into the Review Process**<br>*2 Recommended Activities* | Activities to further integrate the project management team into the review process and equip them with the tools needed to continue servicing sponsors and project teams effectively. |
| **Expand Internal Training and Development Opportunities**<br>*2 Recommended Activities* | Activities to further develop CVM's training programs and expand access to continuing education programs to stay up-to-date on evolving policies, procedures, and scientific advances. |

| Recommendations | Description |
|---|---|
| **Improve Communication and Guidance between CVM and Sponsors**<br>*5 Recommended Activities* | Activities to address lingering communication challenges such as hosting workshops, developing user-friendly public portals for resources, distributing newsletters, and creating clear submission templates. |
| **Set New Compliance Standards for Submission Organization and Quality**<br>*3 Recommended Activities* | Activities to mitigate challenges with submission organization and quality through the development of new standards and exploring the standardization of study data formats. |
| **Capture and Report Reasons for Submission Review Outcomes**<br>*1 Recommended Activity* | Activity for CVM to revamp its approach to providing and tracking submission and application review comments, allowing for further detailed analysis of common reasons for unfavorable review outcomes. |
| **Implement Continuous Workload Analysis and Task Reallocation**<br>*2 Recommended Activities* | Activities to address the challenges associated with maturing science and complexity of submissions by bolstering oversight of reviewer workload and identifying opportunities to reduce reviewer administrative workload. |
| **Enhance IT Systems for Submission Workflows and Tracking**<br>*6 Recommended Activities* | Activities to tackle IT-related challenges experienced by both CVM and Industry. These include implementation of new workflows, improving data capture for submissions and resource hours, and enhancing eSubmitter's user experience and data validation. |
| **Standardize and Streamline Review Process Workflows**<br>*1 Recommended Activity* | Activity to streamline CVM's internal processes by reducing system workarounds, identifying automation points, and regularly monitoring and improving upon the review process. |
| **Track and Report Key Metrics Relevant to Review Process Success**<br>*9 Recommended Metrics* | A detailed list of nine key performance metrics for CVM to track and regularly report on. Each metric is accompanied by a definition, the benefits of tracking them, and the current state of the data required to report on them. |
| **Review and Improve Upon Previous Program Enhancements**<br>*8 Recommendations for Enhancements* | A detailed list of findings specific to eight user fee-funded enhancements to the ADUFA program and the animal drug review process, along with suggestions for additional improvements to enhance these tools and pathways. |

# Introduction

## Background and Assessment Overview

The Animal Drug User Fee Act (ADUFA), initially enacted in 2003 and subsequently reauthorized in 2008, 2013, 2018, and 2023, enables the Food and Drug Administration (FDA) to levy fees for new animal drug applications. The review process under ADUFA plays a critical role in approving new animal drugs that are both safe and effective. During the 2023 ADUFA V reauthorization negotiations, the Center for Veterinary Medicine (CVM[2]) and stakeholders from the animal drug industry reached a consensus to commission an independent assessment of 30 new animal drug applications (NADAs). This retrospective assessment aims to evaluate the ADUFA program's effectiveness in achieving its goals of expediting the animal drug development process and the review of original NADAs, as well as INAD submissions. Eagle Hill Consulting (Eagle Hill) was engaged as an independent third party to conduct this assessment, which began in January 2024.

The primary objectives of this assessment include:

- Evaluating the tools employed by CVM and Industry, including any enhancements, to improve the efficiency of the review process and foster favorable review outcomes for sentinel submissions
- Assessing the utilization and effectiveness of animal drug review processes
- Analyzing the allocation and availability of ADUFA resources, specifically full-time equivalents (FTEs), throughout the review process

The assessment was conducted from January 2024 to December 2024. The analysis consisted of stakeholder interviews with CVM and Industry personnel, a comprehensive review of CVM system records and performance data, and an examination of the activities in the review process.

### *Scope*

The scope of the assessment involved the evaluation of 30 randomly selected animal drug applications, consisting of 20 companion animal applications and 10 food animal applications. This represents a sampling ratio of 21.7% of the 138 applications approved between fiscal years 2009 and 2022 (Figure 2).

2. Throughout this report, CVM will be used to refer to all offices and divisions within the Center, notably the former Office of New Animal Drug Evaluation (ONADE) and current Office of New Animal Product Evaluation (ONAPE).

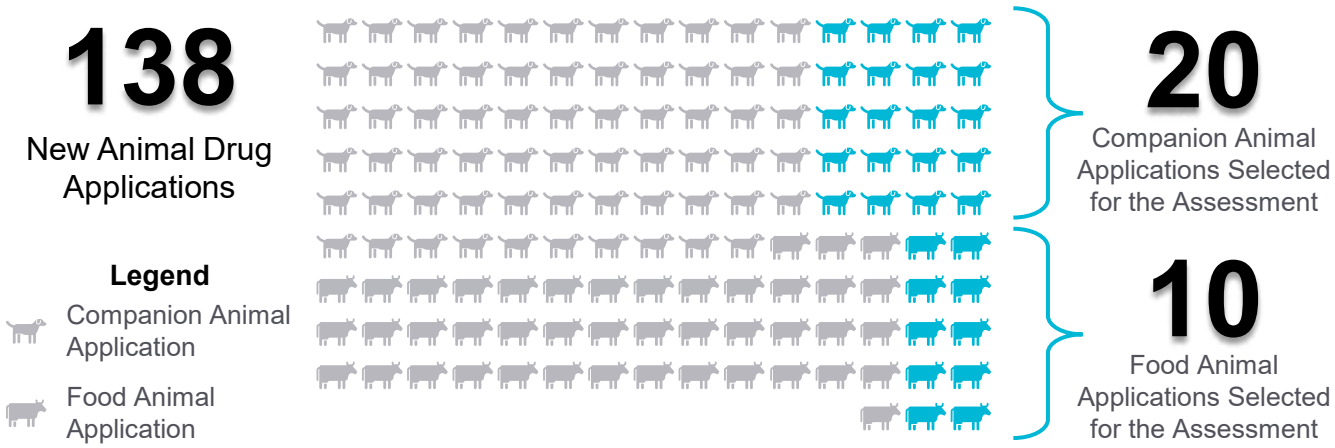



**Figure 2.** Sampling ratio for applications analyzed as part of the assessment.

As part of the ADUFA V agreement to conduct a third-party assessment, CVM and Industry agreed upon set parameters for the 30 randomly selected applications, detailed below in Figure 3.

**A Random Set of 25 to 30 Original or Conditionally Approved NADAs Including:**

- ✓ New chemical entities
- ✓ Multiple Industry sponsors
- ✓ A variety of major animal species
- ✓ No less than 15 companion animal applications
- ✓ Multiple dosage forms (e.g., oral tablet, topical solution, sterile injectable, medicated feed)
- ✓ Between 2 or 3 conditionally approved NADAs

## Assessment Application Parameters

**Additional Human Food Animal Application Parameters:**

- ✓ No less than 10 food animal applications
  - Containing no more than 3 ADAA combinations
- ✓ No less than six of the food animal applications must include:
  - A phase 1 & 2 environmental assessment (not a categorical exclusion)
  - Full Human Food Safety technical section (Microbial Food Safety, Toxicology, & Residue Chemistry)
    - At least 2 food animal applications must include a Residue Chemistry method trial

**Figure 3.** Industry and CVM parameters and conditions for the 30 randomly selected applications.

This assessment also examined user fee enhancements to the ADUFA program and animal drug review process. It assessed the effectiveness of these enhancements against their intended objectives and goals. These enhancements include:

**Table 2.** An overview of user fee enhancements, highlighting their implementation periods under ADUFA and the objectives they are designed to achieve.

| Enhancement | ADUFA Period | Objective |
|---|---|---|
| **End-Review Amendments (ERA)** | II | Enables reviewers to work with sponsors to amend pending submissions, reducing the number of review cycles needed to achieve complete review decisions. |
| **Shortened Review Time (SRT) for Protocols and Data Submissions** | III | Enables reviewers to review resubmissions in a shorter amount of time by providing sponsors with targeted comments on the changes needed in the parent INAD submission for submission completion. |
| **Two-Phased Chemistry, Manufacturing, and Controls (CMC) Technical Section** | III | Permits sponsors to submit CMC data requirements in phased submissions within the CMC technical section, allowing sponsors to begin the CMC technical section earlier in the phased review process. |
| **Early Information (EI) Process** | III | Allows sponsors to submit data and/or supporting information early in the new animal drug development process to allow CVM and the sponsor to reach consensus on the drug development plan at a presubmission conference (PSC). |
| **Animal Drug Availability Act (ADAA) Combinations** | III | Allows for qualifying ADAA Combination Medicated Feeds applications to be approved within 60 days of submission date. |
| **Expanded Conditional Approval (XCA)** | IV | Allows sponsors to legally sell and advertise an animal drug product before proving it meets the "substantial evidence" standard of effectiveness for full approval. |
| **Minor Amendments to Data and Protocol Submissions** | N/A | Grants sponsors an opportunity to provide specific information that corrects one or more deficiencies in the parent INAD submission in question. |
| **H Submissions[3] Supporting Protocols and Meetings** | N/A | Allows sponsors to submit data and/or supporting information in support of more targeted meetings or efficient INAD protocol reviews. |

3. H submission: A submission to provide either specific information/data to support a protocol review or general drug development information under an INAD (this submission should not be used to submit data/information in support of a technical section).

# Methodology and Data Collection

## Methodology Overview

To conduct a comprehensive assessment of the NADA review process and uncover opportunities for further improvement, this assessment used data collected from three primary sources: stakeholder interviews, system records, and process documentation. Key insights related to successes, challenges, and underlying root causes were extracted and validated from the three sources. These insights informed recommendations for future consideration and potential implementation by CVM and Industry.

### *Stakeholder Interviews*

A total of 112 interviews were conducted across two rounds involving 98 CVM personnel and 17 Industry sponsors. Industry interviews adhered to Paperwork Reduction Act (PRA) guidelines, limiting participation to fewer than nine entities per application category (Food, Non-Food, and Conditional Approvals). Interviews with CVM staff and Industry stakeholders focused on the submission process, impacts of ADUFA enhancements, and review challenges. Interviews were conducted in two rounds for each targeted audience (CVM and Industry); the first focused on a broad overview of the ADUFA program and general review processes, while the second focused on 30 individual applications, enabling a deeper exploration of factors influencing approval timelines.

The interviews were guided by semi-structured templates tailored to each audience – CVM personnel or Industry sponsors (**Appendix V: Interview Questions**). Topics included technical review challenges, communication and collaboration, the impact of IT systems, and the effectiveness of ADUFA enhancements. Discussions also identified pain points, approval delays, and root causes of multi-cycle reviews. Responses were anonymized and thematic and sentiment analyses were conducted to highlight recurring issues and assess participant perspectives.

### *System Records*

An analysis of CVM's internal systems, including the Submission Tracking and Reporting System (STARS), Activity Time Reporting (ATR) system, and Microsoft Project plans, provided quantitative data on submission timelines, review cycles, and resource allocation. Data from over 1,600

submissions associated with the 30 sampled applications were consolidated into a centralized master dataset. This dataset integrated submission timelines, resource allocation, and review cycle information, providing a cohesive view of the submission lifecycle. Additionally, linkages between submissions were manually established to evaluate interdependencies and inefficiencies, enabling an analysis of review timelines, first-cycle approval rates, and instances of rework.

## *Process Documentation*

A thorough review of over 200 documents related to the 30 sampled applications was conducted to map current review processes and identify areas for improvement. These include CVM review letters, Freedom of Information Act (FOIA) summaries, and project plans. Internal process documentation was also reviewed, including 80 policies and procedures, 58 standard operating procedures, and 13 scientific reference documents. Insights from these materials informed the development of 14 end-to-end process maps detailing major review activities, roles, and information flows. Process maps were then validated through 20 sessions with CVM subject matter experts (SMEs), who identified gaps, bottlenecks, and opportunities for automation or streamlining. Data from these maps were exported and further analyzed to quantify activity-level data by submission type, IT system use, and other variables and to identify opportunities for automation, enhanced clarity, and streamlined operations.

This assessment integrated qualitative and quantitative data to provide a transparent evaluation of the animal drug review process. The findings from analyzing interviews, system records, and process documentation offered a detailed framework for addressing inefficiencies, improving collaboration, and enhancing decision-making within CVM and Industry. **Appendices II – IV** further outline the approach for collecting and analyzing data from each primary source, along with detailed summaries of the information gathered.

## *Parameters and Limitations*

Two primary limitations exist within this assessment. Various strategies were employed to mitigate risk from these limitations and, as a result, provided comprehensive rigor in the findings from data collection and analysis (Table 3).

**Table 3.** Overview of the two primary limitations in this assessment, their descriptions, and corresponding mitigation strategies.

| Limitation | Description | Mitigation Strategies |
|---|---|---|
| Small Application Sample Size | Out of 138 applications approved between ADUFA II and ADUFA IV, this assessment had a sampling ratio of 21.7% (30 applications, as agreed to by CVM and Industry as a part of the ADUFA V reauthorization). This may have reduced statistical power of the findings and not sufficiently reflected the broader population of applications. | Analysis of submission data was parsed into larger population buckets, ranging from high-level application analysis (30 applications, as agreed to by CVM and Industry during ADUFA negotiations) to detailed, submission-level analysis (1,600+ submissions). This allowed for additional comparisons between an otherwise small sample size. |
| CVM System Records are Missing Key Data Fields and Relationships | Submission data were collected from multiple CVM systems; however, key data fields were missing (e.g., Technical Section) and there were few relationships tracked between submissions. | This assessment supplemented new data fields and created relationships between submissions to address data gaps. This allowed innovative metrics to be developed and analyzed for this assessment, including cycle review time, Time in Agency (TIA), and Time in Industry (TII) ratios. |

## *Assessment Plan and Analysis Framework*

The assessment employed a systematic approach to capture, analyze, and categorize key findings from stakeholder interviews, system records, and process documentation. This effort centered around identifying commonalities between these data, variation, trends, and opportunities that could address underlying challenges in the process. Key findings were cataloged in a Successes and Challenges Database, which served as a central repository of findings, enabling the identification of underlying root causes, recurring challenges, and areas with potential for improvement.

Using the documented challenges, a Root Cause Analysis (RCA) was performed to ascertain thematic insights into the challenges' underlying root causes. Instead of focusing on immediate symptoms, RCA seeks to uncover the fundamental reason behind an issue to prevent it from reoccurring. Root causes are the earliest, most basic cause for a given behavior, often existing as a fault in a system or process. They often go unnoticed by the immediate personnel but can significantly impact and undermine operations across an organization and have wide-ranging impacts on the health and efficiency of an organization overall.

The analysis involved both quantitative and qualitative data, leveraging Lean Six Sigma methodologies such as the Five Whys and hypothesis testing, to identify the causes that directly contributed to the documented challenge. To understand trends in the challenges stakeholders experience, each challenge statement was tagged with at least one or more root cause. This

information helped identify recurring issues affecting CVM and its stakeholders and provides evidence-based support for addressing these underlying issues for long-term sustainability and success.

## *Recommendation Development*

This assessment employed a three-step process to develop recommendations that leveraged challenges identified throughout the analysis of the primary data sources. Root causes identified from the RCA served as the foundation for developing recommendations to address the challenges at hand. These recommendations were then streamlined and placed into thematic groupings with recommendations addressing similar root causes and topics that are connected in scope and outcome.

Concurrently, each recommendation was developed using an approach to aid leadership in considering and prioritizing proposed recommendations for alignment to CVM's vision, strategy, and objectives. The approach facilitates differentiating recommendations comparatively based on the return on investment expected from implementation. It takes into consideration two primary dimensions:

1. The **Impact** of each Recommendation
2. The related **Level of Effort** expected

The impact score considers the measurable and experiential benefits of implementing a recommendation. The level of effort takes into consideration the resources, buy-in, and feasibility of implementing the recommendation. All recommendations were scored utilizing a rating scale created specifically to assess each dimension and visually represented on a two-by-two matrix that serves as a tool for leadership to decide whether to advance certain recommendations and in what order can they be optimally implemented. This matrix can be found in the **Recommendations** section.

# Key Findings

This assessment of the ADUFA program and the new animal drug review process is based on a comprehensive analysis of data from three primary sources: stakeholder interviews, process documentation, and system records. In total, this assessment identified 126 distinct challenges across eight distinct categories, each reflecting common themes that provide valuable insights into the program's operations (Figure 4).


**Figure 4.** Key findings were classified into eight categories, each reflecting thematic similarities.

## Submission Quality

### *Overview*

The quality of investigational animal drug submissions plays a pivotal role in the efficiency of CVM's review process. Submissions that are poorly prepared, unorganized, or lack clarity create significant obstacles, slowing down the review process. The variability in submission quality is often tied to a sponsor's familiarity with CVM's requirements and their experience navigating the review process.

Common challenges with submission quality include incomplete or inadequately supported submissions, disorganized materials that hinder navigation and understanding, and insufficient upfront communication to address potential gaps or concerns. These Not in Good Order (NIGO)

submissions lead to additional review cycles, delaying progress and constraining resources. These resource constraints occur as review teams overservice submissions by attempting to interpret, evaluate, and conduct error correction rather than rejecting submissions and returning to sponsors due to inadequate submission quality.

Despite these hurdles, CVM has implemented process improvements to address submission quality issues. These include enhanced support for sponsors throughout the drug development lifecycle aimed at fostering clearer, more complete, and better-organized submissions. However, persistent challenges underscore the importance of improving upfront submission quality to improve the overall downstream program efficiency.

## *Successes*

As noted in interviews and through review of submission records (i.e., review letters), this assessment identified key practices that have contributed to more efficient reviews and favorable outcomes. Both CVM and sponsors highlighted strategies that address challenges in submission quality and enrich the overall review process. These insights are grouped into two categories: best practices for sponsors and process improvements by CVM.

### Standard Best Practices Improve Submission Quality

Thorough preparation and organization by sponsors play a significant role in improving submission quality and enhancing the review process. Key factors include:

- **Clear Justification and Reasoning:** When sponsors articulate their objective for the submission and identify any concerns or data gaps within a submission, it provides reviewers with a clear understanding of its purpose. Submissions that include detailed explanations of purpose and rationale help reviewers quickly understand the submission's intent and facilitates a more efficient review process. For example, reviewers cite that when sponsors clearly list the justification for each component of their submission, it helps align the objectives of reviewers and the sponsor.
- **Inclusion of Raw Data:** Sponsors who include copies of raw data alongside summaries make it easier for reviewers to verify findings, reducing unnecessary follow-ups. As noted during interviews, CVM has initiated a pilot program to secure direct access to sponsor raw databases to reduce the level of effort of including raw data in electronic submission packages.
- **Use of Specialized Consultants:** Sponsors that are new to the market often benefit from the use of consultants familiar with the animal drug review process. These specialized consultants bring in knowledge of animal drug development and regulatory requirements, enabling sponsors to create well-structured development plans and improve submission quality. By helping sponsors avoid common errors that might otherwise result in incomplete letters or delays, these consultants help align submissions with reviewer expectations, improving their overall quality.

### CVM Invested in Resources to Assist Industry in Improving Submission Quality

CVM has implemented several mechanisms to assist sponsors in improving submission quality. These mechanisms provide sponsors with tools and guidance to enhance submission quality and streamline the review process:

- **Dedicated Project Manager (PM) Support:** CVM PMs provide ongoing guidance to sponsors throughout the drug development lifecycle, helping sponsors navigate submission requirements and deficiencies proactively.
- **Tailored eSubmitter Templates:** CVM has adapted FDA's eSubmitter system to create tailored templates that meet specific needs, offering sponsors the ability to improve the organization and completeness of electronic submissions. Regular updates are made based on sponsor feedback and needs.
- **Refuse-to-Review (RTR) Process:** The implementation of the RTR process allows CVM to screen submissions for quality issues before they undergo full review, helping to identify and address deficiencies early.
- **Guidance Documentation:** CVM provides guidance to help sponsors navigate submission requirements. Since ADUFA was established in 2003, CVM has published 150 Guidance for Industry (GFI) documents (Figure 5), offering clear recommendations for sponsors. Additionally, CVM has issued over 90 Policy and Procedures (P&P) documents, which standardize internal review practices. Together, these resources have helped enhance submission quality and fostered a more efficient and consistent review process, benefiting both CVM and sponsors.

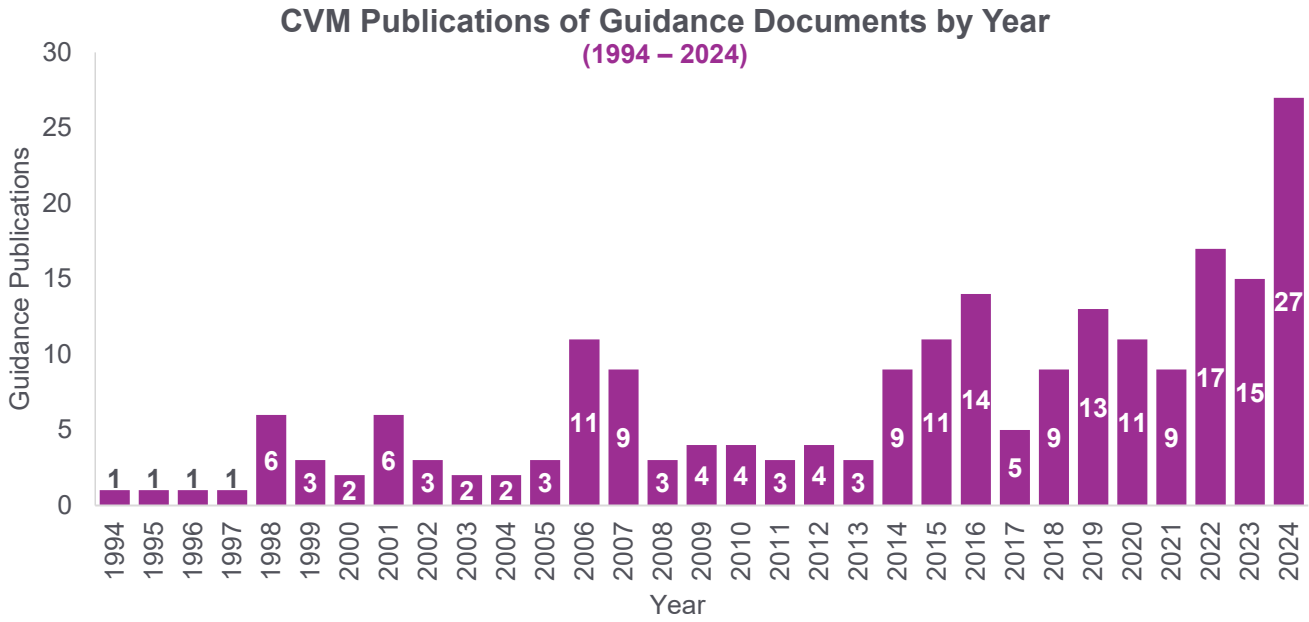



**Figure 5.** CVM publications of guidance documents by year (Source: FDA.gov).

## *Challenges*

While progress has been made, submission quality remains a leading barrier to efficient reviews. Additional focus on education, early communication, and improved alignment between reviewers and Industry is needed to continue addressing these persistent challenges.

### Omission of Essential Organizational Elements in Submissions Impedes the Review Process

Deficiencies in organization and clarity in submissions hinders the efficiency of the submission review process, leading to preventable time spent sorting through unorganized information rather

than focusing on scientific review. During interviews with CVM, several recurring challenges were highlighted, including:

- **Missing Cover Letters:** Since the elimination of the cover letter requirement with the adoption of eSubmitter, submissions lack a clear roadmap for reviewers. Without this document, reviewers struggle to quickly locate critical information, slowing the review process.
- **Absence of a Table of Contents or Bookmarks:** Reviewers report that submissions lack basic organizational tools such as a table of contents or properly formatted bookmarks. The omission of these tools in submissions makes navigation cumbersome, delaying the initial submission triaging to break out consult requests and amendment requests.
- **Exclusion of a Change Log:** Amendments or resubmissions submitted without a change summary or change log prevent reviewers from quickly identifying the changes made and where to focus their review. Without this, reviewers must revisit entire submission packages to identify updates, wasting time and raising the risk of overlooking new details.
- **Unclear Objectives or Justification:** Submissions often fail to clearly articulate their purpose or provide a rationale for the inclusion of studies or data. Reviewers reported that the absence of these explanations requires additional effort to interpret the submission's intent, causing delays before substantive review work can even begin.

### Time Spent on NIGO Submissions Reduces Reviewers' Available Capacity

Submissions that are incomplete, noncompliant, or include extraneous information significantly hinder the review process. These issues often require additional clarity, amendments, or resubmissions, straining resources and delaying approvals:

- **Incomplete Submissions:** Missing key components—such as raw data, explanations for protocol deviations, adverse event details, or complete answers to review comments—often lead to extended review cycles. For example, failing to address all comments in an amendment causes reviewers to reexamine prior communications and direct sponsors back to previously issued GFIs, wasting time and resources. While eSubmitter includes question-based templates for certain technical sections with required fields (e.g., Environmental Impact [ENV] and Chemistry, Manufacturing, and Controls [CMC]), these fields can be bypassed by entering placeholder text, such as "see attached" or "TBD." This causes reviewers to conduct unnecessary exploration by either requesting amendments or initiating additional review cycles to address missing or incomplete information.
- **Noncompliant Submissions:** Reviewers report instances where sponsors disregard explicit guidance and resubmit unchanged or minimally altered materials, accompanied by justifications for why modifications were unnecessary. This requires reviewers to reprocess the submission, revalidate prior recommendations, and direct sponsors back to previously issued communications, such as incomplete letters or Memoranda of Conferences (MOCs) to reference the changes still required.
- **Submissions Containing Extraneous Information:** Reviewers note that some sponsors include extraneous information unrelated to the submission's findings or objectives, cluttering the submission and complicating the review. While tools are in place to reset the review clock in such instances, they often avoid this option to appease sponsors.

### Lack of Standardized Formats for Raw Data Complicates the Review Process

Sponsors often submit study data in inconsistent formats, and when data are provided in PDF format, it can be challenging for reviewers to navigate, especially in a digital review environment. While many Industry sponsors are transitioning to Electronic Data Capture (EDC) systems, which

facilitate the export of data into digital files, CVM lacks the tools to query and search these datasets efficiently. This lack of standardization hinders CVM's ability to automate data quality control checkpoints, resulting in wasted time and resources.

**CVM's Existing Triage Process Fails to Adequately Filter Out Poor-Quality Submissions**
Currently, only 2% of data submissions are rejected outright through the RTR process. When submissions with quality issues proceed to the review stage, it results in unnecessary delays. Reviewers must invest additional time and effort to identify and correct deficiencies, which could have been avoided if these issues were identified earlier. By filtering out low-quality submissions early, CVM could focus its resources on higher-quality submissions that are ready for review, expediting the review process and reducing any unnecessary overservicing.

# Communication and Collaboration

## *Overview*

CVM and Industry both value a collaborative relationship, recognizing its importance in advancing animal drug approvals. This collaboration is built on open communication, early guidance, and the mutual goal of improving the quality of submissions and the review process. Currently, the relationship is strengthened by practices such as presubmission conferences (PSCs), informal communication pathways, and hands-on support provided by PMs. These elements allow for early clarification of expectations, timely feedback, and guidance throughout the review stages, ideally leading to expedited approval timelines. These interactions also foster trust, encourage transparency, and promote a productive working environment.

However, despite these successes, communication challenges remain a barrier to improving process efficiency. Inconsistent feedback from reviewers, misalignment in expectations between CVM divisions, and shifting regulatory guidance creates confusion for sponsors. This issue is compounded by insufficient early communication from sponsors, who may withhold key details out of concern for triggering additional scrutiny or delays. These gaps in communication result in inefficiencies, such as redundant reviews, extended timelines, and rework. By building on the foundation of collaboration that already exists, CVM and Industry can improve review efficiency and ultimately achieve more timely and favorable outcomes in the approval process.

## *Successes*

Both reviewers and sponsors cited that their relationship is characterized by a supportive and collaborative review process, built on communication and effective knowledge transfer. Sponsors emphasized the feeling that reviewers are engaged and easy to communicate with throughout the review process. Stakeholders from both CVM and Industry have identified several key factors that contribute to successful communication practices:

- **Presubmission Conferences:** During interviews, reviewers and Industry emphasized how PSCs are one of the most frequently used enhancements in the drug approval process. These conferences play a critical role in the relationship between CVM and Industry by providing

early guidance and clarifying expectations for the review process. PSCs help sponsors better understand regulatory requirements and generate drug development plans, which help them plan, minimize confusion, and set clear expectations for what CVM requires for their review.

- **Informal Communication:** Sponsors emphasize the importance of informal communication throughout the review process. Regular, less formal touchpoints between reviewers and sponsors allow for relationship building and timely feedback. This improves communication patterns downstream and helps to identify and resolve potential issues early. These conversations also help clarify ambiguities in guidance, allowing both parties to align on requirements.
- **Hands-On Support from PMs:** Sponsors view PMs as vital partners throughout the review process. PMs offer direct assistance navigating the submission and review process. This keeps projects on track and helps sponsors find the resources needed to understand regulatory requirements and assemble submission packages. It is essential that PMs are equipped with the right tools to allow them to be fully integrated into the review workflow, improving their oversight of the process and allowing them to provide sponsors with timely updates and guidance.

Sponsors consistently emphasized the value of the collaborative dynamic with CVM, highlighting the agency's flexibility and responsiveness in addressing complex issues. These qualities foster a positive working environment and smooth submission process, strengthening the mutual trust between CVM and Industry. CVM also supports sponsors through collaborative learning opportunities, offering guidance, post-approval discussions, and educational resources such as public workshops. Feedback opportunities, including lessons learned meetings, enable sponsors to gain a deeper understanding of the review process and continuously improve their submissions, while also enabling reviewers to learn from sponsors on areas upon which they can improve.

## *Challenges*

Though CVM maintains a collaborative relationship with Industry and sponsors express appreciation for their interactions and guidance, the animal drug review process is still hindered by a range of communication challenges between sponsors, CVM reviewers, and CVM PMs.

### Lack of Early, Transparent Communication Limits CVM's Ability to Provide Clear Guidance

During interviews, CVM reviewers indicated a belief that sponsors often withhold key information out of concern that it may negatively affect their application downstream if potential issues are identified during the initial review stages. A tendency to delay full disclosure hinders early identification and resolution of issues, creating a ripple effect that extends review timelines and leads to delayed or redundant reviews due to insufficient information.

### Confusion Over Communication Methods and Protocols

Sponsors are often unsure of which communication methods to use, particularly as there are unclear expectations around when to use informal portals, formal meetings, or email communications. This complicates interactions and has the potential to delay approval timelines. CVM offers sponsors the opportunity to discuss the review process during lessons learned meetings, but sponsors seldom request them. While CVM has implemented tools such as submissions and formal meetings to help reduce review cycles, their impact has been limited, as shown in Figure 6 and Figure 7. Analyzing the impact of both meetings and H submissions on favorable review outcomes for subsequent submissions reveals no significant improvement in the success rates of E and P submissions[4] within the sample. While these data do not reveal a direct impact on the favorable review rates, submission data are not structured to consider the complexity of submissions. Less

complex submissions are not likely to warrant a preceding meeting or H submission. This provides one explanation for the 63% and 71% favorable review rates for E and P submissions, respectively, that are not preceded by either an H submission or meeting.

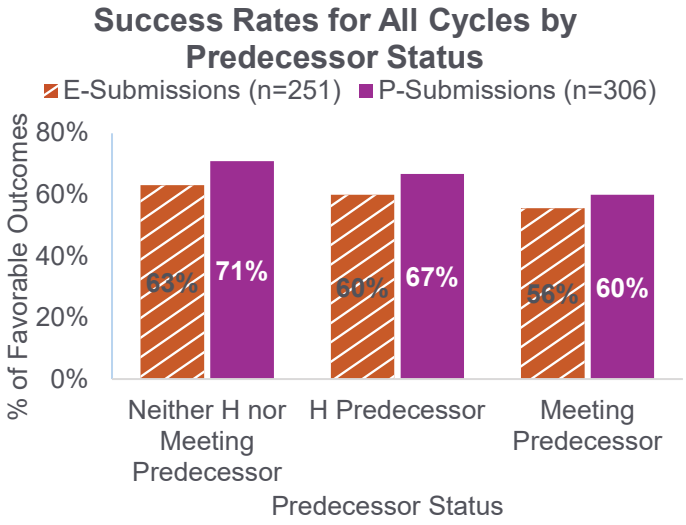



**Figure 6.** Percentage of favorable outcomes for all cycles preceded by meetings and H submissions; within the assessment sample.

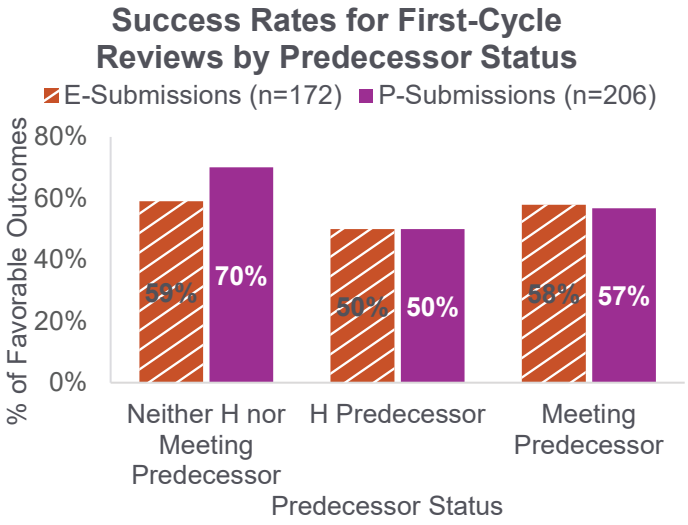



**Figure 7.** Percentage of favorable outcomes for first-cycle reviews preceded by meetings and H submissions; within the assessment sample.

## Inconsistent Internal Communication Practices Lead to Sponsors Feeling Disconnected

Challenges also arise from reduced collaboration and inconsistent communication styles from reviewers, which increases the risk of miscommunication and delays. Following the COVID-19 pandemic, sponsors reported a reduction in informal, collaborative communication. Additionally, varying communication preferences among reviewers – some favoring informal discussions, others adhering to formal protocols – creates uncertainty for sponsors. This issue is compounded by a lack of transparency, with sponsors describing a sense that their submissions are in a "black box" during the review process. CVM's limited tracking tools, notably through the reliance on Microsoft Outlook (email) for 31% of review activities, further hinder real-time progress monitoring and timely review completion. Further compounding this issue is the lack of integration between project management tools (i.e., Microsoft Project Plans and Drug Development Projects [DDP]) and the review teams' systems (i.e., STARS), which limits oversight from PMs of individual submission reviews.

## Conflicting and Unclear CVM Guidance

During interviews, sponsors raised concerns regarding inconsistencies in reviewer communication and guidance, which impact their ability to navigate the submission and review process efficiently. Variability in feedback – depending on the assigned reviewer or division – creates confusion, with misalignment between individual reviewers and leadership often leading to conflicting decisions. This disconnect is especially pronounced in multi-year drug approvals, where evolving CVM practices further complicate efforts to meet requirements. Additionally, sponsors struggle with unclear and unpredictable review comments, which are often perceived as unrelated to specific GFIs.

4. E submission: A submission requesting the review of a study protocol (without data) under an INAD. P submission: A submission of information/data to support a major technical section under an INAD (e.g., manufacturing, target animal safety, etc.).

This lack of clarity leaves sponsors uncertain whether feedback represents critical requirements or optional suggestions, making it difficult to anticipate and address issues effectively. Sponsors have described this as receiving feedback that feel like "nice-to-haves" rather than "must-haves." Once decisions are made, sponsors often find it challenging to engage in meaningful discussions for clarification, leaving unresolved questions that can carry over into future submissions.

### Difficulty Navigating CVM Guidance Documents, Especially with Evolving Regulatory Standards

Sponsors report facing challenges in navigating CVM's guidance documents and resources, often struggling to locate updated or relevant information, especially for specialized drug classes or complex CMC requirements. The frequent updates to GFI materials create further obstacles, as both sponsors and reviewers must constantly adapt to shifting standards. Sponsors noted that the evolving regulatory standards contribute to their struggles, as perceived "moving goalposts" make it difficult to plan effectively and predict outcomes. This sense of unpredictability undermines confidence in the process and often leads sponsors to rely heavily on CVM for drug development guidance, further stretching CVM's resources. Requests for more structured training programs, real-time guidance, and user-friendly resources such as frequently asked question (FAQ) portals highlight the need for improvements in accessibility and communication of guidance.

# Process and Workflow Management

## *Overview*

CVM effectively demonstrates its ability to implement flexible review strategies in the animal drug review process in alignment with sponsors' development plans. Continuous improvements in submission processing times across the ADUFA reauthorization periods also highlight CVM's adaptability and commitment to enhancing its processes. Despite these achievements, CVM relies heavily on manual processes, creating administrative burdens that detract from the focus on scientific reviews and hinder its ability to stay at the forefront of emerging science. Analysis of CVM's processes uncovered several challenges, including process variations, workarounds necessitated by limited IT capabilities, and activities that are redundant, inefficient, or misaligned. Addressing these issues is critical to improving efficiency, optimizing resource allocation, and helping CVM maximize its mission effectiveness.

## *Successes*

CVM's animal drug review process plays a crucial role in ensuring that safe and effective new animal drugs reach the market. Its effectiveness is achieved through a flexible approach used throughout the drug development lifecycle. CVM has improved efficiency in its reviews over time, showing its effort to achieve operational improvements while upholding high-quality standards.

### CVM's Approval Pathways Give Sponsors Flexibility in their Drug Development Strategy

The ADUFA program is unique as it allows for multiple pathways for approval: Administrative NADA and Non-Administrative NADA. There are key differences between these two processes:

- **Administrative NADA:** This process, known as the phased review process, allows sponsors to submit phased technical section submissions at different stages during the drug development, with a final administrative review once all sections are completed. The phased review process provides sponsors with real-time communication and issue resolution throughout the development process.
- **Non-Administrative NADA:** This approach requires submission of all data as a complete package, with a review of all sections done concurrently. This pathway is potentially faster for sponsors who have a comprehensive and finalized set of data.

CVM allows sponsors to begin with the phased review pathway (i.e., Administrative NADA) and switch to the Non-Administrative pathway by submitting the requested data for the remainder of the incomplete technical sections with the Non-Administrative NADA submission. This flexibility allows sponsors to choose the most effective path to bring their new product to market. From the 30 applications analyzed in this assessment, only five applications were submitted as a Non-Administrative NADA submission. "However, 100% of these five applications began using the phased review route and then switched to the Non-Administrative route to save time.

## CVM Consistently Beats Review Timeline Goals and is Improving on Processing Times

CVM has consistently met the sentinel review goals and internal key goals (Figure 8), providing sponsors with predictable and reliable timelines for submission reviews.

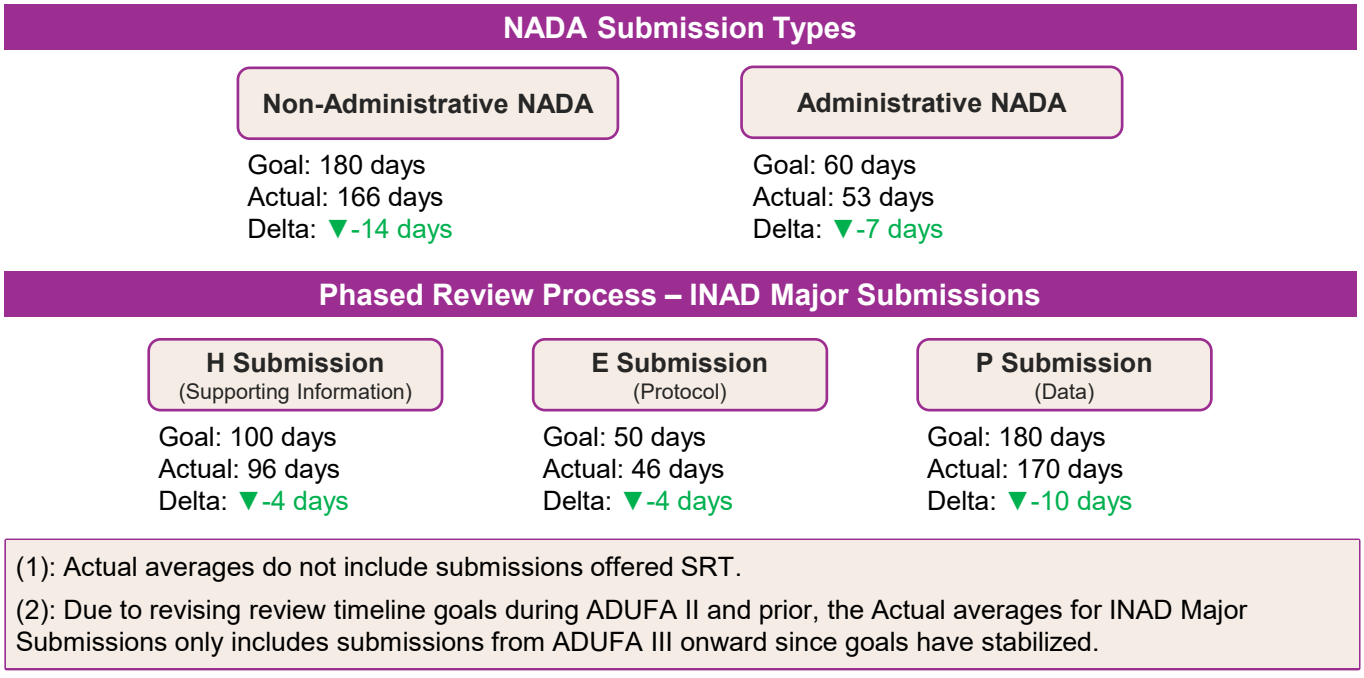
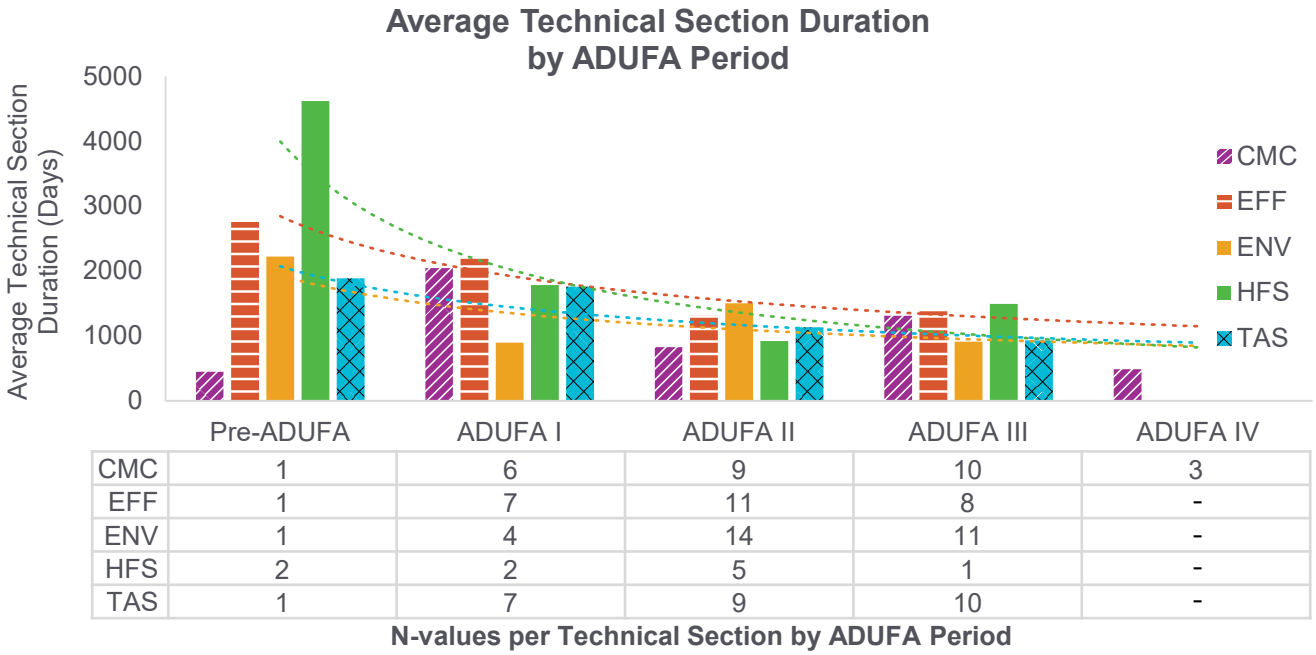



**Figure 8.** Within the 30-application sample, CVM's average review time beats their sentinel or key review clock goals for their NADA submissions and major INAD submissions.

While CVM consistently meets their review goals, they've also been improving on review times across each of the ADUFA reauthorization periods[5], with 82% of submissions being processed ahead of schedule across the two latest ADUFA periods (i.e., ADUFA III and IV). The time to complete all technical sections in the phased review process declined 33% from an average of 1,676 days in ADUFA I to 1,125 days in ADUFA III. Each individual technical section within the assessment sample (excluding CMC), has reduced time to completion (TTC) by over 50% since the ADUFA program was instituted (Figure 9).




| | Pre-ADUFA | ADUFA I | ADUFA II | ADUFA III | ADUFA IV |
|---|---|---|---|---|---|
| CMC | 1 | 6 | 9 | 10 | 3 |
| EFF | 1 | 7 | 11 | 8 | - |
| ENV | 1 | 4 | 14 | 11 | - |
| HFS | 2 | 2 | 5 | 1 | - |
| TAS | 1 | 7 | 9 | 10 | - |

N-values per Technical Section by ADUFA Period

**Figure 9.** Within the assessment sample, average times to complete review of technical sections have decreased over time.

Improvements in process efficiency can be attributed to multiple factors, including:

- Establishing submission review goals in ADUFA I
- Reducing review clock goals from ADUFA I to II
- Continually adding more review goals during each reauthorization period
- Deploying ADUFA enhancements, including the use of review tools like ERA, in ADUFA II, to reduce multi-cycle reviews, and SRT to reduce review time of second (and subsequent) reviews
- Rolling out other continuous improvement efforts, including IT tools such as eSubmitter, updating guidance, and a library of standardized review templates

## *Challenges*

The current challenges faced in the review process stem from variations in workflow, limited IT capabilities, and the presence of low-value-add activities. Variations in the review process, such as inconsistent amendment requests and non-standardized consults, lead to disjointed communication and hinder effective workflow tracking. Additionally, limited IT capabilities force reviewers to resort to inefficient workarounds.

5. Technical sections are assigned to ADUFA reauthorization periods based on the received date of the first submission in the technical section captured in STARS. Within the 30-application sample, only three technical sections were started during ADUFA IV and all three were CMC technical sections.

### Variations in the Review Process Create Inefficiencies and an Inability to Track Workflow

At a high level, the review process shares commonalities across all technical sections for each type of submission. However, variations emerge regarding the order in which specific actions occur. This results in disjointed communications, an inability to track workflows, and inconsistent guidance to sponsors.

Below are various inconsistencies that were uncovered during the review and validation of process documentation:

- **Requesting and Submitting Amendments:** Reviewers noted variability in how amendment requests are made and how they are received due to the lack of a standardized routing system. Amendments are typically requested via email or phone, and information is manually logged by the reviewer, resulting in variation in detail and specificity depending on the reviewer. Additionally, there is no standard timeframe for when requests are sent or how long sponsors have to respond, making it difficult for sponsors to predict if or when they will receive an amendment request. This variation also restricts CVM's ability to consistently track and monitor amendment requests.
- **RTR and Refuse-to-File (RTF) Processes:** Responsibilities for completing activities within the RTR and RTF processes vary. While some teams always have their primary reviewers perform these checks, other teams have additional individuals do so, including consulting reviewers, the Consumer Safety Officer (CSO), or the Quality Assurance Study Reviewers (QASR) from the QA team. Additionally, the primary reviewer may use other pathways, such as an amendment, to obtain missing information. Reviewers often choose this path as it requires less back-and-forth; however, it results in overservicing beyond the scope of a normal review to identify missing elements within the submission to request within an amendment.
- **Requesting Consults and Sub-Consults:** Requesting consults also varies as they are not always requested through Appian. While CVM has a workflow in place, some reviewers request informal consults outside of the system, resulting in inconsistent tracking by the review team. Inconsistencies also exist in the level of detail provided to consulting reviewers to conduct their review, resulting in additional efforts to clarify the objective of the consulting review.

### Limited IT Capabilities Force Reviewers to Create Process Workarounds

Process mapping and documentation sessions revealed that CVM reviewers employ workarounds to circumvent IT system limitations to complete their activities effectively. These workarounds arise due to various challenges, including gaps in available tools, persistent IT malfunctions or bugs, and limited system capabilities. Examples include:

- **Consult Request Workflow:** When a consult review is required, there is a standard template for the information to share in the request, but the Appian text box has limited space to thoroughly document these details. This causes reviewers to communicate outside Appian, typically via email, to provide essential information to complete the consult. This often disrupts the records management process of tracking consult reviews. In cases where the primary reviewer may not follow up with the information, the consult reviewer will follow up directly with the primary reviewer, further complicating and lengthening the workflow.
- **System Generated Errors:** CVM's submission tracking system sometimes generates incorrect information regarding due dates. To mitigate this, reviewers must manage timelines outside of the system and communicate milestones manually to the review team. While there are external spreadsheet templates that can be used to assist primary reviewers in managing the review clock, these require additional manual effort.

- **Lack of an Integrated Collaboration Tool:** There is no integrated collaboration tool within the workflow, creating fragmented management with the use of multiple SharePoint pages and folders and shared drives across divisions. As a result, it can be difficult to locate and track disparate information stored across locations. In addition, each primary reviewer often differs in their preferred methods for managing activities, which causes further confusion for review teams.

### Low-Value-Add Activities Can be Reduced to Better Optimize Resource Capacity

As part of the analysis of CVM's current state process, review activities were individually evaluated using Lean Six Sigma criteria to identify which are Low-Value-Add (LVA). LVA activities are activities that are inefficient or overcomplicated, meaning their effort, time, or cost can be reduced. These activities could be improved through restructuring, simplification, or automation to streamline the process. Examples of LVA activities include:

- **Waste (i.e., overproduction, waiting, defects, etc.):** Where additional time or work is performed and does not contribute to the end goal
- **Redundant Activities:** Activities that are repeated unnecessarily
- **Inefficient Steps:** Actions that do not optimize resources or time
- **Process-Activity Misalignment:** Activities in the process are not aligned to the qualifications and capabilities of the person performing the activity

Within each of the process steps, there are various types of LVA activities, each contributing to inefficiencies at varying levels. However, the majority of LVA activities are manual activities, such as updating review documents based on feedback, downloading individual submission files, and updating M submissions[6] with correctly referenced P submissions. Figure 10 (below) details the activities within CVM's review processes that can be further optimized. A time study of these activities was not conducted as part of this assessment; therefore, these values are not representative of where time is spent within the process.

| Process Type | Process | Activities Identified for Optimization |
|---|---|---|
| NADA Submissions | Non-Administrative NADA | 49 (41.5%) |
| | Administrative NADA | 46 (39.7%) |
| Major INAD Submissions | Z Submission | 63 (47.4%) |
| | H Submission | 36 (45.6%) |
| | E Submission | 29 (40.8%) |
| | P Submission | 34 (39.5%) |
| | X Submission | 22 (37.9%) |
| Minor INAD Submissions | AOI | 35 (47.4%) |
| | FOI | 40 (45.6%) |
| | Labeling | 37 (39.7%) |
| Grand Total (Average) | | **39 (42.5%)** |

**Figure 10.** An average of 39 activities per process were identfied for optimization. These activities are not representative of review time. Percentages of activities identified for optimization are based on the total activities in each given process.

6. M submission: A submission that supports the All Other Information or the Labeling technical sections under an INAD.

Some LVA activities include administrative activities that could be downshifted from scientific reviewers to administrative support staff. These misaligned administrative activities include compiling documentation packages from disparate storage locations, conducting administrative application checks, and organizing meeting logistics (e.g., reserving conference rooms, printing visitor badges, IT setup). The realignment of these administrative activities to support staff or automation may improve the capacity of the scientific reviewers, providing them more time to focus on core scientific review activities.

In addition to the heavy reliance on manual activities, the review process also significantly relies on email for sharing information and communicating review handoffs. The reliance on manual and send activities can be seen in Figure 11, which captures the percentage of activity types that make up the CVM review processes, with each process averaging 47.2% of its activities completed manually and 28.7% focused on the sending of information. CVM's dependence on email, rather than an integrated workflow or task automation tool, leads to variance in communication practices between review teams, while also making it difficult to track real-time status of the submission review.

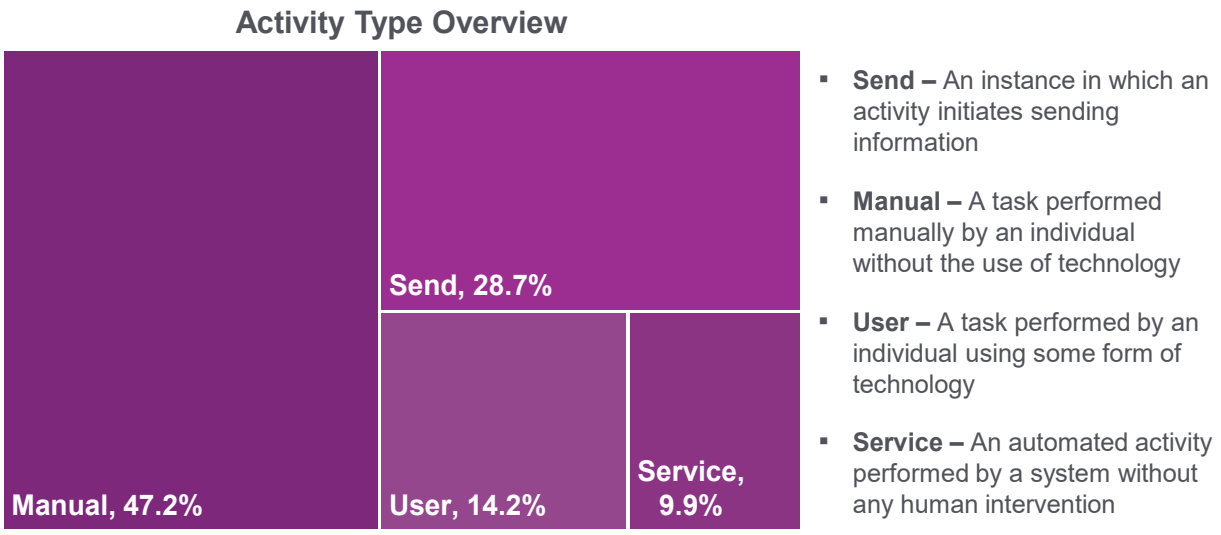



**Figure 11.** Manual and Send activity types dominate the review processes at 47.2% and 28.7%, respectively.

Other LVA activities include redundant feedback loops to complete a final internal compliance check of a submission's review package. Regardless of submission type or complexity, all submissions are required to undergo a two-tiered review process, starting with the Team Leader and followed by the Division Director. These internal reviews introduce points for bottlenecks and wait times to occur. Additionally, this two-tiered review is completed twice, once before material is uploaded into Appian and again within Appian for official signoff, adding unnecessary administrative overhead. Addressing these inefficiencies through consolidated reviews, role clarification, streamlined approvals, and automation can improve process speed, reduce waste, and enhance productivity.

# Regulatory Landscape

## *Overview*

Sponsors perceive CVM's review process as lengthy and cumbersome compared to other international regulators due to stricter safety assessments and additional requirements in the United States. Industry also cited the disparity in raw data and methodology study requirements between CVM and other global agencies, challenges in managing dual reviews[7], and risk-averse approaches from CVM as factors that add complexity to the drug approval process. However, sponsors also stated that they appreciate CVM's efforts to ease barriers to entry and the policies that have been implemented to aid the harmonization of international regulators.

A comparative analysis of international standards and review processes was not in the scope of this assessment. Thus, a thorough review of CVM's policies and practices compared to those of other international regulators can be useful to expand on or validate these perceptions, providing a more empirical and objective perspective of international practices.

## *Successes*

Interviewees noted that CVM's efforts in international harmonization have significantly improved the regulatory landscape for animal drug sponsors, fostering transparency and collaboration. Through initiatives such as user fee waivers and the Veterinary Innovation Program (VIP), CVM has alleviated financial burdens and provided greater regulatory certainty, particularly benefiting small business, Minor Use or Minor Species (MUMS) products, and complex product developments. Moreover, CVM's commitment to international harmonization, exemplified by standardized good manufacturing practice (GMP) inspections, mutual recognition agreements (MRAs), and joint reviews with Health Canada, streamlined review processes.

### CVM Continues to Make Efforts to Reduce Barriers to Entry

Industry interviewees note that CVM has made significant progress in reducing barriers to entry in the animal drug marketplace. Industry and CVM interviewees alike note that two key programs have proven especially helpful for facilitating approvals:

» **User Fee Waivers:** CVM offers five waivers to reduce the financial burden of exploring an animal drug product approval. During interviews, sponsors stated that developing and approving a new animal drug is cost-intensive and the waivers help "level the playing field" for new products coming to the market. These waivers include:
  - Signficant Barrier to Innovation
  - Fees Exceed Costs
  - Free Choice Feeds
  - MUMS
  - Small Business

7. Dual reviews are animal drug reviews that CVM shares with other regulatory bodies. For example, a review conducted via a partnership between CVM and Health Canada.

- **VIP[8]:** Products related to heritable intentional genomic alterations may qualify for the VIP, which allows sponsors to have greater certainty in the regulatory process, encourages development and research, and supports an efficient and predictable regulatory approach for emerging technology products. These products provide a benefit to human and animal health, promote animal well-being, and/or improve food production. Sponsors share that they appreciate the increase in agency interactions, informal meetings, and flexibility, particularly for complex products that qualify for the VIP. As of August 2024, the Agency has enrolled over 50 products into the VIP and continues to refine the benefits offered by this program.

### CVM Maintains Progress in Promoting International Harmonization through New Initiatives

During interviews, sponsors reported several benefits from international regulatory harmonization, acknowledging efforts that streamline the drug approval process and reduce the burden on manufacturers. Key policies include:

- **MRA for GMP Inspections:** The MRA supports the recognition of inspections across different regions, reducing duplicative regulatory efforts. Sponsors note that the MRA helps minimize the burden of additional inspections when new manufacturing sites or suppliers are involved. The standardization of GMP inspections across regions, including foreign pre-approval inspections (PAIs), simplifies the approval process for new sites or suppliers. Sponsors report that foreign GMP inspections are helpful because when all countries accept the same testing, it reduces the burden of adhering to competing standards.
- **Veterinary International Conference on Harmonization (VICH) Guidelines:** By harmonizing technical requirements, VICH guidelines facilitate approval in multiple regions, including the U.S., Europe, and Japan. This standardization helps sponsors reduce times to drug approval globally.
- **FDA and Health Canada Partnership:** CVM reviewers expressed appreciation in having the opportunity to conduct joint reviews with Canada. Health Canada independently validates data, providing CVM with a partner that ensures the accuracy and reliability of the approval process across both countries.

### CVM Leadership is Commended by Industry for Prioritizing a Culture of Flexibility

Although sponsors indicate a perception of CVM's risk aversion as one of their primary concerns, they acknowledged that CVM leadership continues to be open to creative discussions around novel science and new pathways to approval for innovative drugs. Sponsors also commended the Human Food Safety division for their agility in reviewing complex submissions, citing examples such as leveraging data from European studies to reduce the number of studies that need to be produced by sponsors.

## *Challenges*

Industry maintains a perception that CVM's review process is more risk-averse than other international regulatory bodies. Industry claims that prolonged approval timelines and increases in burden of proof for approvals is due to an increase in risk aversion. Sponsors report that CVM's "cautious" stance often necessitates additional research and extensive data submissions, particularly for new chemical entities. This assessment did not evaluate the risk management

8. No VIP products were included in the 30-application assessment sample. Interviewees offered VIP as an example of a successful initiative under the ADUFA program.

strategies of CVM during the animal drug review process compared to other regulatory bodies. However, Industry's perception of the FDA as a "blocker" rather than a resource may contribute, at times, to an adversarial relationship.

### Industry Claims that Risk Aversion is a Leading Cause for Prolonged Approval Timelines

Sponsors reported challenges associated with what they perceive to be a risk-averse approach by CVM. Specifically, when submitting applications involving new molecules or processes unfamiliar to CVM, sponsors noted that they were frequently required to provide extensive explanations and additional data to inform reviewers on these new innovations, prolonging product approval. While sponsors understand that each regulatory agency operates under different legislation and guidelines, they report that CVM's cautious stance compared to other international regulatory agencies leads to inefficiencies, requiring additional time and resources that could be avoided with more flexibility or familiarity in emerging science. For sponsors, CVM's limited resources to quickly review new and innovative products makes them less inclined to seek initial approval for their drugs in the U.S.

### Selective Adherence to Global Standards Increases Sponsor Confusion on Study Requirements

Sponsors seek increased alignment between CVM and international regulatory bodies to reduce duplicative work and streamline processes. While CVM has made efforts to harmonize its requirements in adherence to VICH guidelines, Industry reported that CVM's selective adherence to VICH guidelines creates confusion for sponsors, as they struggle to determine which regulations to follow during drug development. Sponsors believe that a dual review with other regulatory bodies risks a slower approval and may leave them in a worse position due to varying requirements with the partnering regulator.

### Sponsors Fear a Lack of Representation During ADUFA Negotiations

Some sponsors reported during interviews that they are not being sufficiently represented during ADUFA negotiations. These sponsors report that during ADUFA negotiations, Animal Health Institute (AHI) members and large sponsors often have the "louder voices" in the room. This leads to new agreements and enhancements that are more relevant for AHI members and large sponsors than for small businesses or new entrants into the market.

# Technology and System Integration

## *Overview*

Outdated IT systems pose challenges for both Industry and CVM. Industry experiences challenges with establishing accounts and continual changes to eSubmitter that can cause issues with submitting complete content. CVM, meanwhile, has challenges stemming from the lack of integration between internal systems, manual workarounds, and challenges in maintaining a single system of record. There is a need for improved IT infrastructure to support the overarching review and submission processes.

## *Successes*

The transformation of CVM's review process through electronic submissions and strategic IT investments has significantly enhanced efficiency and data management. The shift to electronic submissions via eSubmitter has streamlined the submission process, reducing the physical and logistical burdens associated with paper files, while improving tracking, access, and traceability. Additionally, internal IT advancements, such as the Corporate Database Portal (CDP) and automated business processes, have centralized access to critical resources and facilitated consistent review practices.

### Electronic Submission Transformed CVM's Review Process

CVM has made a series of investments and updates to its IT systems over the years, both as part of ADUFA agreements and as enhancements to internal operating systems outside of formal agreements. The most successful update – via consensus among Industry and CVM personnel during interviews – was moving submission of materials to electronic format via eSubmitter.[9] Shifting to this approach has allowed:

- Reduced physical and logistical burden of submitting, processing, and storing paper files
- Easier tracking, access, and traceability
- Continuous improvement to the system over time
- More efficient management and access to records via text searches and digital markups
- Pilots to explore CVM directly accessing data in sponsor systems

Not only did CVM mandate the creation of an electronic submission tool in ADUFA II,[10] but it also invested resources into tailoring the FDA's generic eSubmitter template to the needs of the animal drug industry and the NADA review requirements. By building CVM-specific eSubmitter templates, CVM can continuously update the system to guide sponsors through the submission process and improve the user interface.

### Internal IT Investments Improved CVM's Tracking and Reporting Capabilities

In addition to eSubmitter, CVM introduced new IT elements internally to better facilitate organizing, managing, and accessing content, as well as new elements to codify and normalize business processes. First, CVM introduced CDP, a web application that provides CVM users a unified User Interface (UI) to access various underlying IT modules and services, including timekeeping reporting (i.e., ATR) and submission tracking databases (i.e., STARS). By centralizing access to these resources in one place, CVM provides review staff with a single gateway to search and access relevant records. In terms of processes, CVM implemented a business process management (BPM) tool, Appian, to automate business processes and facilitate the routing of submissions for review across consults and supervisors. Appian is also used to manage the closeout of both paper and electronic submissions, standardizing handoff processes to enable further data collection and tracking. Specifically, this allows for tracking of key review milestones, when consults are requested and received, and when final approvals are approved and sent. While this practice adds consistency to the review process within and across review teams, opportunities exist to realize its full potential.

### CVM's Comprehensive Timekeeping Data Collection Enables In-Depth Data Analysis

In 2003, CVM introduced the ATR system, along with corresponding policies and procedures, to track

9. Electronic submission of records to eSubmitter should not be confused with submission of digital records, especially trial records. Please see Key Findings: Regulatory Landscape and Recommendation 4: Set New Compliance Standards for Submission Organization and Quality for more details on this topic.
10. Electronic submissions were mandated as part of the ADUFA IV reauthorization.

time and attendance. Over time, CVM has adjusted this system and associated business processes, including the introduction of governance policies to monitor and evaluate for consistency in structure and changes in time charging behaviors or patterns. Today, CVM has more than 20 years of records, encompassing 600+ personnel and nearly 10 million work hours against 200,000+ submission records.


Importantly, the current system and processes allow CVM to document personnel and hours against individual submission records, enabling detailed analysis at the submission level. The existence of these records has not only made key elements of this assessment possible, but also facilitated further operational enhancements, including the development of user engagement dashboards and the establishment of a Resource Capacity Planning (RCP) program to improve planning of future resources and streamline reporting functions.

## *Challenges*

Throughout the course of this assessment, many challenges were raised by both Industry and CVM personnel with regards to IT systems and underlying records, including: difficulty locating and accessing content in a timely manner; timeliness and transparency of updates to IT systems; stagnant or outdated systems; and limited or truncated functionality.

### Electronic Submission Constraints Place Additional Burden on Sponsors

Sponsors reported multiple challenges with electronic submission tools (i.e., eSubmitter and WebTrader). Sponsors noted that it can be difficult and time consuming to establish an account, often taking weeks, if not months, for the account to be established. While the eSubmitter helpdesk is helpful, there is consensus that the WebTrader helpdesk, which is managed at the Agency level, provides little to no support. Subsequent research validated that WebTrader support is generally limited to email correspondence with little or no ability to directly reach FDA representatives via phone. Further, the account structures can also be limited, as they are associated with individuals and do not allow for group or system accounts. This limits the ability for companies to share logins and can create issues if the individual who created the account or who is listed on a submission is out of the office or left the company.

Once accounts are set up, users indicated the system has limitations in both the UI and underlying functionality. The UI presents users with redundant fields and questions, along with small text and a confusing flow of the digital form and questions. Together these issues can result in sponsors missing critical fields and increase the chances of poor submission quality. Either of these can result in rejections, amendment requests, or requests for additional submissions. In addition, the system experiences issues due to limited functionality. For example, large attachments (greater than 100 megabytes) are not accepted, which requires creative workarounds for industry to partition files. This includes submitting multiple amendments to the submission, which artificially inflates the number of amendments required to complete the review, skewing data analysis around submission quality.[11]

11. Per CVM Recommended File Specifications for eSubmitter the limitation for individual files is 100MB. By contrast the European Union's guidance for submissions through their electronic submission system as of version 3.1 (Guideline on the specifications for provision of an electronic submission (e-submission) for a veterinary medicinal product stipulates a 200MB threshold.

### Internal IT System Limitations Act as a Barrier to Streamlined Reviews

Internal systems pose challenges for review staff to navigate and review content without interruption. Different elements of the review (submission, submission metadata, project management, etc.) are housed in different systems. While these systems point to each other, they are not dynamically connected. For example, the workflow management system generates an assignment with a reference to a submission number but does not allow for users to directly access the assigned submission. Instead, reviewers must manually search and bring up the record in the submission tracking system. Likewise, reviewers are not easily able to tell if there are relevant concurrent submissions being processed in other divisions or teams.[12] This process increases the risk for data quality issues – specifically discrepancies between systems – and increases the complexity of workflow automation due to the nature of multiple back-end systems and platforms.

These limitations extend to reviewers not having the ability to track performance on more modern processes such as Conditional Approvals. For example, review staff do not have easy access to identify ongoing projects or applications for Conditional Approval, often relying on institutional knowledge of which applications have Conditional Approvals. This requires workarounds and manual tracking via email of required deadlines. Interviewees reported that not having a document type unique to Conditional Approval exacerbates challenges with the tracking of phased Conditional Approval requirements. Similarly, records of certain activities (e.g., labeling changes) do not exist in systems. Exacerbating this issue, decisions not tracked within a system are often communicated back and forth by email. This makes it difficult to track revisions and the version history of label decision-making between multiple data submissions and/or parties. In turn, there is no centralized way for reviewers to look up and reference relevant information during the course of their activities. This can prove especially challenging for review staff processing ADAA submissions that require staff to review and validate appropriate labels.

### System Functionality Gaps Limit Future Analysis of Process Performance

Throughout the assessment, several features were identified as missing from the IT systems that would enhance CVM's ability to conduct future analysis of process performance. The lack of these features is not due to technological limitations, but rather whether CVM has sufficient resources and can implement policy enhancements to address them. Examples include:

- **Lack of Communication Documentation:** Systems do not provide a means to capture and document communications. Digital correspondence is captured via email records, but as these records exist outside the system, they do not allow for understanding the full journey of a submission and the nuances along the way. Likewise, ad hoc phone correspondence is not reflected unless it is captured through a follow-up email. These place additional burden on the review staff when authoring the review, as it requires sifting through email correspondence (from themselves and any affiliated with consults) for inclusion in the review.
- **Missing Fields for Amendment Records:** There are currently no fields associated with amendment records to reflect conditions related to the amendment. This includes whether reviewers requested an amendment, when the amendment was requested, or why it was requested.
- **Partial Tracking of Submission Relationships:** There are also limitations on the ability to track relationships between submissions. While CVM's data systems have fields to track

12. While reviewers have limited insight, the project management team manually runs reports to maintain oversight of project status. However, limitations with project management IT systems hinder the ability of PMs to systematically maintain real-time updates.

submissions related to each other, this is dependent upon manual input by Industry at time of submission. Regardless, at present the system does not have means to associate submissions to each other, in line with the branch analysis (**Appendix VI: TIA vs. TII Case Studies**) this report generated. Without capturing these data, tracking and reporting on review cycles relies on manual formulation of these relationships, as was done during this assessment.

- **Partial Tracking of Enhancement Utilization:** CVM also has limited fields tracking the implementation or adoption of select enhancements (e.g., EI, Two-Phased CMC, Conditional Approval). While some enhancements have made their way into CVM's data systems (e.g., ERA, SRT), others depend on manual intervention to identify if an enhancement was used to assess the success or adoption of these user fee enhancements.
- **Insufficient IT Maintenance Support:** Due to limitations in the operations and maintenance of IT systems, review staff have been required to operate with systems inconvenienced by bugs or poor performance. This has led to the development of workarounds, which creates challenges when fixes are eventually implemented, requiring reviewers to change their routine, workflows, and habits.

### CVM Staff Perceive IT Modernization as Low-Priority for Executive Leadership

While CVM is working to modernize its IT systems, organizational and cultural challenges persist. Staff have struggled with these issues for years and, in some cases, have developed homegrown tools to address workarounds or fill analysis gaps, such as tools to catalog and analyze comments from review letters. On a day-to-day basis, staff also encounter routine issues with existing systems, like web browser errors that require frequent manual intervention and software reboots to temporarily resolve issues. This has led to a perception among staff that technology challenges are not a priority for senior management, which discourages involvement in efforts to address them. Many staff members reported feeling that participating in these initiatives involves considerable effort for minimal reward.

Since 2019, CVM has been undertaking an effort to modernize its IT systems under a holistic approach on how data are collected, handled, and used. CVM personnel were included in these efforts early on, but, as of Summer 2023, they have limited or no visibility into the status or active involvement as efforts evolve. It is a risk to CVM and the larger review process if this approach to IT modernization persists.

# Utilization of Enhancements

## *Overview*

Since the inception of ADUFA, CVM has continuously innovated and adapted the program to fit the needs of the animal drug industry. CVM has collaborated with Industry during ADUFA negotiations to introduce a variety of enhancements to the ADUFA program aimed at improving the efficiency and effectiveness of the animal drug review process. Among these innovative tools and pathways, enhancements such as requiring electronic submissions and SRT have been touted as improvements by both CVM and Industry. However, despite the potential benefits, many of these enhancements remain underutilized, largely due to barriers related to clarity, scope, and communication. To realize the full potential of these enhancements, CVM must address these challenges and refine how they are offered and implemented.

# *Successes*

The ADUFA program enhancements have been widely acknowledged by Industry sponsors as impactful, with key improvements significantly benefiting the animal drug review process. Notably, enhancements such as electronic submission and review, SRT, ERAs, PSCs, and Expanded Conditional Approval have collectively accounted for most of the positive feedback from sponsors. These enhancements, particularly the mandatory electronic submissions, have led to faster processing times and more effective data tracking.

## Majority of Industry Sponsors Align on Most Beneficial ADUFA Program Enhancements

Most enhancements resulting from the ADUFA negotiations have made a meaningful impact, with certain key improvements consistently cited as highly beneficial by sponsors during both rounds of stakeholder interviews. Specifically, there were five enhancements that were highlighted as the most beneficial across most sponsors, accounting for 65% of all positive feedback regarding ADUFA program enhancements (Figure 12).

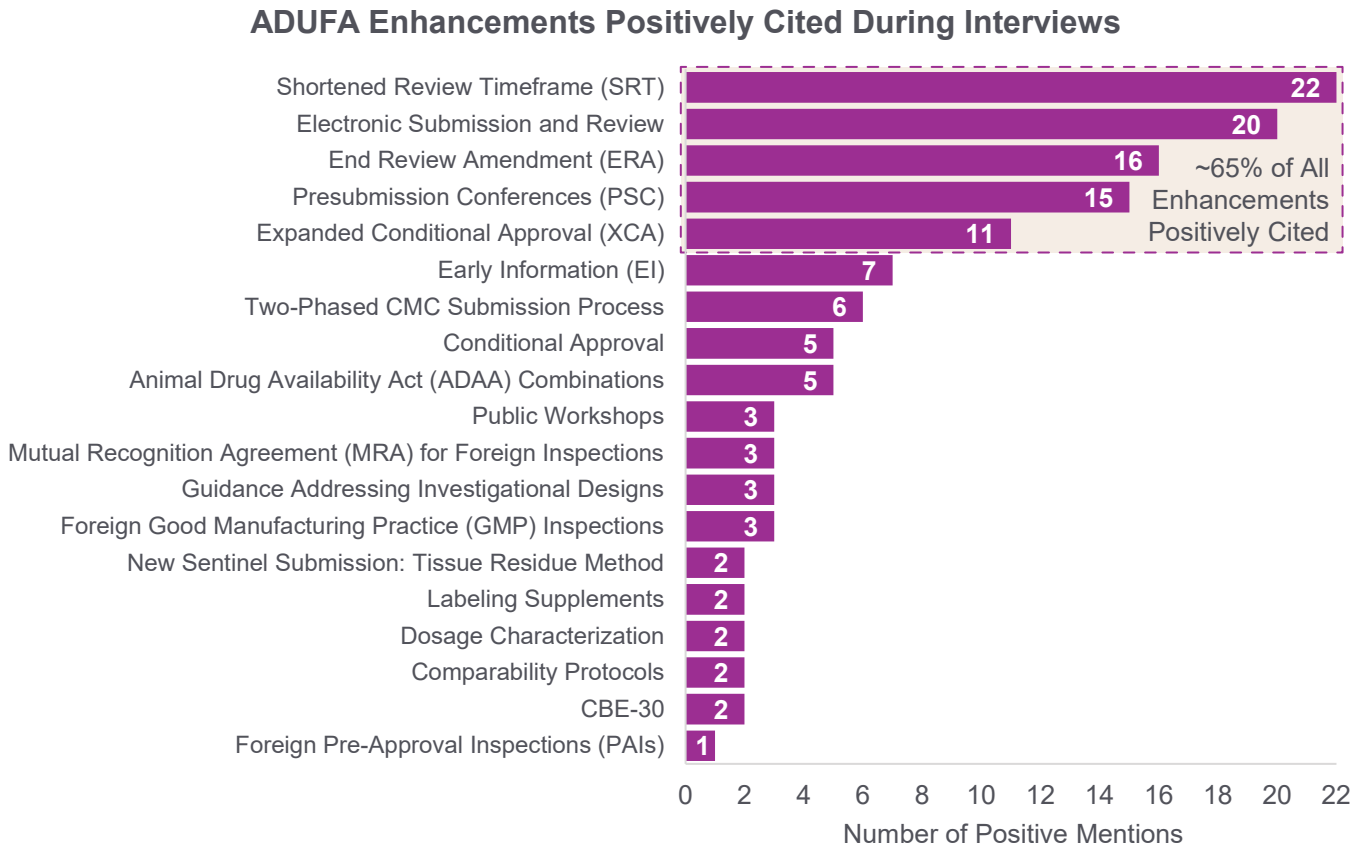



**Figure 12.** List of enhancements to the animal drug review process that were mentioned across all stakeholder interviews, with five of those making up around 65% of the most beneficial improvements.

These include:

» **SRT:** This enhancement aimed to speed up the review of resubmitted protocols, technical sections, and new animal drug applications. Industry sponsors often cited the flexibility in response time, along with more targeted comments from reviewers in SRT letters as major benefits of the SRT enhancement. For submissions that underwent a second review cycle, SRT reduced the total time to reach a favorable review outcome by a median of 251 days.

- **Electronic Submission and Review:** The introduction of eSubmitter revolutionized the submission and review process. Despite some bugs in the system, stakeholders reported a strong positive response to the transition. The eSubmitter helpdesk is also consistently praised for its support, contributing to the overall satisfaction with the electronic submission process.
- **ERA:** ERAs were particularly beneficial for submissions that did not meet favorable review criteria following the first review. While CVM has since replaced ERAs with SRT, both CVM and Industry appreciated the ability to quickly resolve outstanding issues without requiring a second review cycle. ERAs took a median of 16 and 59 days to review E submissions and P submissions, respectively, which is less than the average of 44 and 161 days, respectively, it took to review resubmissions without an ERA.
- **PSCs:** Formal PSCs between sponsors and CVM to establish a drug development plan allow for early feedback and alignment, helping to clarify expectations and reduce the likelihood of delays later in the review process. Sponsors reported experiencing a smoother development and approval process when CVM provides more guidance early in the process.
- **Expanded Conditional Approval (XCA):** The ADUFA IV legislation also revised section 571 of the FD&C Act to expand Conditional Approval beyond minor uses and minor species, offering an additional quicker pathway to market for qualifying new animal drugs, helping to meet urgent market needs (e.g., new animal drugs for serious or life-threatening conditions or unmet animal or human health needs). However, its scope remains limited, which has tempered its overall impact.

The impacts of these enhancements on the efficiency of the review process vary; however, the broader, more holistic enhancements, such as mandating electronic submission, have had an overwhelmingly positive impact on the review process. The requirement of electronic submissions was a sweeping enhancement that impacted every submission received by CVM, resulting in faster processing times and more effective tracking of data for reporting and analysis. Other than mandating electronic submission, there are few enhancements with as far-reaching of an impact, with the next closest being ERAs and SRTs.

### ERAs Increased Single-Cycle Reviews during ADUFA II

Under ADUFA II, the use of ERAs had a significant positive impact on submission outcomes. Specifically, 63% of submissions that would have otherwise received an unfavorable decision were granted the opportunity to address identified deficiencies and resubmit, leading to an 87% rate of favorable review outcomes. Additionally, ERAs were demonstrated to be an effective tool in fostering successful first-cycle reviews. By allowing for amendments to submissions initially deemed unfavorable, CVM substantially increased the number of successful submissions, as evidenced by a 75.4% increase in the number of single-cycle reviews during ADUFA II (Figure 13).

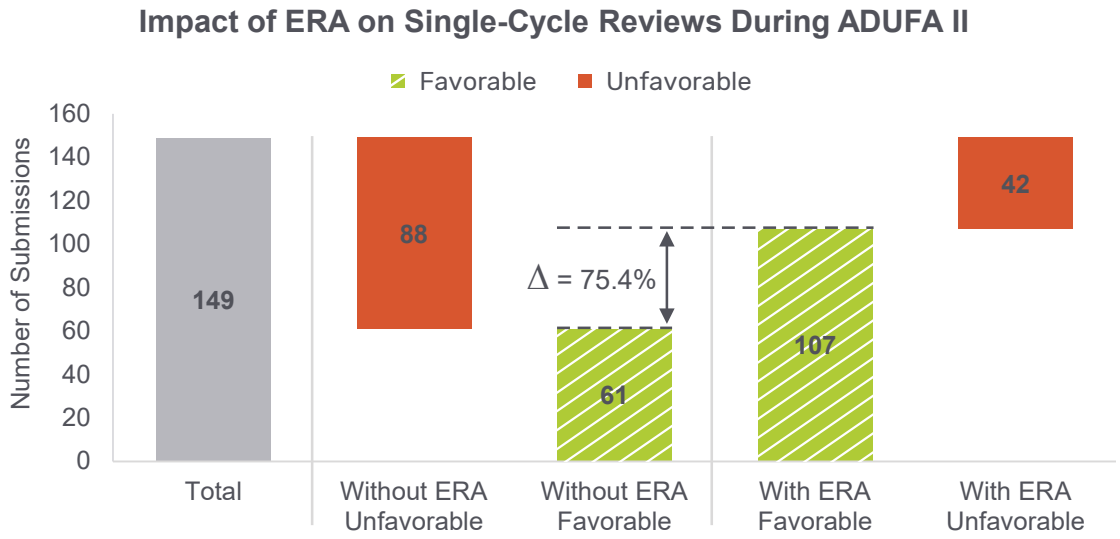



**Figure 13.** Impact of ERA on single-cycle reviews during ADUFA II (its only period of usage).

## SRTs Add Additional Flexibility to Streamline the Review Process

The introduction of SRT had a similar, albeit less pronounced, effect. Following the implementation of SRTs, 69% of second-cycle (or subsequent) protocol submissions benefited from a shortened review clock. The overall trend indicates that SRTs have been effective in reducing the total review time for resubmissions of technical sections; the median time it takes Industry to resubmit was reduced by 62% and the median CVM resubmission review time was reduced by 65.2%. Submissions that receive SRTs often have more easily addressed issues, which could also factor into the quicker turnaround time. Not only do SRTs reduce the review clock goal for CVM, but they also reduce the time required for secondary reviews. Due to the targeted nature of comments in SRT letters, updates made to SRT submissions are often more manageable, even in a shortened review clock. For the second cycle (or subsequent review cycles), CVM averaged 57 review hours for protocols and 186 hours for data submissions without an SRT. When submissions were reviewed under an SRT, CVM saw a 53% reduction in review hours for protocols and a 71% reduction for data submissions (Figure 14).

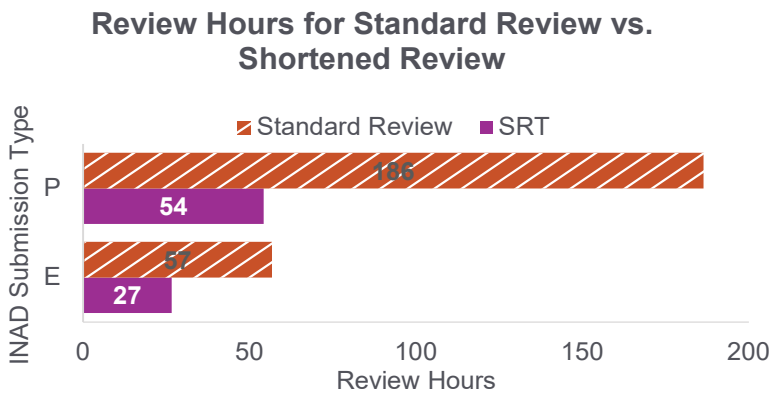



**Figure 14.** Submissions reviewed under a shortened review clock required up to 71% fewer hours to review, on average. This indicates SRT successfully shortens the review clock without straining the bandwidth of CVM's scientific review staff.

CVM has seen substantial successes from implementing broad enhancements to the ADUFA program, which have the potential to significantly improve the animal drug review process if expanded. However, many of the enhancements made throughout the years focus on specific, infrequent situations, limiting their impact due to the substantial investments required for implementation. This may include training, IT system upgrades, and communication improvements.

## *Challenges*

While there have been notable successes, several key challenges remain in the implementation and adoption of ADUFA program enhancements. Although none of the enhancements have resulted in unexpected negative consequences for the review process, most are underutilized. This is due to factors such as limited scope, misalignment of anticipated outcomes, and inconsistent implementation by CVM. These challenges have prevented the full realization of the benefits these innovations can provide.

### Narrow Scopes of Some Negotiated Enhancements Limit Their Reach and Impact

One of the primary criticisms of the ADUFA program enhancements is their narrow application. Many of the enhancements are designed to address specific circumstances or markets, meaning they do not have widespread applicability to all animal drug applications. These require investment in IT system modification, updates to GFI documents, and training for reviewers. Once these limited scope enhancements are implemented, they are often rarely used and do not make up for the investment it took to incorporate the additional pathway into the review process. For instance:

- **ADAA Combination Medicated Feeds Applications:** In 2019, CVM agreed to review and act on 90% of these submissions within 60 days. However, the stringent qualification criteria for this accelerated review have led to dissatisfaction among sponsors, as few applications qualify for the 60-day review clock. Within the sample of applications this assessment reviewed, only three were for ADAA combinations. Of these, one application was submitted following the introduction of the new 60-day ADAA combination application review process; however, it was unable to fully utilize the enhancement and was required to go through the normal phased review process capped off by a 60-day administrative NADA. This application was unable to fully realize the benefits of this enhancement due to the following reasons:
    - Excessive back-and-forth communication with CVM
    - Multiple review cycles for protocols and data studies
    - Multiple iterations of labeling submissions requested
    - High burden of proof for CMC technical sections
    - Statutory limitations on the types of feed-use combinations that qualify for the streamlined approval process

- **Expanded Conditional Approval:** During stakeholder interviews, Industry sponsors commended CVM for supporting the expansion of Conditional Approval beyond MUMS products. However, many sponsors contend that the limited scope hinders the introduction of new, innovative animal products into the market. Some sponsors also argue that while a five-year Conditional Approval period is generous, additional time to run effectiveness studies could alleviate some of the financial burden of running the required studies for full approval. Of the three Conditional Approval applications included in this assessment's application sample, only one had its Effectiveness technical section completed following the codification of XCA in ADUFA IV, the remainder were completed prior to the expansion of conditional approval. This application's Effectiveness technical section lasted for over 2,800 days, from the first Effectiveness meeting to the final P submission, including six meetings, four protocols, two H submissions, and one data submission. The data submission to prove reasonable expectation of effectiveness was submitted and had a single-cycle review, clearing the path for Conditional Approval. While there is only one example of XCA included in the sample, this application required

12 developmental submissions (i.e., Z[13] , E, and H submissions) prior to submitting the full data submission, resulting in an extended Effectiveness technical section. It is unclear whether this sponsor was originally pursuing conditional approval, or whether XCA became available partway through the review. Further analysis of the impact of XCA is required, as this assessment only contains one example, and therefore cannot form a meaningful conclusion as to the impact of this enhancement.

### CVM and Industry Differ on How to Best Utilize Enhancements for Maximum Impact

Another significant challenge is the lack of clear guidance on enhancements once they are implemented into the program, such as EI Submissions and the Two-Phased CMC Technical Section. Both enhancements have faced underutilization, largely due to confusion or lack of confidence among sponsors about how and when to use them. Specifically, the following challenges have manifested from this misalignment in understanding the purpose of these enhancements:

- **EI Submissions:** This enhancement was designed to allow sponsors to submit early-stage data for informal feedback. This could be done by including data within an A-0000 INAD submission or as an H submission preceding a formal PSC. While this enhancement was enacted to improve CVM's challenge of encouraging sponsors to improve transparency and be more upfront with communications (See **Communication and Collaboration**), many sponsors still reported reluctance with using this communication pathway, fearing that early submission of potentially incomplete data could be held against them later in the review process. CVM began tracking the usage of EI in 2018. Out of 53 Z submissions and one H submission since then, there were zero examples of EI submissions in the sample of applications reviewed. Outside of the 30 applications, data suggest a significant gap in understanding or trust in this process, with only 5.1% of Z submissions and 9.8% of H submissions including EI (Figure 15).

- **Two-Phased CMC Technical Section:** Introduced in 2014, this enhancement allowed sponsors to submit the CMC technical section in two phases. Within the data sample, CMC had the lowest rate of single-cycle reviews, at just 27.3%. While breaking up the CMC technical section into two phases could improve the rate of successful partial reviews, only a small percentage of sponsors attempted to follow this pathway, with many encountering rejections after submitting the first phase. There is a clear misalignment on the expectation of this enhancement, as only 4 of the 17 eligible applications split up the CMC technical section into two phases, with just 25% beginning with a favorable Phase 1 review outcome (Figure 16). There is also an absence of tracking functionality within CVM's systems for these phased submissions, making it difficult to assess the effectiveness of this enhancement and whether it is meeting its intended goals.

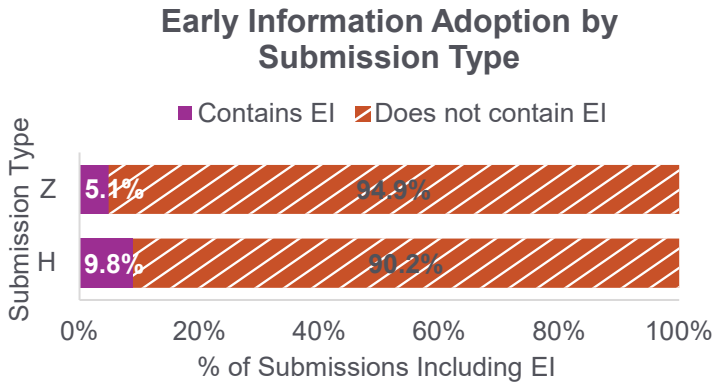



**Figure 15**. Adoption of early information since 2018, when CVM began tracking submissions with EI, for meetings (Z) and supporting data submissions (H).

13. Z submission: A submission to request either a presubmission conference or other ONADE meeting under an INAD.

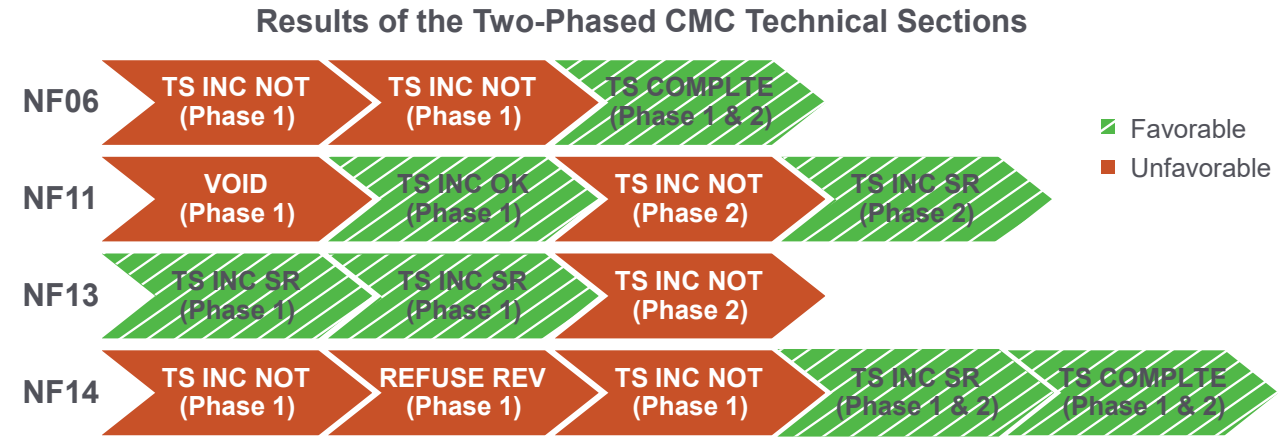



**Figure 16.** For the projects that attempted to use the CMC Two-Phased enhancement, only 25% began with a favorable Phase 1 review in the CMC technical section.

## Mid-Review Enhancements Offered by CVM Experience Inconsistent Usage Rates

Finally, one primary challenge for enhancements aimed at expediting the review clock is low offer rates from CVM to Industry to use these enhancements. This became more evident with the transition from ERA to SRT. While 63% of unfavorable submissions received an ERA, only 47% of these submissions were offered a SRT, a discrepancy that highlights inconsistent application of these expedited review paths. There is also inconsistency in when SRT is offered based on the type of submission (Figure 17). For protocols, for example, reviewers offered a SRT for 69% of all incomplete reviews. However, reviewers only offered shortened review to 28% of all incomplete data submissions.

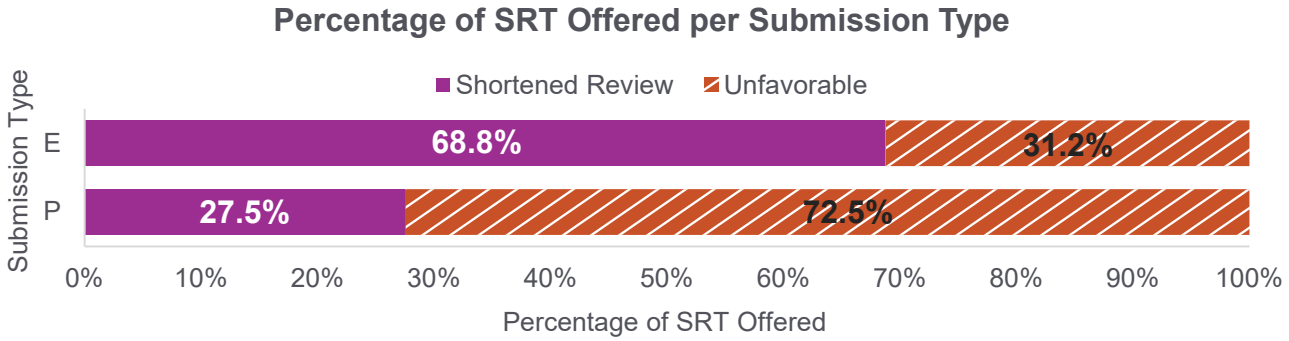



**Figure 17.** There is a 41% difference in the SRT offer rate for protocols (E Submissions) vs. data (P Submissions).

While CVM's and sponsors' views on ERA compared to SRT varied, there was consistent agreement that these tools are valuable for expediting the review process when used appropriately. Sponsors appreciate ERA and SRT for different reasons. ERA provided a final opportunity to address minor issues at the end of the review cycle, allowing for a favorable first-cycle decision, although it required a quick turnaround from Industry. SRT provides targeted feedback for Industry to address, while also extending the turnaround time for Industry, in exchange for a longer review than ERA and an additional, yet expedited, review cycle. Although SRT was intended to replace ERA, there appears to be support for retaining both options, depending on the specific circumstances.

# Workforce Capacity and Capabilities

## *Overview*

In order to continue achieving the goals established in the ADUFA program, it is essential that CVM's workforce capacity and capabilities keep pace with the scientific innovation of the animal drug industry. Collaboration throughout CVM stands out as one of the organization's greatest strengths; however, the bandwidth available to CVM staff is stretched thin by a variety of competing priorities.

## *Successes*

The flexibility and dedication of CVM's staff to their mission allows the Center to maximize the effectiveness of their resources. A culture of collaboration and an experienced and specialized review staff are among the strengths of CVM's workforce. Some of the key success themes noted during interviews related to CVM's workforce capacity and capabilities include:

### CVM Fosters a Highly Collaborative Environment

In addition to being a strong collaborator with Industry, CVM interviewees highlighted internal collaboration as a strength of the Center. They also identified reviewer ability to manage review workload burden by sharing submission reviews as a strong example of this collaboration. Their willingness to share the review workload among teams, even if the area is outside a reviewer's normal review area, is an important factor that allows reviewers to meet their ADUFA review times on over 97% of sample submissions reviewed during this assessment.

### Low Staff Turnover Creates an Experienced Workforce

Despite challenges, turnover among reviews teams, such as the Food and Companion Animal groups, is low. Low turnover helps CVM maintain a high quality, experienced review staff that are leading experts in the field of veterinary medicine. During interviews, Industry sponsors reiterated the value of working with experienced reviewers. In particular, Industry noted that the review process was more successful when they were able to work with reviewers with whom they had established relationships over time. Established relationships between reviewers and Industry fosters trust, resulting in increased informal communications that could expedite the approval process.

### Specialized Review Teams Provide Industry Tailored Support

Industry reports that the ADUFA program has helped CVM hire and assemble specialized review teams that are capable of better serving Industry needs. As the complexity of applications continues to increase with the proliferation of novel molecules and scientific approaches, it is essential to have specialized review staff that can keep pace with scientific innovation in the field. CVM's expansion of specialized review teams, such as the Aquaculture team, provides Industry with better support for specialized applications in these areas.

## *Challenges*

While the available workforce at CVM is often sufficient for the agency to prioritize and complete its ADUFA review work, the current burden on CVM staff creates a static review process due to the lack of time available for CVM staff to spend improving the review process. Key challenges in the capacity and capabilities of the workforce are detailed below.

### CVM Staff Believe They Lack the Capacity for Tasks Beyond Scientific Review Work

CVM staff state they often do not have the time to complete tasks such as composing new or updating existing GFIs, participating in internal working groups aimed at improving CVM systems, hosting training sessions for Industry, or conducting independent research or training to bring themselves up to speed on the latest scientific advances. CVM staff reported in interviews that they prefer not to participate in internal working groups to improve systems at CVM because they believe that participation would not be worth the additional strain that it would place on their workload.

According to data from ATR, the amount of time CVM staff spends working on new GFIs has increased with each successive ADUFA reauthorization. During ADUFA IV, 1.4% of time logged by CVM staff related to GFI development for pioneer animal drugs. This represents a 56% increase in the share of time logged related to GFIs in ADUFA III (0.9%) and a 100% increase relative to ADUFA I (Figure 18).

While these data demonstrate that reviewers are allocating more time working on GFIs, reviewers are still spending less than 1.5% of their time in this area. The perception from reviewers gathered in interviews was that they still do not have enough time available to work on GFIs or complete other non-review work. This disconnect between an increase in percentage of hours spent and staff perception may be due to the complexity of necessary GFIs increasing along with scientific advances. Alternatively, this may be reflective of CVM staff feeling that there is an existing deficit of GFI documents that staff are unable to adequately address with their current resources.

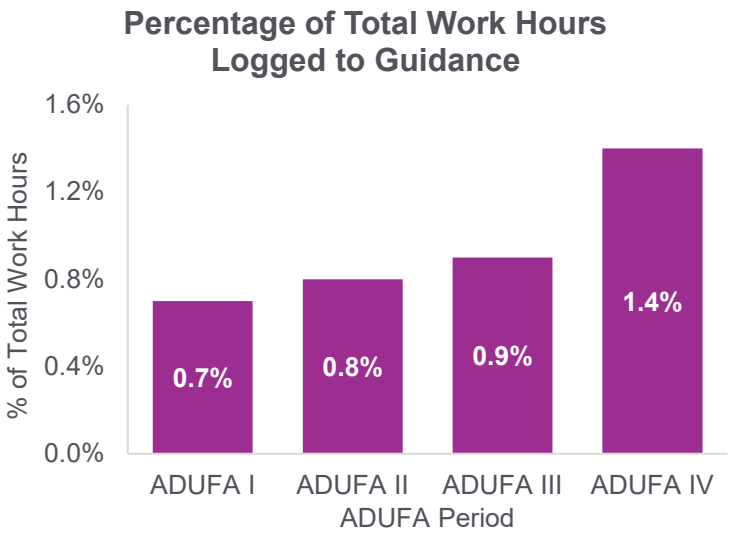



**Figure 18.** Percentage of CVM time spent developing GFIs across ADUFA periods.

When looking within ADUFA IV, the percentage of hours logged towards GFI development slightly declined. The first full year of ADUFA IV[14] (2019) represents the peak annual percentage of hours spent on developing GFIs since the inception of ADUFA: 1.6% of pioneer drug activity time. However, by 2023 that share of annual hours decreased by 31% (Figure 19).

The 2019 peak corresponds with an ADUFA IV enhancement for CVM to issue GFIs addressing investigation designs. This decrease in percentage of time could be indicative of a de-prioritization

14. Calendar year 2018 is split between multiple ADUFA reauthorization periods (ADUFA III and ADUFA IV) and is not included in this analysis.

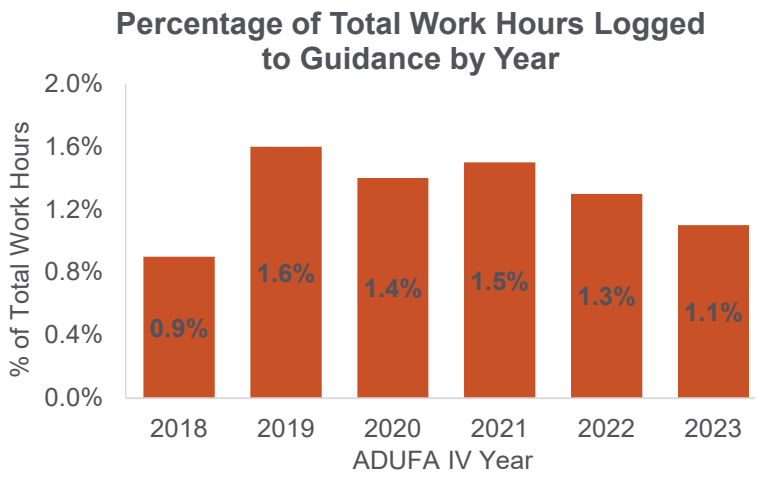



**Figure 19.** Percentage of CVM time spent developing GFIs annually within ADUFA IV.

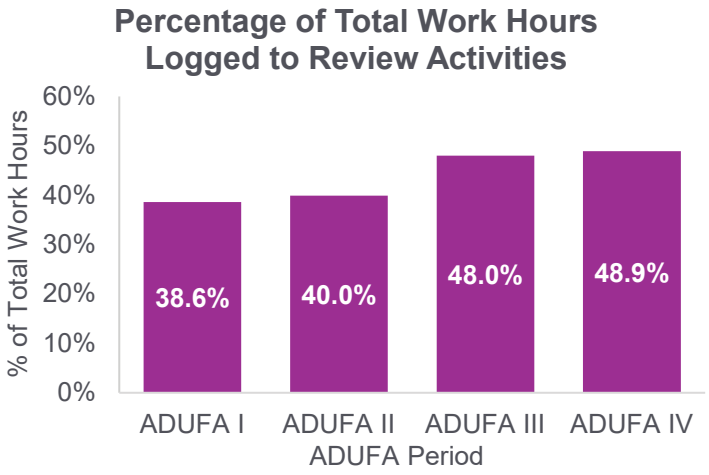



**Figure 20.** Percentage of CVM time spent on review activities across ADUFA periods.

of GFI development over time during ADUFA IV. However, this could also be driven by an increase in time demanded by the submission review process that is limiting the available resources for GFI work, as suggested by CVM staff during interviews. Further exploration would be needed to better understand the root causes of variation in time reported towards the development of GFIs.

## Reviewer Workload Steadily Rising Over Time

CVM's review staff is logging a higher percentage of their capacity to "Direct Review" and "Review Support" time codes in ATR. In ADUFA IV, 49% of hours logged in ATR by staff working on pioneer drugs was attributed to review activities. The percentage of time spent working on direct reviews or review support rose by 21% between ADUFA II (40%) and ADUFA III (48%) (Figure 20). CVM streamlined the ATR code structure in 2011 (during ADUFA II) to improve reviewers' ability to accurately assign their time. This consolidation of ATR codes may have contributed to the increased percentage of time spent on review work after ADUFA II.

Looking at direct review and review support percentages from a yearly perspective, reviewers have logged more than 50% of their time to these activities in 3 out of the 20 years since the inception of the ADUFA program: 2015 (50.8%), 2020 (50.4%) and 2023 (50.5%). CVM does not currently have a target percentage of staff hours spent on review activities. Development of a review activity percentage goal and the adoption of a formal metric to measure against it, such as percentage of review activity, could give CVM a better understanding of changes in the workload of their reviewers.

The average number of hours it took reviewers to review a protocol submission was relatively flat across ADUFA periods, ranging from a minimum of 47 hours in ADUFA I to a maximum of 65 hours in ADUFA II. The time spent reviewing data submissions, on the other hand, has steadily risen across ADUFA periods, nearly doubling from an average of 125 hours in ADUFA I to 242 hours in ADUFA IV (Figure 21). This suggests that the review of data submissions is a particularly important factor in the increasing reviewer workload.[15]

15.Submissions with ERA and SRT are included in this analysis. ERA submissions are only present during ADUFA II and likely contribute to the increased number of review hours for protocols seen in ADUFA II. SRT submissions during ADUFA III and ADUFA IV would be expected to decrease the number of hours per submission. However, that effect is not apparent in the assessment sample. This may be due to a small sample of SRT submissions within the dataset.

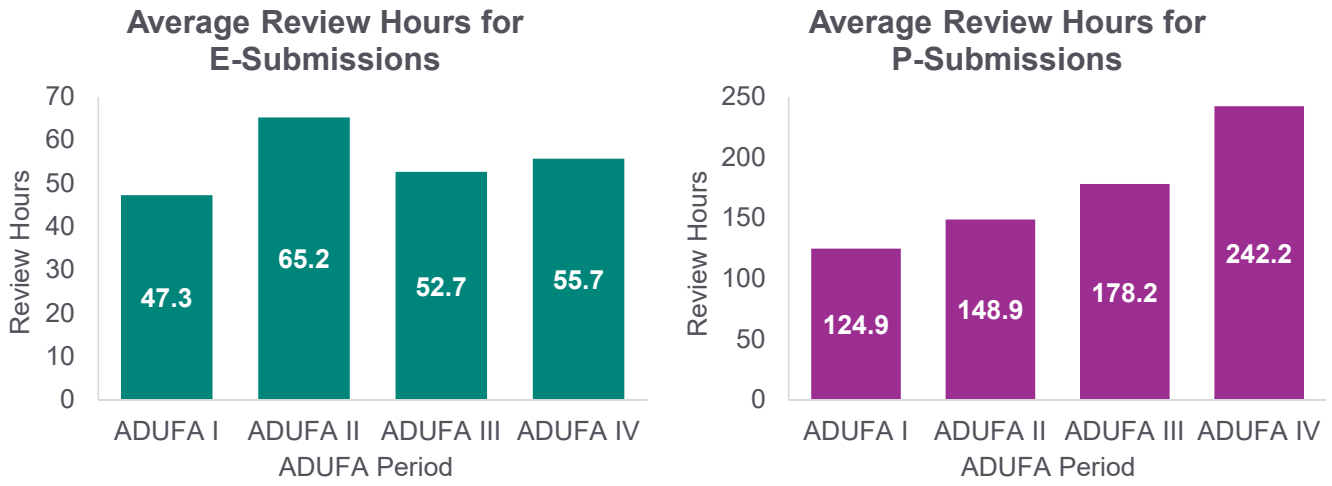



**Figure 21.** Average number of hours spent reviewing a protocol submission (left, green columns) or data submission (right, purple columns) across ADUFA periods, based on all submissions with ATR data since 2003.

## Tight Review Timelines Increase Burden on Staff

A major contributing factor weighing on the bandwidth of review staff are the tight review timelines in place, especially pertaining to consulting reviews and amendments. Within the 50-day review clock for protocol submissions or 180-day review clock for data submissions, consulting reviewers have 56% (28 days) and 63% (114 days) of the review clock, respectively, to complete their consulting reviews. Within the assessment application sample, the average consulting review for a protocol took 54% of review clock time (27 days) and 53% (96 days) for a data submission. These data are calculated using the review timelines templates for protocol and data submissions established by CVM during ADUFA III. While actual consulting timelines may vary, these values are suggestions provided by the template for primary reviewers. Consulting reviewers of protocols in particular require almost all the allotted time to complete their reviews. Any single submission may also require multiple consulting reviews, with each additional consult involving more reviewers and increasing the total FTE hours required to complete a review. Furthermore, enhancements such as SRT or ERA shrink these review timelines even further and place additional strain on CVM's resources in order to meet established review timeline goals.

## CVM Staff Report Disparities in Workload Distribution Among Review Divisions

Interview data uncovered a perception among CVM staff that the work distribution between divisions is inequitable. This sentiment came particularly in regard to the Division of Companion Animal Drugs experiencing the bulk of the application submissions. From FY09 - FY22, CVM approved 138 original NADAs; 79 approvals (57%) were for Companion Animal drugs compared to 59 approvals (43%) for Food Animal drugs (a ratio of 1.3 Non-Food Animal drug application approvals for every 1 Food Animal drug approval).

CVM staff cited one reason for this inequitable distribution of work was a decline in the number of Food Animal drug applications submitted by Industry, especially relative to Non-Food applications. During the FY09 - FY22 window, there are no strong trends related to the number of Food and Non-Food applications by year (Figure 22).

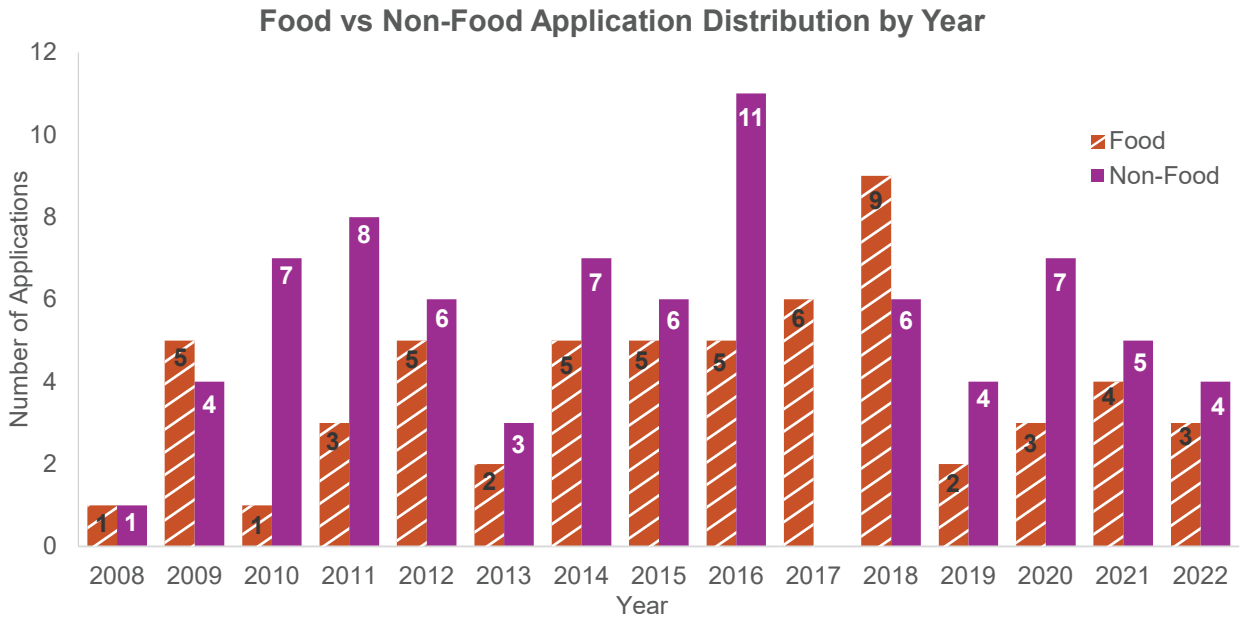



**Figure 22.** Number of approved Food and Non-Food original NADAs per year from FY09 - FY22.

This perception may stem from the years 2017 and 2018 representing the peak for number of Food Animal drug approvals. The ratio of Non-Food to Food application approvals by year has been relatively stable throughout the FY09 - FY22 window. In 9 of the last 11 years, the ratio of Non-Food to Food approvals has ranged between 1.2 to 2.3 (Figure 23).

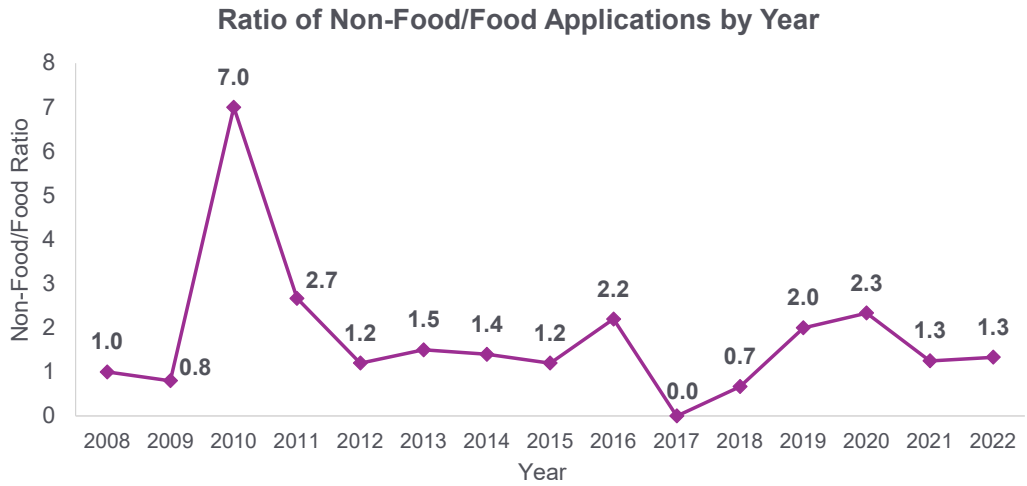



**Figure 23.** Ratio of approved Non-Food to Food original NADAs per year from FY2009-FY2022.

## CVM Senior Management Reported Difficultly Hiring and Onboarding New Staff

The hiring process at CVM represents a significant resource barrier. CVM has difficulty attracting top talent to their scientific review staff. Hiring challenges may be the result of a lengthy hiring process that can take as long as year and are limited because CVM often cannot compete on salary with private industry for qualified candidates. While other Centers, such as the Center for Drug Evaluation and Research (CDER), are already leveraging Title 21 to offer competitive salaries, CVM has only just committed to pilot the use of Title 21 as part of their new Senior Scientist Program in December 2024.

The ramp-up time necessary to train quality reviewers also presents a consistent challenge for CVM. In part due to the existing hiring limitations, CVM is often placed in a position in which they are only able to hire new or inexperienced reviewers. CVM leadership estimates that it often takes up to three years for new staff to become fully independent primary reviewers. During this multi-year period, training new review staff places an additional burden on the existing reviewers and contributes to the perceived lack of available time for reviewers to work on GFI documents or any other initiative to improve the review process. Staffing changes in tandem with a perceived rise in the complexity of submissions compound to increase the burden of reviews that staff still must complete within the specified goals of ADUFA.

### Broad Time Reporting Categories Prohibit More Detailed Analysis

Assessing the performance and process of individual reviews within CVM is difficult because reviewers do not segment out how time is spent within the review clock; instead, all time spent on a given review is captured within one broad bucket. The inability to break down time spent in these broad categories into activity time (e.g., primary review, consulting review, Team Leader approval) prevents CVM from capturing valuable information into how the review process could be improved. A deeper look into the specific review activities occurring within each submission review would provide CVM with insight on how to optimize the review process to improve the efficiency of individual reviews and better distribute CVM's review workload. The inability to capture more detailed time data prevents CVM from identifying existing gaps or bottlenecks that lead to inefficiencies in review. It also hinders CVM's ability to quantify the administrative burden associated with its current review formatting processes, an existing pain point mentioned in interviews by reviewers and potentially an area that is ripe for improvement via modernization. When designing time reporting codes, CVM must weigh the level of detail needed against the added reporting time to prevent additional administrative burden to reviewers.

### Sponsors Reported a Belief that Idle Time is Wasted During Submission Reviews

Some industry sponsors share a perception that submissions, while often returned by or on the final day of the ADUFA review clock, lay idle at points during the review window. This may be attributed to the upward trend in workload burden felt by review staff. Process documentation and ATR data were analyzed to identify areas of idle review time to determine if there is any validity to these claims:

- **Idle Time Before Beginning Review:** Industry reported in interviews the perception that reviewers do not begin reviewing submissions promptly within the review window. CVM's time reporting data show that for the 251 protocol submissions included in the assessment sample, reviews began an average 10 days into the review clock, accounting for 18% of the total review clock for protocol submissions. Reviews for the 306 data submissions started an average of 40 days into the review clock, accounting for 20% of the total review clock time (Figure 24). For this analysis,

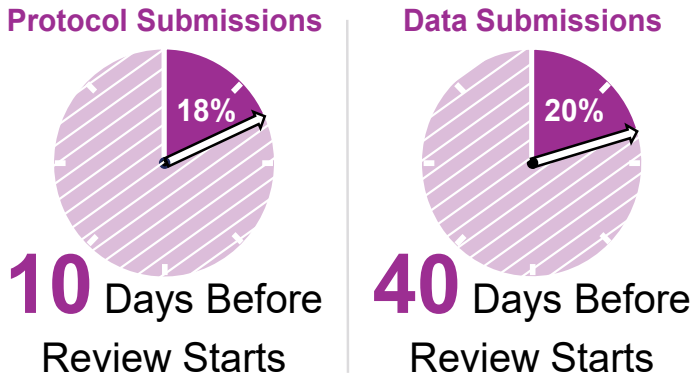



**Figure 24.** Infographic showing the number of days between receipt of a protocol submission (left) or data submission (right) and the first day of the submission review (shown as a percentage of the submissions total review window).

review start times are based on the first day in which a reviewer charged time to a submission. Additionally, the first step for a review is an initial triage of a submission to determine whether it should receive a refuse-to-review or refuse-to-file (See **Process and Workflow Management**). Therefore, the actual review of submission content (e.g., study data or protocol) likely starts even later. Reviews getting a late start is having only a minimal impact on reviewer ability to meet ADUFA target goals, as only 13% of all protocol and data submissions from the entire sample were returned overdue.

» **Team Leader Review Bottleneck:** CVM staff report that Team Leaders can represent a bottleneck in the review process, as there may be multiple submissions completed by reviewers that are building up in their review queue waiting for approval. This bottleneck could explain some of the non-active review time that exists towards the end of the review window. To get a clearer picture of the impact that this reported bottleneck is having, CVM requires more granular ATR data that could segment the review clock into different time reporting components. With existing ATR data, CVM could look at when idle days are occurring within the review window to help identify bottlenecks in the review process. Idle days occurring between the end of the consulting review period and before finalizing the review may be indicative of an internal review and approval bottleneck.

# Performance Metrics and Reporting

## *Overview*

CVM collects a wealth of information regarding its submission process and staff workload. However, outside of the individual submission review goals established by the ADUFA program, a limited amount of data are being leveraged to assess the holistic performance of the new animal drug review process. In fact, the few metrics that are available may not accurately reflect efficiencies within the holistic review process. There is a need to develop updated performance metrics to better understand CVM's current performance and determine key goals for improvement. Industry stakeholders have requested aggregated data metrics be made publicly available by CVM, such as average TTC for technical sections, number of application approvals by year and application type, and the distribution of TII and TIA at the technical section level. Reporting out metrics such as these could help improve transparency and trust between CVM and Industry, but in the current environment, many metrics are difficult to track or are unattainable.

## *Successes*

CVM provided the assessment team with submission data dating back to the 1980s as part of this analysis, as well as more than 20 years of ATR data. Without CVM's extensive repository of existing submissions and ATR data, a retrospective analysis such as this one would not have been possible. CVM has improved data accessibility through FDA-TRACK and publishes annual performance reports showcasing their consistency in achieving review clock goals (Figure 25).

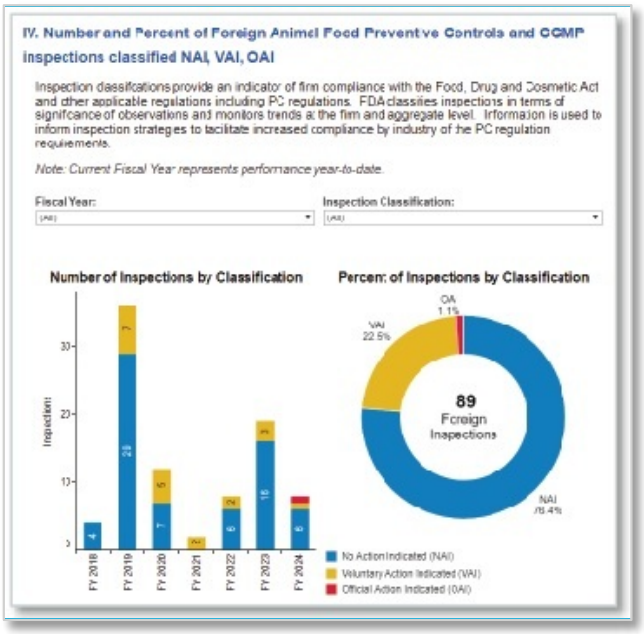



**Figure 25.** Example metrics currently published by CVM on FDA-TRACK.

## CVM Prioritizes Data Accessibility

To increase the accessibility of all its data, CVM undertook a large effort to digitize files that were originally submitted via paper and not captured within their current data system infrastructure. Additionally, CVM's project management team also began creating project plans for active projects starting in 2005, when the project management team was established. Using their wide repository of data, CVM updates their FDA-TRACK dashboard quarterly, reporting on performance measures aligned to six key initiatives that highlight its contributions towards protecting human and animal health.

## CVM Consistently Returns Industry Submissions On-Time

CVM consistently meets its established ADUFA review clock goals. From ADUFA II onwards, in the assessment sample, only 2.7% of all submissions were returned to sponsors overdue[16] (Figure 26). Providing sponsors with reliable and timely responses has improved the predictability of the drug approval process, building trust between CVM and sponsors. Reliable submission timelines can be used to empower accurate projections for the TTC for technical sections in the phased review process.

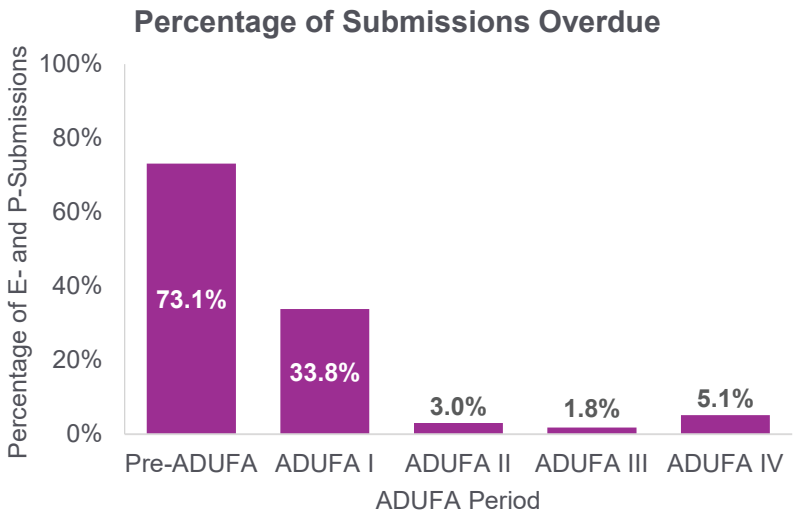



**Figure 26.** Percentage of submissions, within the assessment sample, returned to Industry after their due date across ADUFA periods.

## Technical Section TTC Has Improved Across ADUFA Reauthorization Periods

In addition to establishing the review timeline goals for individual submissions, the inception of the ADUFA program has decreased the TTC for all technical sections. In the assessment sample, from ADUFA I to ADUFA III the average technical section TTC decreased 33% from an average of 1,676 days to 1,125 days. Furthermore, with the exception of the CMC technical section, the TTC for each individual technical section within the assessment sample has decreased by over 50% since pre-ADUFA (Table 4).

16. Submission overdue status was calculated using the received date and submission due date in STARS. This allowed the analysis to account for changes in the review timeframes within and across ADUFA periods.

**Table 4.** Average TTC, in days, for all technical sections within the 30 applications across all ADUFA periods.

| ADUFA Period | Average TTC – All Technical Sections (Days) | Average CMC TTC (Days) | Average EFF TTC (Days) | Average ENV TTC (Days) | Average HFS TTC (Days) | Average TAS TTC (Days) |
|---|---|---|---|---|---|---|
| Pre-ADUFA | 3016 | 448 | 2756 | 2222 | 4203 | 1890 |
| ADUFA I | 1676 | 2047 | 2187 | 894 | 1025 | 1759 |
| ADUFA II | 1128 | 826 | 1313 | 1501 | 668 | 1135 |
| ADUFA III | 1125 | 1310 | 1381 | 911 | 1491 | 932 |

The adoption of the ERA (ADUFA II) and SRT (ADUFA III to present) enhancements were also important contributing factors to the overall reductions in time to technical section completion. These enhancements established pathways for Industry to receive expedited review timelines if unsuccessful submissions met certain criteria. The decrease in TTC from ADUFA I to ADUFA III demonstrates that these enhancements, in addition to adoption of electronic submission, are achieving their intended goal. See the **Utilization of Enhancements** section for a more detailed look at the impact of enhancements.

## *Challenges*

CVM and the animal drug industry both recognize there is a need for more data-driven decision-making throughout the new animal drug review process. CVM should expand and update data collection procedures and tools that allow for the tracking, development, and reporting of critical performance metrics that can then be used to empower objective decision-making and continuous improvement of the review process. Challenges persist around performance metrics and reporting for CVM, including those detailed below.

### Lack of Established Standard Criteria to Evaluate Application Complexity

Application complexity is a critical factor that determines how long it will take for an NADA to get approved or a technical section to be completed. Currently, CVM does not have any metrics or mechanisms in place to capture the complexity of a new animal drug application or its associated submissions. The new chemical entity (NCE) status of an application could be used as a proxy for application complexity; however, without a mechanism in place to determine the complexity of submissions, CVM is unable to understand the impact that submission complexity plays on the animal drug review process. Complex applications could skew mission-critical performance metrics, including resource allocation, submission success rate and TTC.

**Contributing Factor: Application Complexity**

Application complexity is likely an important factor in forecasting whether a submission will receive a favorable outcome after a single cycle. Using the proxy of new chemical entity status, **only 60% of NCE submissions received a single cycle review** compared to 72% of non-NCE submissions. This 12-percentage point difference is one of the contributing factors to the longer time to completion for NCE applications.

### Review Cycles are Not Tracked Despite Industry's Goal for Single-Cycle Reviews

Both Industry and CVM consider a single-cycle review the goal for every submission. Single-cycle reviews represent the minimum possible time required for a submission to receive a favorable

review outcome. Across the five major technical sections within the assessment application sample, 66% of all submissions received a favorable review outcome following a single review. Single-cycle reviews were much less common in the CMC technical section (27%) than in the other four technical sections (Figure 27). The lack of single-cycle reviews contributes to Industry stakeholders reporting that receiving a technical section complete letter for CMC is most often the rate limiting step to receiving an approval of an NADA. Furthermore, CVM does not currently track review cycles or submission relationships to facilitate manual tracking of review cycles. Without review cycle data, CVM is unable to identify trends in single-cycle reviews or report out on review cycle analyses.

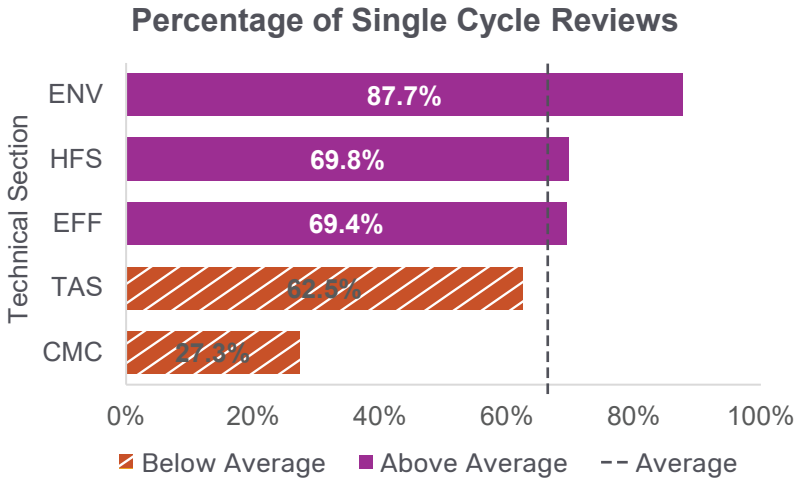



**Figure 27.** Percentage of submissions that received a favorable review outcome after one review cycle by technical section; within the assessment sample.

### CVM Systems are Not Equipped to Link Submissions for Detailed Analysis

Aggregate data analysis and comparison of the drug review process between different applications is difficult because each individual drug review follows its own unique path. These difficulties are exacerbated by challenges within CVM's existing data systems. CVM's systems are not set up to link submissions within an INAD or technical section to one another; each submission essentially exists in isolation. In the current data environment, making connections between submissions requires a review of individual submission documentation, a large manual effort that CVM does not have the bandwidth to implement. The current lack of linked submissions prevents CVM from being able to accurately report out on desired metrics, such as single-cycle reviews, review cycles, and the share of review time attributed to CVM vs. Industry.

### Submission Information is Collected in Multiple Data Systems that Need Reconciliation

Currently, submission information is tracked in disparate data sources, primarily STARS, DDP, and isolated Microsoft Project Plans maintained by the project management team. This assessment uncovered a disconnect between these data sources that has the potential to cause internal confusion. Oftentimes, standalone project plans did not match submission data stored within CVM's official submission tracking system (i.e., STARS), resulting in reduced confidence in these data. Data contained within these two data sources needs to be reconciled to confirm its accuracy before it can be used together, which is another high effort process.

### Gathering Insights from Review Comments Requires a Great Deal of Manual Intervention

Most of CVM does not track the reasons that submissions are unsuccessful or categorize the comments that are provided in their reviews. The inconsistency of comments provided between reviews was a common pain point mentioned by Industry stakeholders in interviews. The Division of Manufacturing Technologies (DMT) created a comment database prototype to improve consistency between reviews, help train new reviewers, and identify potential recurring issues that they can discuss with drug sponsors. However, in large part due to technical insufficiency, management of DMT's existing comment database is difficult and time-consuming due to the manual nature of the

work. Review staff in other departments likely do not have the bandwidth available to establish a similar database for their comments or expand the current DMT prototype. The inability to track comments contributes to misunderstandings between Industry and reviewers and ongoing frustration from Industry regarding the consistency of comments they receive from CVM. The lack of comment tracking also hinders continuous improvements of the animal drug review process because CVM and Industry are unable to analyze and learn from previous review comments.

### Current ADUFA Performance Metrics Do Not Accurately Represent the Holistic Review Process

CVM's performance metrics, established during ADUFA negotiations, focus on timeliness in reviewing submissions. While CVM consistently meets its goal of responding to 90% of submissions on time, this metric does not fully capture the performance of the phased review process throughout a drug's development lifecycle. Both CVM and Industry have discussed introducing new metrics, such as technical section TTC, TIA, and TII. These could better reflect the time required to complete technical sections but present challenges in reporting.

One issue with TTC is that it cannot distinguish between delays caused by CVM compared to those caused by Industry. TTC consists of time CVM spends reviewing submissions (i.e., TIA) and time spent by Industry preparing submissions and revising materials following unsuccessful submissions (i.e., TII). In the assessment sample, Industry took an average of 195 days to resubmit a protocol after receiving a nonconcurrence letter and 288 days to resubmit a data submission.[17] A TTC metric alone is unable to differentiate the time it takes CVM to review a submission from Industry revision time. A solution would be to track TIA and TII separately (Figure 28); however, CVM currently lacks reliable systems to link submissions, making this difficult. Tracking TII and TIA requires establishing relationships between submissions to monitor review cycles, which CVM's systems currently do not have the capability to do (See **Appendix VI: TIA vs. TII Case Studies** for sample case studies on calculating TII and TIA).

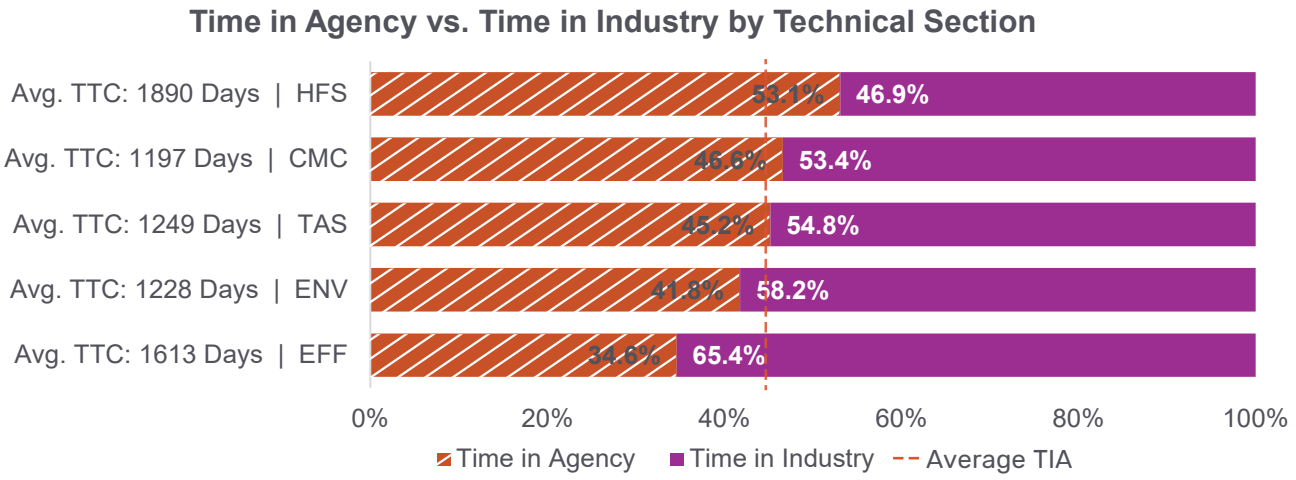



**Figure 28.** Average percentage of time attributed to CVM (orange) and Industry (purple) to complete each technical section within the assessment sample.

17.These calculations exclude submissions that were reviewed under an SRT.

# Root Cause Analysis

Analysis of the system records, current process documentation, and stakeholder interviews revealed 126 distinct challenges. These were analyzed for root causes and attributed one or more RCA categories (Table 5). Patterns were analyzed to understand recurring themes and found that the following four root causes resulted in 45% of the challenges experienced by CVM and Industry:

1. Outdated or unreliable systems (13%)
2. Data quality and governance challenges (13%)
3. Insufficient IT capabilities (12%)
4. Lack of standardization (12%)

Addressing these challenges will allow for sustainable implementation of improvements that will enhance the operations and CVM's ability to protect and promote human and animal health through the evaluation of the new animal drug applications for safety and effectiveness.

**Table 5.** List of 15 root causes that manifest in 126 distinct challenges in the animal drug review process.

| Root Cause | Definitions | % of Challenges |
|---|---|---|
| **Outdated or Unreliable Systems** | Legacy systems or technologies that are slow, incompatible with modern solutions, or prone to errors and bugs and challenging for users to navigate without extensive training | 13% |
| **Data Quality and Governance Challenges** | Inaccurate, incomplete, or inconsistent data, data structures stemming from inconsistent governance standards, stewardship, or unclear ownership | 13% |
| **Insufficient IT Capabilities** | Limited capabilities in IT systems, including automation, tools, and scalable solutions, resulting in inefficiencies in managing repetitive tasks, facilitating collaboration, and supporting effective decision making | 12% |
| **Lack of Standardization** | Processes and actions that are inconsistently executed across teams, locations, or systems, leading to inefficiencies and variable outcomes | 12% |

| Root Cause | Definitions | % of Challenges |
|---|---|---|
| **Poor Communication Practices** | Poor information flow, inconsistent messaging, and inadequate engagement and transparency leading to misunderstandings or gap in information sharing | 10% |
| **Unclear Expectations** | Sponsors are not informed about processes, timelines, or other key elements | 10% |
| **Misaligned Objectives** | A lack of alignment between the standards, priorities, or goals of two or more parties, resulting in differing expectations, interests, or approaches | 9% |
| **Siloed Systems** | Disconnected tools or platforms that prevent seamless data sharing and collaboration across teams or functions | 8% |
| **Suboptimal Resource Allocation** | Inefficient distribution or lack of personnel, tools, or funding needed to execute processes effectively | 8% |
| **Poor Workflow Design** | Processes that are overly complex or poorly structured, leading to recurring bottlenecks, duplicate steps, and delays at specific stages | 6% |
| **Lack of Trust and Transparency** | A breakdown in confidence caused by past experiences leading to skepticism, apprehension, and reluctance | 5% |
| **Inadequate Training and Lack of Clear Resources** | Employees or sponsors do not receive sufficient instruction, guidance, or are unable to easily access necessary materials to perform tasks effectively | 5% |
| **Undefined or Misaligned Metrics** | Key performance indicators (KPIs) or other timeline targets are missing or do not accurately measure process effectiveness | 5% |
| **Processes Not Optimized for Scale or Efficiency** | Workflows rely heavily on manual steps and are not designed to handle increased volume or complexity, including limitations with reviewer tools (e.g., tools such as SRT) | 4% |
| **Regulatory Constraints** | Agency regulations impose inefficiencies or limitations, such as financial barriers to entry | 2% |

# Recommendations

Based on the findings provided above, the following ten recommendations were developed:

1. Integrate the Project Management Team into the Review Process (1.1 – 1.2)
2. Expand Internal Training and Development Opportunities (2.1 – 2.2)
3. Improve Communication and Guidance between CVM and Sponsors (3.1 – 3.5)
4. Set New Compliance Standards for Submission Organization and Quality (4.1 – 4.3)
5. Capture and Report Reasons for Submission Review Outcomes (5.1)
6. Implement Continuous Workload Analysis and Task Reallocation (6.1 – 6.2)
7. Enhance IT Systems for Submission Workflows and Tracking (7.1 – 7.6)
8. Standardize and Streamline Review Process Workflows (8.1)
9. Track and Report Key Metrics Relevant to Review Process Success
10. Review and Improve Upon Previous Program Enhancements

For the first eight recommendations, an overview of specific activities, along with benefits, risks, and metrics to measure progress are provided. Each recommendation also includes a list of root causes that is addressed through the implementation of each of the activities within this section; each recommendation is designed to address root causes rather than symptoms, sometimes addressing multiple root causes. For the last two recommendations, a table with an analysis of current state and recommended next steps is provided.

To facilitate the prioritization of the recommendation activities, each activity was scored on level of effort for implementation from 1 (low) to 5 (high) and on impact 1 (low) to 5 (high). The prioritization scores for each activity were then plotted on to a two-by-two matrix for ease of visualization (Figure 29). The proposed level of effort for these recommendations does not currently account for potential resource and budget constraints that may arise due to any incoming legislative changes. We acknowledge that changes in the CVM's operating environment will affect the financial and staffing resources necessary for implementation. These recommendations are based on current conditions and assumptions, which should be adjusted to reflect any significant organizational or fiscal changes.

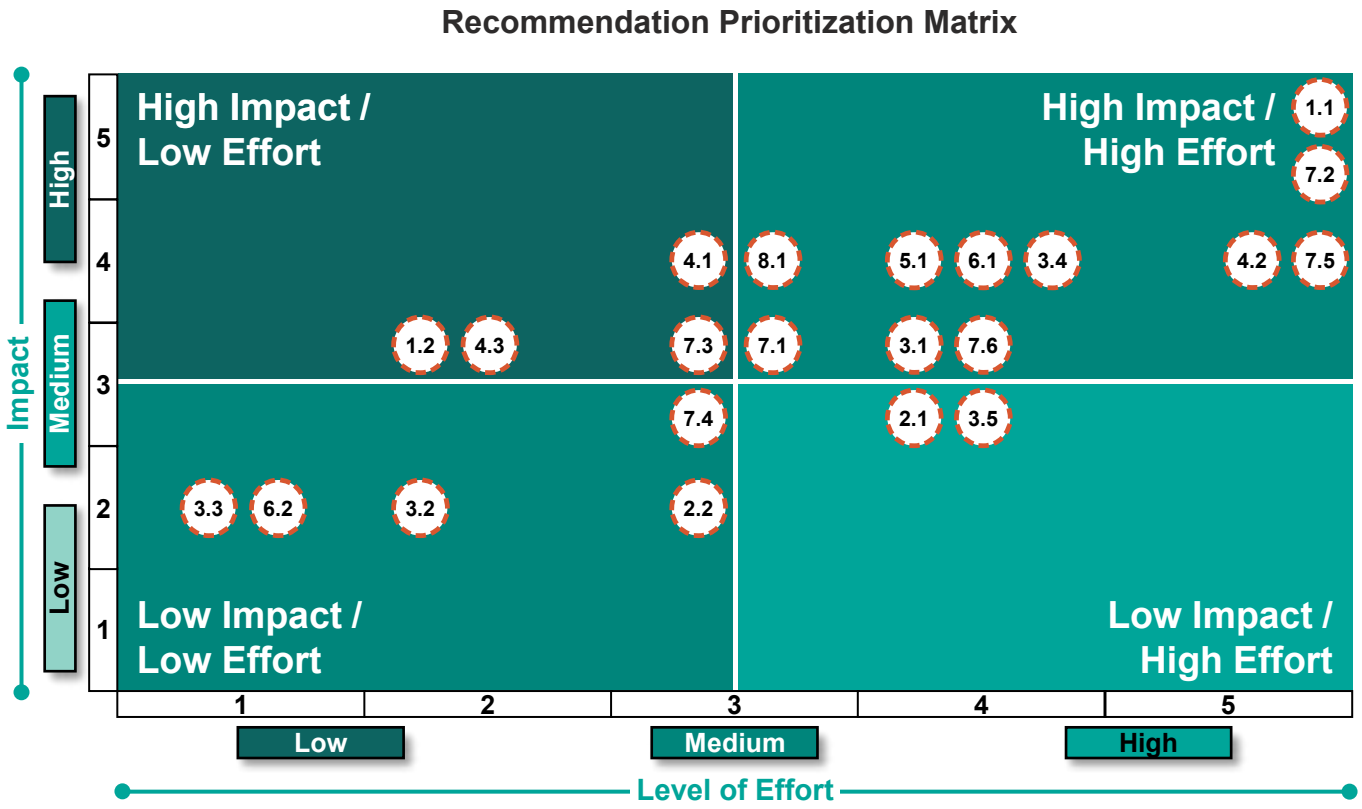



**Figure 29**. Prioritization matrix charting the impact against the level of effort for each activity, denoted by its unique ID, within the recommendations.

# 1.0 Integrate the Project Management Team into the Review Process

The Project Management Team (PMT) facilitates a more organized and responsive submission process by acting as the primary sponsor touchpoint during a project's lifecycle. Industry consistently cites the PMT as one of the most valued elements of the ADUFA program. CVM must continue to invest in the PMT to strengthen its role as the cornerstone of the new animal drug review process.

## *Current State Analysis*

In the current structure of the ADUFA program, PMs act as key intermediaries between reviewers and Industry, and they have consistently been cited by Industry as one of the program's strongest assets. PMs play an essential role in facilitating communication during PSCs, acting as sponsor liaisons throughout the development lifecycle of the drug, and coordinating the project team during the endgame process. During PSCs, PMs coordinate participation with the project team,[18] enabling sponsors to receive thorough and early input on their drug development plans, which is highly valued by sponsors. Throughout the project lifecycle, PMs regularly collect quarterly forecasts from Industry sponsors, allowing CVM to proactively allocate resources and sponsors to better understand the next steps in the phased review process.

While PMs are crucial to the early and final stages of the process, their current involvement during the actual review phase is limited. Since they primarily serve as intermediaries between reviewers and Industry, there is an inherent risk of miscommunication or misinterpretation of key information. PMs themselves have expressed a strong desire to be more integrated into the review process, where they can directly engage with the project team, provide timely insights, and help mitigate the risk of communication breakdowns. By fully integrating PMs into the review process, team leaders would gain capacity by reducing manual tracking efforts and delegating the responsibility of being the sole point of contact. Currently, CVM's systems are not set up in a manner that allows for seamless integration of PMs in the review process. Providing PMs and project teams with a new database that centralizes project and individual review planning would improve transparency among members of the project team, enhancing alignment and streamlining interactions. This would benefit both CVM and Industry sponsors by ensuring clearer, more efficient communication and better coordinated resource planning.

## *Recommended Activities and Prioritization Scoring*

18. The project team includes the PM plus a representative from each of the ONADE review teams responsible for the primary review of the applicable major technical sections. The review team includes the group working on a particular submission including all consultants.

Low High

| ID | Activity Description | Impact | Effort |
|---|---|---|---|
| 1.1 | **Equip PMs with Tools to Track Project Lifecycle:** Develop a centralized, user-friendly Project Management system to integrate project timelines, sponsor communications, submission tracking, and reviewer updates into a single platform. | 5 | 5 |

**Implementation Activities**

- Document the current roles and responsibilities of PMs and Team Leaders throughout the review process, including systems used and activities performed across the program
- Develop a future-state process, incorporating process improvements to formalize PM responsibilities across the program
- Update P&Ps and Performance Management Appraisal Program (PMAPs) to reflect new duties of the PMT
- Assess options to build or buy a platform that meets the identified core functionalities, using the requirements to guide the decision and select the best option
- Create an integration plan for the new system, aligning it with CVM's business operations, databases, and Standard Operating Procedures (SOPs)
- Develop a change management and communications plan to ensure organization-wide implementation, with user training and feedback mechanisms during launch
- Conduct beta tests with select teams, refine the system based on feedback, and validate updated procedures with CVM
- Implement the system as per requirements and the future-state design, ensuring full integration and operational functionality

**Outputs**

- PM roles and responsibilities map
- Future state process maps
- Updated P&Ps
- Updated PMAPs
- List of IT requirements
- Build vs. buy evaluation report
- Data migration plan
- Beta testing feedback reports
- Communications and change management plans
- Training materials and sessions

| | | | |
|---|---|---|---|
| 1.2 | **Gather and Report on Sponsor Satisfaction:** Develop a standard satisfaction survey and request that sponsors complete it after finalizing technical sections or approving an application. Gather feedback on what worked well and areas for improvement, using the insights to enhance the review process, communications, and GFIs. | 3 | 2 |

| Implementation Activities | Outputs |
|---|---|
| • Develop a set of questions that consistently measure the experience of sponsors during the review process<br>  • Key areas to focus on should include:<br>  • Clarity of communication throughout the review process<br>  • Timeliness of responses or approvals<br>  • Availability and helpfulness of project team<br>  • Clarity and usefulness of guidance (e.g., GFIs, review letter comments)<br>  • Overall satisfaction and areas for improvement<br>• Create a system to collect, organize, and analyze feedback for ongoing process improvement<br>• Develop a centralized database or tool to track feedback responses by application and technical section | • Sponsor satisfaction survey<br>• Feedback collection system<br>• Sponsor satisfaction dashboard<br>• Feedback review and reporting plan |

## *Identified Benefits*

- Improved collaboration among project team members
- Improved communication and trust between CVM and Industry
- Improved efforts at continuous improvement
- Reduced manual reporting and scheduling of tasks
- Increased data-driven decision making

## *Potential Risks*

- User resistance from staff accustomed to existing platforms and processes
- Significant costs to design, integrate, and maintain a new centralized IT platform
- Challenges with data migration from legacy systems
- Industry fatigue from having to provide CVM feedback through multiple channels
- Potential for the introduction of bias due to an unrepresentative sample of sponsors providing feedback

## *Root Causes Addressed*

- Insufficient IT Capabilities
- Siloed Systems
- Poor Communication Practices
- Misaligned Objectives

## *Recommended Performance Metrics*

| | |
|---|---|
| **Internal Review Milestones** | Tracks the achievement of key milestones (e.g., primary review deadlines, supervisory review completion) |
| **Sponsor Response Rate** | Tracks the percentage of sponsors who complete the satisfaction survey |
| **Sponsor Satisfaction Scores** | Measures overall satisfaction through a rating scale. This can be broken down into granular categories (e.g., communication, timeliness, etc.). |

# 2.0 Expand Internal Training and Development Opportunities

CVM must address the need for enhanced expertise and consistency among reviewers. The following initiatives aim to improve the quality, consistency, and regulatory compliance of reviews, increase reviewer confidence and adaptability, and foster a culture of continuous improvement. Trainings to address these recommendations will need to be factored into capacity planning (See **6.0 Implement Continuous Workload Analysis and Task Reallocation** below).

## *Current State Analysis*

Industry stakeholders consistently reported during interviews that reviewers may not be as well-versed in emerging novel science as Industry, leaving them feeling as though they need to educate reviewers on the latest scientific advances. Sponsors also noted that a lack of specialized expertise and periodic reviewer turnover at CVM exacerbates the issue because it can take several years for new reviewers to become proficient in the review process. Additionally, CVM interviewees reported that streamlined and effective cross-training is difficult due to staff specialization and inconsistent training practices, with new consulting reviewers having limited understanding of the drug approval process. In fact, CVM reported the average time it takes for new staff to become fully independent primary reviewers can be up to three years. During this period, training new reviewers places an additional burden on existing reviewers, highlighting the need for a revamped training program that removes the burden from primary reviewers, incorporates emerging scientific advances, and streamlines the onboarding time for new review staff.

## *Recommended Activities and Prioritization Scoring*

Low — High

| ID | Activity Description | Impact | Effort |
|---|---|---|---|
| 2.1 | **Develop a Standardized Reviewer Training Program with Periodic Re-Certification:** Launch a standardized reviewer training program on CVM policies and procedures to promote consistency, accuracy, and quality in the review process. Establish a regular cadence for re-certification to ensure that reviewers stay up-to-date on evolving policies, procedures, and scientific advances. Hold standing meetings to discuss new innovations and process improvement opportunities, potentially stemming from Science Visioning and Animal and Veterinary Innovation Agenda (AVIA) efforts occurring at the agency level. | 3 | 4 |

| | | | |
|---|---|---|---|
| | **Implementation Activities**<br>• Conduct a needs assessment to identify core concepts, policies, and review criteria to be covered in the training curriculum<br>• Research similar Agency training programs to leverage best practices from, such as the former CDER Commissioner's Fellowship Program<br>• Develop training modules that address the identified core concepts, policies, and review criteria<br>• Develop training materials, including manuals, online resources, and job aids<br>• Create assessment and certification tools, including exams to evaluate competency<br>• Establish a certification tracking database and integrate into the Learning Management System<br>• Develop a mechanism to collect feedback<br>• Pilot and refine the program based on feedback collected<br>• Roll out the training program to all reviewers<br>• Develop schedule of standing meetings and agendas to regularly discuss new innovations and opportunities for process improvements | **Outputs**<br>• Needs assessment<br>• Training curriculum<br>• Training materials<br>• Assessment and certification tools<br>• Feedback collection tools<br>• Training program pilot<br>• Recurring meeting cadence and agendas | |
| **2.2** | **Establish and Maintain a Schedule of Frequent Webinars and Learning and Development Opportunities:**<br>Provide staff with opportunities to advance their education on the latest scientific advances, emerging trends, regulatory changes, innovative methodologies, and other relevant topics. Develop a consolidated training repository for future access to these resources. Alternatively, provide reviewers the opportunity to enroll in external training opportunities. | **3** | **4** |
| | **Implementation Activities**<br>• Conduct a gap analysis to identify knowledge gaps among reviewers<br>• Collect existing trainings and identify gaps in resources currently available<br>• Establish a schedule for regular opportunities for Continuing Professional Education (CPE) courses to address identified knowledge gaps<br>• Determine need for in-person or classroom style training opportunities | **Outputs**<br>• Report identifying specific knowledge gaps and areas of interest<br>• Detailed CPE course schedule<br>• Collection of recorded CPEs<br>• On-demand learning library | |

- Develop, deliver, and record CPE sessions
- Create an on-demand learning library
- Gather feedback and evaluate effectiveness after each session
- Collected feedback and evaluation reports

## *Identified Benefits*

- Enhanced quality and consistency of reviews
- Reduced variability in review outcomes
- Increased compliance with regulatory policies
- Strengthened reviewer confidence
- Improved reviewer flexibility in effectively responding to emerging challenges
- Increased collaboration across disciplines
- Increased culture of continuous learning

## *Potential Risks*

- Resistance to change and additional training requirements
- Limited capacity for reviewers to complete training
- Constantly evolving regulatory landscape makes it difficult to establish consistency with training program content
- Low attendance or engagement from review staff

## *Root Causes Addressed*

- Inadequate Training and Lack of Clear Resources
- Misaligned Objectives
- Lack of Trust and Transparency

## *Recommended Performance Metrics*

| | |
|---|---|
| **Training Completion Rate** | Percentage of reviewers who complete the initial training and re-certification |
| **Assessment Scores** | Average scores on initial certification exams and re-assessments |
| **Reviewer Satisfaction Scores** | Survey results measuring reviewer confidence and satisfaction with the training program |

# 3.0 Improve Communication and Guidance Between CVM and Sponsors

The following recommendations aim to address lingering communication challenges through activities such as hosting workshops, developing user-friendly portals, distributing newsletters, and creating clear submission templates. These efforts enhance transparency, collaboration, and efficiency, ultimately improving the submission and review process for both CVM and Industry.

## *Current State Analysis*

CVM's communication and guidance practices were identified as inconsistent by sponsors during interviews, leading to challenges for sponsors in meeting regulatory expectations. Key challenges identified include sponsors' difficulties in accessing relevant information, unclear submission requirements, and inconsistent feedback from reviewers. Sponsors frequently cited these issues as contributing factors to multiple review cycles, delays, and inefficiencies in the approval process. However, reviewers noted that some sponsors do not fully adhere to the instructions provided to them, and contribute to the lack of early, transparent communication, which can result in errors or misaligned submissions. Additionally, the reliance on manual communication channels, such as email, has contributed to inefficiencies and delays in clarifying guidance. To combat these issues, clearer guidance documents and more proactive communication from both CVM and Industry would greatly enhance the submission review experience for both parties.

## *Recommended Activities and Prioritization Scoring*


| ID | Activity Description | Impact | Effort |
|---|---|---|---|
| 3.1 | **Hold GFI Workshops with Industry:** Conduct interactive workshops with Industry to identify and address gaps in guidance, clarify CVM expectations, and obtain input from Industry to develop or revise GFI documents. | 3 | 4 |

| Implementation Activities | Outputs |
|---|---|
| • Schedule and host workshops with Industry to identify guidance needs and clarify CVM expectations<br>• Develop new or revised GFIs incorporating input from sponsors and CVM staff<br>• Establish thresholds for staff allocation of time in support of the development and refinement of GFIs | • Schedule for GFI workshops and development plan<br>• Stakeholder workshops<br>• New or revised GFIs |

| | | | |
|---|---|---|---|
| | • Publish updated GFIs on the CVM website, providing clear, actionable guidance for sponsors<br>• Create a recurring schedule for stakeholder engagement to address future guidance needs | | |
| **3.2** | **Improve Accessibility of Existing Guidance and Public Resource Repository:**<br>Enhance the internal and external availability and promote awareness of centralized location of up-to-date information on submission requirements, guidance documents, and other key resources. | **2** | **2** |
| | **Implementation Activities** | **Outputs** | |
| | • Integrate advanced keyword-based search functionality into the existing repository of GFIs, P&Ps, and other resources<br>• Populate the existing documentation repository with FAQs, clear answers, and links to related resources such as GFI documents and submission templates<br>• Maintain the portal by regularly updating content to reflect current recommendations and CVM expectations<br>• Develop internal and external communications to improve awareness of CVM documentation repository | • User-friendly public resource portal, providing centralized access to key information<br>• Accurate, up-to-date content<br>• Reduction in CVM staff workload from inquiries | |
| **3.3** | **Launch a Public CVM Quarterly Newsletter:**<br>Develop a quarterly newsletter summarizing public meeting discussions and outcomes, updates to regulatory policies, guidance revisions, and shared challenges. | **2** | **1** |
| | **Implementation Activities** | **Outputs** | |
| | • Develop a communications plan including cadence for newsletter, medium, content schedule, and additional details<br>• Identify resources, content developers, and desired cadence for fulfilling this activity<br>• Draft newsletter and garner approval from the appropriate levels of leadership<br>• Distribute newsletter across the Center and across the animal drug industry<br>• Continuously garner feedback on newsletter content to improve relevancy of distributed content | • Communications plan<br>• Quarterly newsletter<br>• Documented feedback | |

**3.4**

### Expand the Use of Question-Based Review Templates:

Develop question-based review (QbR) templates – a series of questions that focus on the critical information needed to evaluate product quality – tailored to specific submission types and/or technical sections, providing sponsors with clear instructions and formatting guidelines to align their submissions with CVM expectations.

| 4 | 4 |
|---|---|

| Implementation Activities | Outputs |
|---|---|
| • Identify submission types and technical sections most in need of standardized QbR templates<br>• Request input from reviewers on designing questions and the order of inputs for new QbR templates<br>• Develop QbR templates tailored to the needs of reviewers and the submission type, including clear instructions and guidelines for data and formatting<br>• Pilot new QbR templates with a select group of sponsors to garner feedback and improve the template<br>• Update QbR templates based on feedback gathered during the pilot<br>• Communicate the new process for submissions with QBR templates in eSubmitter to Industry and collect feedback to continuously improve the templates over time | • Development plan for templates<br>• QbR templates<br>• Pilot testing plan<br>• Communication and change management plan |

**3.5**

### Mandate Regular "Lessons Learned" Meetings:

Conduct post-approval debrief sessions between CVM and sponsors to analyze application timelines, rejection reasons, and share best practices. Consider mandating these meetings following the completion of a technical section, as well.

| 3 | 2 |
|---|---|

| Implementation Activities | Outputs |
|---|---|
| • Schedule and host post-approval lessons learned meetings to review components that went well, application timeline delays, and rejection reasons<br>• Update the lessons learned P&P to reflect new process for conducting lessons learned meetings and collecting standardized insights across divisions | • Lessons learned meetings SOP<br>• Data collection form for lessons learned<br>• Routine debrief sessions conducted with sponsors |

| | |
|---|---|
| | • Establish standard questions and data to collect during lessons learned meetings<br>• Share insights with sponsors, providing actionable feedback to improve future submissions<br>• Use outcomes from meetings to improve submission quality, develop related metrics, and strengthen collaboration between CVM and Industry |

## *Identified Benefits*

- Enhanced transparency and trust in the submission and review process
- Reduced sponsor frustration
- Reduced number of NIGO submissions
- Improved alignment of expectations between CVM and sponsors, minimizing review cycles
- Established foundation for long-term collaboration and process improvement with Industry

## *Potential Risks*

- Limited stakeholder engagement during workshops
- Additional resource constraints developing new GFI materials
- Ongoing costs to keep public guidance repositories up-to-date

## *Root Causes Addressed*

- Poor communication practices
- Unclear expectations
- Lack of standardization
- Trust Issues
- Inadequate training and lack of clear resources

## *Recommended Performance Metrics*

| | |
|---|---|
| **Reduction in Incomplete Submissions** | Tracks rate or decline in submissions returned to sponsors due to being incomplete and/or NIGO |
| **Sponsor Satisfaction Scores** | Measures overall satisfaction through a rating scale via periodic surveys to assess sponsor perceptions of CVM guidance clarity |
| **Allocated GFI Development Hours** | Definition of a threshold for time and effort CVM should contribute to GFI development activities as a KPI |
| **Count of GFI Publications** | Set goals for GFIs to be developed within a given period of time and track the count of published GFIs against that goal |

# 4.0 Set New Compliance Standards for Submission Organization and Quality

CVM must combat decreasing levels of submission organization and quality by setting new standards for submission organization and quality. By imposing new requirements for submission quality, CVM improves consistency among sponsors, reducing the burden of reviewing unorganized submissions.

## *Current State Analysis*

CVM's current review process is hindered by submissions that are poorly organized, unclear, or in sub-standard condition. This assessment uncovered that reviewers experience difficulties with submissions that are missing critical information, do not comply with CVM guidance, or include unnecessary data. These issues require additional requests for clarification, amendments, or resubmissions, ultimately extending the approval timeline. The process is further impeded by submissions that lack key organizational elements, such as a table of contents, cover letter, change summary, study inclusion justification, or a clearly stated objective. Disorganized submissions make it difficult for reviewers to quickly locate the necessary information, causing unnecessary delays. To address these challenges, these recommended activities aim to improve the quality, organization, and clarity of submissions.

## *Recommended Activities and Prioritization Scoring*


| ID | Activity Description | Impact | Effort |
|---|---|---|---|
| 4.1 | **Establish Mandatory Submission Quality and Organizational Standards:** Set new submission standards across all Industry submissions. For submissions to be considered complete, require organization tools such as a table of contents, submission purpose statement, study inclusion justification, and change summary for amendments or resubmissions. | 4 | 3 |

| Implementation Activities | Outputs |
|---|---|
| • Commission a CVM-wide working group to set new submission organizational standards and set RTR thresholds<br>• Present new submission standards to Industry for their review and update based on public feedback<br>• Develop GFIs, templates, checklists, and training for the new submission standards<br>• Develop a standardized change summary | • GFI on submission organizational and data standards<br>• Change summary template<br>• Sponsor and reviewer trainings |

| | | |
|---|---|---|
| | template to be included in all amendments and resubmissions<br>• Train staff across all review teams on data compliance checklists and RTR use thresholds for consistent application | • Data compliance checklist and RTR threshold training for review staff |
| **4.2** | **Explore a Tiered Submission System with Differentiated Review Timelines Based on Submission Complexity:**<br>Assign a working group to evaluate the feasibility of assigning submissions different review timelines based on the complexity, organization, quality, or other aspects of a submission that aligns with the time and resources required for CVM to review. | **4** **5** |
| | **Implementation Activities** | |
| | • Commission a working group to investigate the feasibility of tiered submission timelines<br>• Establish a method to score complexity, organization, quality, or other aspects of a submission that aligns with the time and resources required for CVM to review<br>• Establish the number of tiers and associated timeline goals for each submission tier<br>• Determine the procedure to receive legal authorization of the initiative<br>• Present the proposed initiative to Industry for feedback and consideration<br>• Implement any necessary feedback from Industry to the tiered submission system and garner the required approval for the new tiered review goals | • Proposal for tiered submission system<br>• Complexity scoring framework<br>• Quality scoring framework |
| **4.3** | **Standardize Digital Record Submissions by Adopting Clinical Data Interchange Standards (CDISC) and Study Data Tabulation Model (SDTM) study Data Standards:**<br>Adopt the SDTM study data exchange standards developed by the CDISC, which sets how data should be structured, defined, formatted, or exchanged between systems. | **3** **2** |
| | **Implementation Activities** | **Outputs** |
| | • Develop training modules for Industry on how to standardize data into the SDTM standard<br>• Provide guidance and training to Industry for protocol development and post-processing of data into SDTM format | • SDTM GFI<br>• SDTM training for Industry and review staff |

- Mandate study data to be submitted following SDTM standards
- Set up systems to be able to intake and automate data quality checks based on SDTM standards

## *Identified Benefits*

- Increased efficiency for reviewers to navigate submissions and identify the critical components of a submission
- Improved consistency in quality of submissions
- Reduced time spent reviewing resubmissions and amendments
- Reduced cycle times for less complex submissions
- Standardized data formats allow for automation of data quality checks

## *Potential Risks*

- Added administrative burden for sponsors to learn and implement new submission standards
- Added administrative burden for reviewers to conduct initial submission quality assessment and return low quality submissions
- New standards introduce an additional level of subjectivity into review timelines
- Additional sponsor burden for post-processing of study data into the study data exchange standard
- Pushback from AHI members, who have expressed that implementing SDTM standards may cause bandwidth constraints

## *Root Causes Addressed*

- Data Quality and Governance Challenges
- Lack of Standardization
- Unclear Expectations

## *Recommended Performance Metrics*

| | |
|---|---|
| **Frequency of Single-Cycle Reviews** | Tracks the percentage of submissions presented with all necessary information and reviewed in a single-cycle |
| **Rate of Submission Amendments for Study Data** | Measures the reduction of necessary revisions for study data due to standardization |

# 5.0 Improve Capture and Reporting of Reasons for Submission Failures

To maximize the likelihood of single-cycle reviews, CVM and Industry need to improve tracking and analysis of review comments to better understand common trends in unsuccessful submissions.

## *Current State Analysis*

Industry and CVM both share a goal for each submission to receive a favorable review within a single-review cycle. Receiving single-cycle reviews represents the quickest path to receiving an approval for a new animal drug. Most challenges in the animal drug review process arise when submissions are unsuccessful and Industry stakeholders must revise and resubmit their submissions. CVM has an incomplete understanding of the reasons that animal drug review submissions are unsuccessful. This is primarily the result of an absence of data regarding why submissions are unsuccessful. DMT collects and manages its own comment database just for CMC submissions, with the primary purpose being to improve consistency between its reviews, which is a common pain point mentioned by Industry sponsors. IT challenges limit the effectiveness of DMT's comment database, making management of the database burdensome. Other review divisions are not systematically capturing information on the comments they provide to Industry or the reasons for unsuccessful submissions. Expanding data capture and reporting in this area allows CVM and Industry to continuously learn from submissions that received unfavorable review outcomes.

## *Recommended Activities and Prioritization Scoring*


| ID | Activity Description | Impact | Effort |
|---|---|---|---|
| 5.1 | **Revamp CVM's Approach to Review Comments:** Develop a standardized template for review comments that will allow for collection, aggregation, and analysis of comment data. Accompany this new process with a centralized repository to store and aggregate these new data. Establish regular reporting schedules to continuously improve on the review process. | 4 | 4 |
| | **Implementation Activities** | **Outputs** | |
| | • Develop a format for a standardized template for review comments (e.g., consider breaking up comments into components such as: subject, submission text, rationale, references)<br>• Develop definitions for categories of review comments that could be tracked (e.g., study | • Standard template used for all review comments<br>• Data dictionary of comment categories<br>• List of system | |

design, statistics, formatting, data quality)
- Assess the established definitions by capturing previous review comments and bucketing them into categories to set benchmarks
- Develop a centralized repository to log and track review letter comments
- Gather requirements on essential database functionalities (e.g., import/export, searchability, etc.)
- Make a build or buy decision for an IT solution to manage comment database
- Pilot templated comments in reviews for one technical section or within one team
- Beta test comment database upkeep with comments from pilot and gather reviewer feedback
- Launch comment templates and database for all review teams or technical sections
- Devise a process for auditing submissions by rejected reason to uncover patterns in submission rejections
- Establish a cadence to perform routine audits for rejection reasons
- Publish reports with audit findings, including trends by sponsor, review team, or submission type, along with recommendation for reducing submission rejection rates

requirements from review staff
- Build or buy report
- Centralized review comment database
- Comment audit P&P
- Published comment audit reports

## *Identified Benefits*

- Improved consistency of reviewer feedback
- Augmented data to assess review process performance
- Enhanced insight into unfavorable review outcomes
- Streamlined access to historical review comments
- Strengthened ability to identify and address systemic review issues
- Enhanced transparency with Industry stakeholders via published audit results
- Increased opportunities for lessons learned for continuous improvement

## *Potential Risks*

- Standard comment format may not work across different technical sections
- Resistance to adopting new approach from CVM review staff
- Workload capacity concerns while piloting, developing, and populating database
- Introduced burden of maintenance and quality control of new comment database
- Retrospective auditing may miss emerging trends

## *Root Causes Addressed*

- Lack of Standardization
- Inadequate Training and Lack of Clear Resources
- Lack of Trust and Transparency
- Undefined or Misaligned Metrics
- Poor Communication Practices

## *Recommended Performance Metrics*

| | |
|---|---|
| **Leading Review Comment Categories** | Using categorizations determined for review comment tracking, collect the most frequent comment categories (and subcategories, if applicable) |
| **Frequency of Submission Failure Reasons** | Based on review comment tracking, identify a failure reason(s) for each unsuccessful submission and track the frequency of submission failure reasons over time segmented by submission type |
| **Average Number of Review Comments** | A comparison within CVM review divisions of the average number of review comments per submission type. This should also be tracked over time to identify any changes to comment approaches within or between divisions. |

# 6.0 Implement Continuous Workload Analysis and Task Reallocation

CVM must address the challenge posed by the impact of maturing science and complexity of submissions. The recommendations aim to address these challenges by bolstering oversight of reviewer workload and identifying opportunities to reduce reviewer administrative workload.

## *Current State Analysis*

CVM has tools and processes in place to facilitate workload analysis and allocation of work. However, these tools prove to be challenging and limited by outdated IT capabilities, especially when accounting for increased complexity in composition and content of submissions. Reviewers cited a belief that they lack the capacity to complete additional activities outside of review activities, such as supplemental learning and development opportunities and developing new GFIs. In ADUFA IV, staff spent 48.9% of their time on activities related to ADUFA submission reviews, an increase of 26.7% from ADUFA I. In order to better manage the increasing workload of reviewers, CVM must act to enhance workload capacity and allocation tracking tools or processes to better facilitate dynamic work allocation and align resources to work based on a mixture of bandwidth, skills, and experience.

## *Recommended Activities and Prioritization Scoring*


| ID | Activity Description | Impact | Effort |
|---|---|---|---|
| 6.1 | **Implement a Workload Management System to Monitor and Evaluate Assignment Distribution:** Provide CVM supervisors with enhanced tools to evaluate submission assignments in a systematic manner that accounts for the complexity of submissions and existing reviewer workloads | 4 | 4 |

| Implementation Activities | Outputs |
|---|---|
| • Establish schema to evaluate and categorize submissions based on complexity (See **Recommendation 4.2**)<br>• Gather requirements on attributes required to facilitate real-time monitoring and tracking of assignments<br>• Coordinate with IT group to define required changes to systems to accommodate changes and obtain level of effort<br>• Update existing CVM systems and tools (e.g., | • Complexity scoring framework<br>• Updated IT system(s)<br>• Revised planning tools |

| | | | |
|---|---|---|---|
| | STARS, work management queue reports, resource capacity or user engagement dashboards, etc.) to incorporate complexity schema | | |
| **6.2** | **Redistribute Administrative Tasks to Non-Scientific Staff:** Reassign non-scientific submission-related work (e.g., meeting scheduling, visitor badge printing, room reservations) to administrative staff to alleviate workload. | **2** | **1** |

| Implementation Activities | Outputs |
|---|---|
| • Evaluate roles and responsibilities of staff<br>• Review current state process to identify non-review work related activities with potential for redistribution<br>• Determine appropriate venue(s) for where work can be-reassigned<br>• Generate processes (e.g., workflows) to facilitate request of administrative actions<br>• Adjust position documentation, P&Ps, workflows, etc. to account for changes<br>• Conduct required communications and training to facilitate transfer of activities | • Revised list of roles and responsibilities<br>• Administrative action request workflow<br>• Current and future state process maps<br>• Updated PMAPs<br>• Updated P&Ps |

## *Identified Benefits*

- Improved monitoring and management of distribution of work by supervisors
- Improved time dedicated for review staff on primary assigned submissions
- Enhanced tracking of administrative process activities
- Limited overextending of review work (e.g., spike in review time at expense of training, policy development, etc.)

## *Potential Risks*

- Operationalizing complexity scoring will require adjustments to submission requirements
- High cost of time and resources to update IT elements (e.g., adding fields to reflect identified complexity factors)
- Uptick in hiring costs for new personnel to undertake administrative activities
- Union considerations for personnel related changes
- May require updates to PMAPs to fully enforce and realize updated roles and responsibilities

## *Root Causes Addressed*

- Suboptimal Resource Allocation
- Lack of Trust and Transparency
- Process Not Optimized for Scale or Efficiency
- Insufficient IT Capabilities
- Undefined or Misaligned Metrics

## *Recommended Performance Metrics*

| | |
|---|---|
| **Percentage of Time Spent on Review-Related Activities** | Threshold for time and effort CVM should contribute to review activities, including by role |
| **Number of New or Updated Tools Introduced** | Number of new tools introduced to address challenges, or core updates to existing tools with substantial impact |
| **Number of Redistributed Administrative Actions** | Number of administrative actions requested by reviewers in the new administrative action request workflow tool |

# 7.0 Enhance IT Systems for Submission and Workflows Tracking

The recommendation to enhance IT systems and submission workflows addresses challenges experienced by Industry partners and CVM personnel. The initiatives aim to address these challenges, providing more transparency and confidence in systems supporting operations.

## *Current State Analysis*

CVM personnel experience challenges in daily processing of work and limitations on how systems are used or what they can capture, which limits planning or work analysis. Meanwhile, Industry stakeholders have noted challenges regarding submitting their content to CVM and having the ability to understand the status and who is servicing their work. Much of the analysis for this report relied on decades' worth of records collected and retained by CVM that required manual tabulation to facilitate analysis. Additional insights can be gleaned from records if more attributes exist (e.g., robust analysis around amendments) or processes and systems are better utilized (e.g., package routing for review and approval). To the extent any of the analysis or outputs from this report need to be repeated, updates are required to CVM's systems to facilitate more routine analysis that will not require the same degree of time and effort as this report.

## *Recommended Activities and Prioritization Scoring*


| ID | Activity Description | Impact | Effort |
|---|---|---|---|
| 7.1 | **Implement Workflow for Requesting Amendments from Sponsors:** Implement a systematic process to request amendments from sponsors to capture the reasons for the request, date of the request, and requested due date. | 3 | 3 |

| Implementation Activities | Outputs |
|---|---|
| • Gather requirements for desired attributes for the amendment request workflow<br>• Create new submission fields to reflect associated metadata (e.g., request date, requested due date, etc.)<br>• Evaluate existing systems and fields to determine if existing areas can be updated (e.g., new submission type codes (STC) or submission class codes (SCC) can be added) or if new fields need to be introduced entirely | • Updated SOPs and associated processes<br>• New submission fields<br>• Amendment request system workflow |

| | | | |
|---|---|---|---|
| | • Build new process and/or workflow to facilitate amendment requests and routing<br>• Develop accompanying policies and procedures and updates to existing manuals regarding amendments<br>• Develop communications materials with accompanying events (e.g., training, webinars, etc.) to facilitate release as needed | | |
| **7.2** | **Develop Case Management Tool to Support Standardized and Streamlined Review Process Management and Execution:**<br>Enhance the current systems environment to provide a unified means to access and share information on projects and submissions (including submission relationships, a segmentation of activities by phase such as administrative, administering the review, authoring findings, and review and approval). Enhanced systems should provide real-time visibility into the status of submissions and be used to reduce manual burden on staff. | **5** | **5** |
| | **Implementation Activities** | **Outputs** | |
| | • Conduct gap analysis between SOPs and process maps and IT systems to identify elements not being tracked<br>• Define requirements to support planned process to standardize and streamline activities to include additional capabilities such as:<br>  • Integrate collaboration tools<br>  • Update data fields and selection capabilities<br>  • Linking capabilities to submission repository<br>  • Adjust users features, such as assignment dates<br>• Update Appian to allow and track internal review cycles and reasons for revisions during supervisory reviews<br>• Revise ATR to allow staff to charge time to new activity codes for authoring, reviewing and approval against submissions<br>• Conduct pilot to test tracking and feedback analysis before wider rollout<br>• Implement new capabilities and set up structures to share key information and integrate with necessary data sources<br>• Provide training on new system features and processes | • List of technical requirements<br>• Deployment plan<br>• Updates to IT system(s) and integration<br>• Updated SOPs and user guides<br>• Internal workflow system revisions<br>• Updated ATR activity codes<br>• Pilot feedback results<br>• Training material and plan<br>• Training sessions<br>• Change management plan<br>• Communications plan | |

| | | | |
|---|---|---|---|
| **7.3** | **Enhance Submission Data Capture to Reduce Manual Tabulation Efforts:**<br>Update policies, processes, and systems to promote better data capture around submission data to facilitate tracking and analysis. This includes related technical section, related project, enhancements utilized, referenced submissions, study components, submission relationships.[19] | **3** | **3** |
| | **Implementation Activities**<br>• Update STARS to facilitate association of submissions with other submissions<br>• Update eSubmitter to check and/or validate association of submissions | **Outputs**<br>• Updated STARS data fields<br>• Updated eSubmitter validation tools<br>• Revised P&Ps | |
| **7.4** | **Revise Timekeeping Record Structures to Differentiate between Review Functions:**<br>Update ATR categories to require staff to better reflect time and effort against different components of the review process. This includes distinguishing between conducting the review, writing letters (including amendments requests), and authoring the final review. | **3** | **3** |
| | **Implementation Activities**<br>• Review existing ATR codes and draft requirements to facilitate full tracking of internal review milestones<br>• Hold discussion with IT group to understand implications and limitations on implementing updates (e.g. tracking to package level)<br>• Submit requirements to ATR change control board for review and approval<br>• Update ATR codes<br>• Update reporting and monitoring tools<br>• Create and execute change management communications to facilitate rollout | **Outputs**<br>• Updated IT system(s)<br>• Updates to ATR documentation<br>• Revised ATR codes<br>• Revised SOPs | |
| **7.5** | **Develop a Shared Tracking Platform for CVM and Sponsors to View the Current Status of Work:**<br>Update policies, processes, and systems to promote better data capture around submission data to facilitate tracking and analysis. This includes related technical section, related project, enhancements | **4** | **5** |

19. While STARS currently supports the concept of submission IDs and parent IDs fields, records are not robust in this regard. These are either optional, not supported, or not enforced through the eSubmitter interface.

utilized, referenced submissions, study components, submission relationships.[20]

| Implementation Activities | Outputs |
|---|---|
| • Validate submission attributes into which Industry requires insights<br>• Work with FDA IT groups to evaluate if updates can be made to Electronic Submissions Gateway (ESG) or another approach is required<br>• Obtain buy-in from Executive Management and Finance to support build-out<br>• Develop agreed upon solution<br>• Develop accompanying policy and procedures and updates to existing guides or manuals<br>• Create communication and policy around engagement, outreach, etc. (i.e., allow Industry to see who has been assigned submissions) | • Updated IT system(s)<br>• New shared tracking platform<br>• Revised guidance to Industry and CVM P&Ps |

**7.6**

**Modernize eSubmitter to Improve User Experience (UX), User Interface (UI), and Data Validation:** Build enhancements into eSubmitter to modernize the platform and allow for a better user experience. CVM should undertake a robust approach to collect requirements that build off existing known issues and bugs and validate with Industry via a prioritization schema.

| 3 | 3 |
|---|---|

| Implementation Activities | Outputs |
|---|---|
| • Hold sessions with internal and external stakeholders to collect detailed requirements<br>• Coordinate with IT group to translate requirements to IT updates and designated level of effort. Some requirements that have already been identified from this assessment include:<br>  • Improved materials on the website and within the application itself to aid new users with setup and submitting data<br>  • Updated UI based on modern design and coding languages (e.g., multi-platform accessible, responsible design, dynamic data validation, etc.)<br>  • Having team assignment and routing | • Updated IT system(s)<br>• Updated documentation<br>• Communications and/or training sessions |

20. This assessment recognizes FDA is actively undertaking larger efforts to modernize its ESG under the auspices of Electronic Submission Gateway Next Gen (ESG NG). Part of this effort includes introducing a Unified Submission Portal where submission history and packages can be viewed. However, at present only the following information is being built into the functionality: Center/Submission Type, Date/Time of Submission, Submitter, and Acknowledgements (source: ESG NextGen Frequently Asked Questions | FDA).

automatically established based on criteria users select
    - Means to validate base information (sponsor names, Data Universal Numbering System numbers, etc.) against values on record to prevent mismatches based on incorrect values from manual entry. [21, 22]
- Develop detailed project plans to facilitate building out updates
- Deploy updates to eSubmitter software
- Develop communications to Industry on revisions; include website updates, Industry days, or part of planned ADUFA V engagement events

## *Identified Benefits*

- Reduced manual reporting efforts
- Improved consistency in approach for reviewers to request amendments
- Improved ability to evaluate time and effort against amendments
- Improved tracking of internal review cycles and review milestones
- Enhanced tracking of affiliated submissions
- Improved ability to analyze against the lifecycle of affiliated submissions towards NADAs
- Enhanced ability to quickly reference and retrieve affiliated submissions outside an INAD

## *Potential Risks*

- Resistance to IT change from review staff and Industry
- Updates and modifications to ATR, STARS, and Appian may create technical issues in the future
- Updates will involve time and resources to IT elements (e.g., adding fields to reflect identified complexity factors)
- Changes based on IT funding and/or resources, including organizations above CVM (e.g., Office of Information Management and Technology)
- There may be an impact to sponsor flexibility on how they organize and package submissions

## *Root Causes Addressed*

- Outdated or Unreliable Systems
- Data Quality and Governance Challenges
- Lack of Standardization
- Processes Not Optimized for Scale or Efficiency
- Insufficient IT Capabilities
- Siloed Systems
- Undefined or Misaligned Metrics
- Poor Communication Practices

21. As cited, FDA is undertaking enhancements to the ESG via ESG NG. This enhancement could fit well within that framework, with eSubmitter possibly folded in as a web application. This would provide Industry with a unified experience and allow dynamic data validation through a “live” system that can connect and reference FDA systems.
22. Interviews cited issues with file size and UI limitations. However, FDA and/or CVM have taken steps to address these concerns. Specifically: ESG NG is designed to increase file size threshold to 1 TB before requiring files to be broken up; eSubmitter Font Scaling Project (circa 2021) added ability for users zoom and deal with difficult to read fonts.

## *Recommended Performance Metrics*

| | |
|---|---|
| **New Tools Introduced or Updated** | Number of new tools introduced to address challenges, or core updates to existing tools with substantial impact. This should extend to content introduced to Industry or CVM personnel. |
| **Updated or New Guidance Documents** | Number of updated policy documents introduced or updated with substantial updates. This should extend to internal documentation for CVM as well as external content made available to Industry. |
| **IT System Uptime** | Measures the percentage of time IT systems are operational without malfunctions |
| **Adoption Rate** | Measures how many users are using the tools for end-to-end reviews |
| **Data Access and Reporting Efficiency** | Measures the percentage of time IT systems are operational without malfunctions |
| **User Satisfaction** | Surveys used to assess user satisfaction with the new IT solutions |

# 8.0 Standardize and Streamline Review Process Workflows

As scientific reviews become more complex, CVM must prioritize standardizing and streamlining their review process to improve efficiency, transparency, information sharing, and scalability. This involves designing workflows to eliminate inefficiencies, reduce redundancies, and ensure consistency across all tasks. It is also essential to integrate tools and templates within the process to standardize information collection and sharing, allowing for regular monitoring and continuous process improvement.

## *Current State Analysis*

Current animal drug review processes under ADUFA have several variations and workarounds, leading to inefficiencies and an inability to track progress of review handoffs. Many of these inconsistencies are due to deficiencies in current IT systems. While there are several tools and templates available, usage of tools and associated processes vary across offices. For example, while consult requests have a standard workflow within Appian, sub-consults or small informational request are handled in a variety of ways as it is often easier to request outside Appian. While in the current design this is more efficient, it exacerbates tracking challenges.

Within the process, around 40% of activities were identified as LVA activities, such as redundant tasks, inefficient steps, and misaligned activities that would be suitable for streamlining or automation. Other process enhancements around centralizing data validation and storage would improve efficiency, as reviewers often cited the burden in having to request updated drug information from reviewers in separate divisions or teams.

Within the current process there is a heavy reliance on manual activities. Due to the lack of a dedicated case management tool, reviewers often rely on email to communicate and move submissions along in the process, leading to inconsistencies in sharing of information and difficulty in tracking real-time status. The reliance on manual activities exacerbates the inefficiencies of the review process. By implementing automation and workflow tools, along with optimizing existing process inefficiencies, CVM would enhance the efficiency of the review process, reducing reviewer workload and freeing up valuable resource hours.

## *Recommended Activities and Prioritization Scoring*


| ID | Activity Description | Impact | Effort |
|---|---|---|---|
| 8.1 | **Standardize and Streamline Submission and Application Review Process Activities:** Design and implement future state processes that reduce time and effort to complete tasks and improve consistency. This includes restructuring, simplifying, or automating LVA activities to optimize process and | 3 | 3 |

resource inefficiencies. Enable standardization by executing the process within a dedicated workflow tool (see **Recommendation 7.2**), as well as identifying required updates to existing IT systems.

| Implementation Activities | Outputs |
|---|---|
| • Conduct a review of current state process documentation to identify LVA tasks, repetitive tasks, and inefficiencies where the process can be restructured, simplified, or automated<br>• Design a future state process by updating documentation to include new standardized and streamline process activities<br>• Update P&Ps and PMAPs to reflect new duties of reviewers<br>• Develop a change management plan and communication plan to effectively communicate the plan for changes to the process and incorporate input from review teams<br>• Develop SOPs and training modules on the new streamlined and standardized process and updates to system workflows<br>• Define requirements and determine updates to Appian and STARS or assess if a new IT system is required to enact the streamlined review process<br>• Continuously refine and improve the process by monitoring performance and compliance, regularly collecting feedback, and establishing continuous improvement cycles for reviewing and acting on feedback | • Future state process maps<br>• Updated P&Ps<br>• Updated PMAPs<br>• Change management plan<br>• Updated SOPs and user guides<br>• Training material<br>• Monitoring plan<br>• Feedback channels and reports<br>• Improvement action plans |

## *Identified Benefits*

- Improved efficiency and consistency within the review process
- Increased process standardization across reviewers and teams
- Reduction in bottlenecks
- Enhanced resource allocation and responsibilities
- Improved clarity and access to information
- Enhanced communication and information sharing
- Improved tracking and reporting

## *Potential Risks*

- Change resistance or lack of stakeholder buy-in
- Changes rely on success of implementation of IT-related activities in **Recommendation 7.0**
- Additional costs and resources to deploy changes
- Additional training, adding administrative burden to reviewers
- Feedback not being acted upon promptly, leading to frustration

## *Root Causes Addressed*

- Lack of Standardization
- Suboptimal Resource Allocation
- Processes not Optimized for Scale or Efficiency
- Poor Workflow Design
- Poor Communication Practices

## *Recommended Performance Metrics*

| | |
|---|---|
| **Average Processing Time** | Average time taken to complete a review from start to finish |
| **Cycle Time Reduction** | Reduction in the time taken to process reviews compared to previous periods |
| **Throughput Rate** | Number of reviews processed within a specific period |
| **Consistency Rate** | Percentage of reviews that follow standardized procedures |
| **Reviewer Productivity** | Number of reviews completed per reviewer within a specific timeframe and the average time it takes to complete a review |
| **Reviewer Satisfaction Surveys** | Results from surveys measuring reviewer satisfaction with the process and tools |

# 9.0 Track and Report Key Metrics Relevant to Review Process Success

A lack of available metrics related to review process success is a current point of frustration between CVM and the animal drug industry. Currently, there is publicly available information related to the percentage of favorable and unfavorable review outcomes, but additional metrics could provide a more comprehensive picture of the NADA review process. Such metrics could help both CVM and Industry identify existing pain points within the animal drug review process and target efforts and resources to addressing them.

There is a current emphasis placed on collecting metrics at the application level. However, the independent nature of technical sections within the phased review process makes more granular metrics captured at the technical section level more informative. Industry has expressed a desire for access to more longitudinal metrics to track trends over time. The lack of granular metrics is a major contributor to Industry's perception of a lack of transparency in the review process. Developing metrics that provide more transparency in reviews could help build trust between CVM and Industry and foster more productive collaboration between the two sides in the future.

The table below represents recommendations for additional metrics to track as part of the ADUFA program, along with benefits, considerations, and a categorization of the current state of the data for each. The current state of data is sorted into one of three groups: Readily Available (metrics use data that CVM already collects and could begin reporting out on immediately); Data Exists, Requires Significant Manual Calculation (metrics require calculations or adjustments to existing data); and Requires Creation of New Data (metrics require data that CVM does not currently capture to report on).

**Table 6**. Additional metric recommendations.

| Metric | Definition | Benefits | Data Current State |
|---|---|---|---|
| **Overdue and Ahead of Schedule Submissions** | Percentage of submissions that are returned to Industry overdue or ahead of the scheduled due date, and the average number days overdue or ahead of schedule, respectively | • Reinforces the consistency of CVM review times<br>• Aligns with existing ADUFA goal of having over 90% of submissions returned on time | **Readily Available** |

| Metric | Definition | Benefits | Data Current State |
|---|---|---|---|
| **Application Complexity Score** | Score, developed by CVM, to determine the complexity of a review (**See Recommendation 4.2 and 6.1**) | • Addresses an existing gap: CVM currently has no metrics or criteria related to application complexity (or other appropriate proxies)<br>• Application complexity likely has a meaningful on impact review timelines<br>• Complexity scores could allow for more fair comparisons between applications<br>• Could assist with reviewer workload planning | **Requires Creation of New Data** |
| **Technical Section TTC** | Number of days from the beginning of a technical section until technical section complete | • TTC comparisons at the technical section level are more equivalent than at the application level[23]<br>• Identifies the rate limiting technical sections to application approval | **Data Exists, Requires Significant Manual Calculation** |
| **TII/TIA Distributions** | Percentage, and days, of the technical section TTC that is attributed to Industry (i.e., TII) and to CVM (i.e., TIA) | • Provides a more complete understanding of the path a drug takes to approval<br>• Provides an opportunity for a metric to discuss individual applications and/or technical sections with Industry at lessons learned meetings to improve the review process<br>• Fulfills a request of Industry for these specific metrics | **Requires Creation of New Data:** Submission relationships |

23. For example, some applications may pursue technical sections simultaneously, while others may focus on each technical section individually. Comparing TTC at the technical section level removes bias related to technical section timing.

| Metric | Definition | Benefits | Data Current State |
|---|---|---|---|
| **Industry Resubmission Time** | The time between the final action date of an unsuccessful submission and the received date of the revised version of that same submission | • Captures the most variable part of the review process: response time to unsuccessful submissions (review times are mostly static)<br>• Quantifies how long it takes Industry to respond to reviewer comments<br>• Quantifies the impact of multiple review cycles (e.g. how much time an unsuccessful submission adds to a review) | **Requires Creation of New Data:** Submission relationships |
| **Breakdown of CVM Review Window** | Separates out the time allocated to submission reviews into component pieces such as:<br>• Average number of days from submission receipt until review begins<br>• Average number of days and/or hours of active review time<br>• Average hours attributed to submission review by role (e.g., primary review, consulting review, Team Leader) | • Requested by Industry in interviews<br>• Allows CVM to better understand potential bottlenecks and identify inefficiencies within the review window<br>• Increase transparency between CVM and Industry, if reported out | **Data Exists, Requires Significant Manual Calculation** |

# 10.0 Review and Improve Upon Previous Program Enhancements

This assessment aims to evaluate the utilization and effectiveness of user fee enhancements introduced between ADUFA II and ADUFA IV. While the sample of applications offered limited insight into some of these enhancements, process documentation and interviews with CVM reviewers and Industry sponsors provided valuable perspectives into the effectiveness of each of them. The table below outlines key findings for major enhancements and recommendations for their continuation and potential improvements.

**Table 7.** Key findings and recommendations for past user fee-funded enhancements.

| Enhancement | Findings | Recommendation |
|---|---|---|
| **End-Review Amendments (ERAs)** | • ERAs allowed CVM to increase the number of single-cycle reviews during ADUFA II by 75.4%<br>• Both CVM and Industry appreciate the ability to close out a submission with an ERA to avoid a second full review<br>• The tight timeline was the most challenging aspect for both sides | • **Reinstate and modify** the ERA process for minor adjustments towards the end of the review clock<br>• **Leverage best practices and tools** from the ERA process to inform the upcoming clock-stop pilot |
| **Shortened Review Timeframes (SRT) for Protocols and Data Submissions** | • SRTs effectively reduced review times for resubmissions of technical sections, with Industry's median resubmission time reduced by 62% and CVM's median review time reduced by 65.2%<br>• Sponsors appreciate the 120-day response window, compared to the 8 and 31-day average for ERA submissions for E and P submissions, respectively<br>• SRT was only offered for 28% of incomplete data submissions[24] | • **Evaluate and adjust** the SRT process to address the discrepancy in adoption rates across submission types<br>• **Standardize SRT criteria** to ensure consistent application<br>• **Leverage best practices and tools** from the SRT process to inform the upcoming clock-stop pilot |

24. In the context of this analysis, incomplete data submissions received a final action of TS INC NOT.

| Enhancement | Findings | Recommendation |
|---|---|---|
| **Two-Phased CMC Technical Section** | • There was misalignment in expectations, with only 25% of sponsors receiving a favorable review for their Phase I CMC submissions<br>• CVM's systems lack tracking functionality for phased submissions, making it difficult to evaluate the effectiveness of this enhancement | • **Improve tracking and data collection** for two-phase CMC submissions<br>• **Clarify guidance** on the two-phase CMC submission process<br>• **Evaluate and adjust** the enhancement for better alignment with sponsor expectations |
| **Early Information (EI)** | • Sponsors hesitate to use this pathway, fearing incomplete data could be held against them<br>• Uncertainty exists regarding what qualifies as early information and its benefits<br>• Only 5.1% of Z submissions and 9.8% of H submissions contained EI since tracking began in 2018 | • **Evaluate and adjust** the expectations and benefits of utilizing the EI pathway<br>• **Pilot** the EI process with a select group of sponsors to identify areas for improvement |
| **ADAA 60-Day Review** | • There was insufficient data on ADAA 60-day reviews to assess its impact on streamlining the review process | • **Evaluate and adjust** the ADAA 60-day review clock to improve adoption and effectiveness |
| **Expanded Conditional Approval (XCA)** | • Industry sponsors praised CVM for supporting the expansion of Conditional Approval beyond MUMS products<br>• Sponsors expressed that the limited scope hinders the introduction of new, innovative animal products | • **Continue** exploring opportunities to offer expanded Conditional Approval<br>• **Explore alternative pathways** for sponsors to qualify for Conditional Approval<br>• **Improve tracking and data collection** for Conditional Approval projects |

| Enhancement | Findings | Recommendation |
|---|---|---|
| **Minor Amendments to Data and Protocol Submissions** | • Amendments offer flexibility within the review process, allowing sponsors to address issues identified during the review clock<br>• Amendment data are not captured sufficiently to evaluate their full impact<br>• CVM received, on average, between 2 and 3 amendments for each E and P submission | • **Continue with modifications** to enhance the flexibility of the amendment process<br>• **Explore root causes** for delays or inconsistencies in amendment requests<br>• **Improve tracking** of amendments |
| **H Submissions Supporting Protocols and Meetings** | • Data do not indicate that H submissions impact the success rate of E and P submissions<br>• Sponsors are unclear on the purpose of H submissions, leading to frustration over the increasing number of submissions requested by reviewers | • **Evaluate** the resource cost and benefit of requesting H submissions prior to meetings or protocols |

# Conclusion

The third-party assessment of the ADUFA program provided valuable insights into the effectiveness of the current NADA review process and the historical improvements made during each reauthorization period. The assessment included detailed analysis of the following:

- **112** interviews with stakeholders, including CVM's review teams, CVM leadership, and Industry drug sponsors
- **1,600+** INAD submissions encompassing nearly 115,000 review hours analyzed across 30 applications
- **14** distinct process and sub-process documentation reviewed and mapped, covering both the Administrative and Non-Administrative review process

From this analysis, key findings were identified across eight categories, each including an overview of the current state of the review process, along with successes and challenges specific to that category. This approach provided a balanced view of the program's effectiveness and areas for improvement.

Throughout the assessment, **126** distinct challenges were documented, including persistent and significant issues affecting the review process, systems, and stakeholders. Using Root Cause Analysis, the underlying causes of these challenges were identified, aiming to uncover the fundamental reasons behind each issue to prevent recurrence. The assessment identified **15** root causes that must be addressed to mitigate the impact of these challenges moving forward.

To address these challenges, **eight** recommendations were developed based on the root cause analysis and persistent issues within the new animal drug review process. These recommendations include **22** unique activities to address the root causes of challenges faced within the animal drug review process. Additionally, **nine** new reporting metrics were proposed, along with suggestions for future iterations of **eight** existing ADUFA program enhancements. By implementing these recommendations and addressing the root causes of current pain points, CVM can streamline approvals, improve relationships with Industry, enhance communication practices, and reduce the burden of reporting meaningful performance metrics.

# Appendix

## Appendix I: Acronyms

**Table 8**. List of acronyms used throughout this assessment and their definitions.

| Acronym | Term |
|---|---|
| **ADAA** | Animal Drug Availability Act of 1996 |
| **ADUFA** | Animal Drug User Fee Act of 2003 (and subsequent reauthorizations) |
| **AHI** | Animal Health Institute |
| **ATR** | Activity Time Reporting |
| **AVIA** | Animal and Veterinary Innovation Agenda |
| **BPM** | Business Process Management |
| **CDER** | Center for Drug Evaluation and Research |
| **CDISC** | Clinical Data Interchange Standards Consortium |
| **CDMS** | Corporate Document Management System |
| **CDP** | Corporate Database Portal |
| **CMC** | Chemistry, Manufacturing, and Controls [Technical Section] |
| **CPE** | Continued Professional Education |
| **CSO** | Consumer Safety Officer |
| **CVM** | Center for Veterinary Medicine |
| **DBISM** | Division of Business Information Science and Management |
| **DCAD** | Division of Companion Animal Drugs |
| **DGAD** | Division of Generic Animal Drugs |
| **DDP** | Drug Development Projects |
| **DFAD** | Division of Food Animal Drugs |
| **DHFS** | Division of Human Food Safety |
| **DMT** | Division of Manufacturing Technologies |
| **DSS** | Division of Scientific Support |
| **EI** | Early Information |

| Acronym | Term |
|---|---|
| **EFF** | Effectiveness [Technical Section] |
| **ENV** | Environmental Impact [Technical Section] |
| **ERA** | End-Review Amendment |
| **ESG** | Electronic Submission Gateway |
| **ESS** | Electronic Submission System |
| **FAQ** | Frequently Asked Question |
| **FDA** | Food and Drug Administration |
| **FOIA** | Freedom of Information Act |
| **FTE** | Full-Time Equivalent |
| **GFI** | Guidance for Industry |
| **GMP** | Good Manufacturing Practice |
| **HFS** | Human Food Safety [Technical Section] |
| **INAD** | Investigational New Animal Drug |
| **IO** | Improvement Opportunity |
| **LVA** | Low-Value Add |
| **MOC** | Memorandum of Conference |
| **MRA** | Mutual Recognition Agreement |
| **MUMS** | Minor Use and Minor Species Act of 2004 |
| **NIGO** | Not in Good Order |
| **OMUMS** | Office of Minor Use and Minor Species Animal Drug Development |
| **NADA** | New Animal Drug Application |
| **NCE** | New Chemical Entity |
| **P&P** | Policy and Procedure |
| **PAI** | Pre-Approval Inspection |
| **PM** | Project Manager |
| **PRA** | Paperwork Reduction Act |
| **PSC** | Presubmission Conference |
| **QASR** | Quality Assurance Study Reviewer |
| **RCA** | Root Cause Analysis |
| **RTF** | Refuse-to-File |
| **RTR** | Refuse-to-Review |
| **SME** | Subject Matter Expert |
| **SCC** | Submission Class Code |
| **SOP** | Standard Operating Procedures |
| **SRT** | Shortened Review Timeframe |

| Acronym | Term |
|---|---|
| **STC** | Submission Type Code |
| **STARS** | Submission Tracking and Reporting System |
| **TAS** | Target Animal Safety [Technical Section] |
| **TIA** | Time in Agency |
| **TII** | Time in Industry |
| **TS** | Technical Section |
| **TTC** | Time to Completion |
| **UI** | User Interface |
| **VICH** | Veterinary International Conference on Harmonization |
| **VIP** | Veterinary Innovation Program |
| **XCA** | Expanded Conditional Approval |

**Table 9**. List of submission types used throughout this assessment and their definitions.

| Submission Type | Definition |
|---|---|
| **A** | A submission used to establish an investigational new animal drug (INAD) file |
| **E** | A submission requesting the review of a study protocol (without data) under an INAD |
| **H** | A submission to provide either specific information/data to support a protocol review or general drug development information under an INAD (This submission should not be used to submit data/information in support of a technical section) |
| **M** | A submission that supports the All Other Information or the Labeling technical sections under an INAD |
| **P** | A submission of information/data to support a major technical section under an INAD (e.g., manufacturing, target animal safety, etc.) |
| **X** | A submission that supports the environmental evaluation under an INAD |
| **Z** | A submission to request either a presubmission conference or other ONADE meeting under an INAD |

# Appendix II: Stakeholder Interviews Methodology and Data Collection

## *Approach*

The assessment gathered firsthand perspectives from CVM and Industry through stakeholder interviews. These interviews focused on the submission process, impacts of ADUFA enhancements, review challenges, and overall areas of improvement for the program. Stakeholder interviews were conducted in two rounds:

**Table 10**. Details of the scope, objectives, and outcomes for each round of stakeholder interviews.

| Category | Round 1 Interviews | Round 2 Interviews |
|---|---|---|
| **Scope** | Broad focus on ADUFA program and CVM's general review processes | Focus on the review process of 30 individual applications |
| **Objectives** | Identify challenges, successes, and recommended improvements across the program | Explore application-specific details to understand factors influencing approval |
| **Outcome** | Insights into general program performance and potential areas for improvement | Deeper understanding of submission nuances and factors affecting approval timelines |

Interview guides were developed for both CVM and Industry participants to collect comprehensive feedback on the NADA review process, frequent challenges, and recommended best practices. Separate guides were developed for CVM personnel and Industry stakeholders to address each group's unique perspectives. The interview guides included standardized questions, with specific questions based on the animal drug application type (**Appendix V: Interview Questions**). Below is a representative sample of the discussion topics in the interview guides:

**Table 11**. Representative sample of discussion topics from interview guides, noting the audience (CVM vs. Industry) and topics covered in each interview type.

| Audience | Topics Discussed |
|---|---|
| **CVM**<br>Food, Non-Food, and Conditional Approval | 1. Demographic information about interviewees' roles to better understand their contribution in reviewing applications<br>2. Challenges and successes with the ADUFA program, including technical sections and process complexity<br>3. Impact of user fee-funded process enhancements on specific applications and the ADUFA program<br>4. Inter-office and Industry interactions to identify operational gaps, collaboration efforts, and resource capacity within CVM<br>5. The role of IT systems in supporting CVM's review processes, as well as system limitations or user challenges |

| Audience | Topics Discussed |
|---|---|
| **Industry**<br>Food, Non-Food, and Conditional Approval | 1. Challenges in the ADUFA program, including specific issues within the selected application, to address stakeholder pain points<br>2. Industry's perspective on past ADUFA program enhancements and recommendations for future improvements<br>3. Desired metrics for improved visibility into the performance of the NADA review process<br>4. Challenges within the review process to identify approval delays, multi-cycle reviews, and the root causes behind these setbacks<br>5. Interaction and communication with CVM personnel to understand the quality of communication between CVM and Industry<br>6. The role of IT to understand Industry feedback on the IT systems and tools used for submissions, reviews, and communication |

To enhance the interview process and subsequent data analysis, the assessment included several preparatory and analytical steps:

1. **Development of Application Summary Profiles:** Application summary profiles (Figure 30) were created as a quick-access resource for interviewers ahead of the discussions. The application profiles include an overview, as well as details on the usage of ADUFA program enhancements, the application type, technical section TTC, the number of amendments and consults, and investigational submission information. This approach streamlined the interviews and provided a common foundation for both CVM personnel and Industry sponsors and were referenced during interviews as needed.

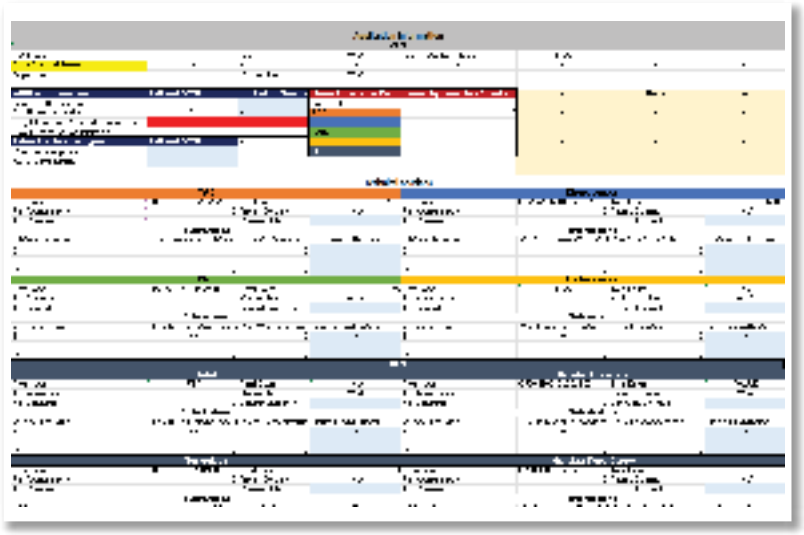


**Figure 30**. Screenshot of an application summary profile.

2. **Data Processing and Anonymization:** After collecting responses, the interview data were anonymized to ensure privacy and confidentiality. Each response was anonymized, removing identifying information to focus purely on the perspectives offered.
3. **Thematic and Sentiment Analysis:** With the data organized into themes, both thematic and sentiment analyses were conducted. The thematic analysis highlighted recurring topics and key areas of interest, offering insight into key themes across the interviews. The sentiment analysis gauged the tone of responses, identifying sentiments that participants associated with specific themes. Natural Language Processing was used to conduct the initial grouping of responses based on common themes. These were validated by interviewers to ensure accuracy.

# Data Collection

In total, 78 interviews were conducted with CVM staff members engaged in reviewing the 30 selected applications. The interviews were split across two rounds:

» **Round 1** included 8 interviews, with a total of 14 personnel
» **Round 2** included 70 interviews, with a total of 84 personnel

A breakdown by CVM division is provided in Figure 31 below, illustrating the distribution of interviews across different operational groups within CVM. In this graph, roles were classified based on staff titles: individuals with supervisory titles were categorized as Supervisory, those with director-level titles as Leadership, and all other employees were classified as Staff.

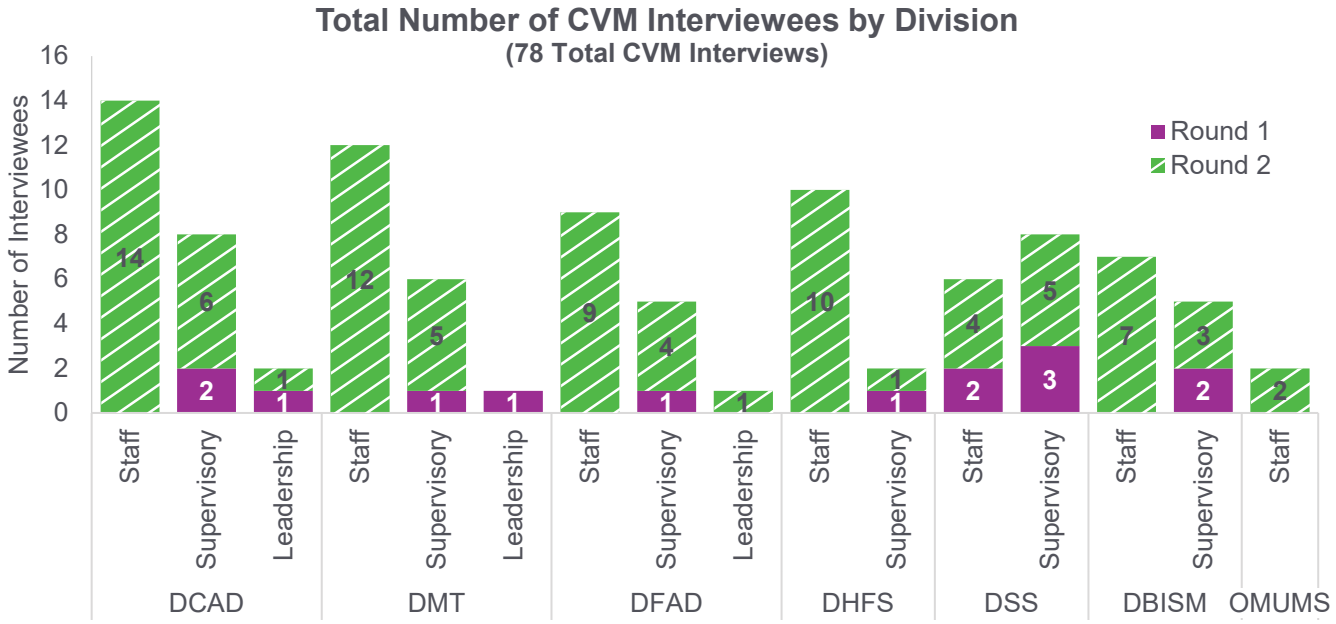



**Figure 31**. Total number of CVM interviewees by division and role. Staff who participated in both rounds of interviews were included in the counts for each round they participated in. See Appendix I: Acronyms for full division names.

Interviews were also held with Industry sponsors who submitted applications within the selected sample, covering 17 unique sponsors across 34 interviews (Figure 32):

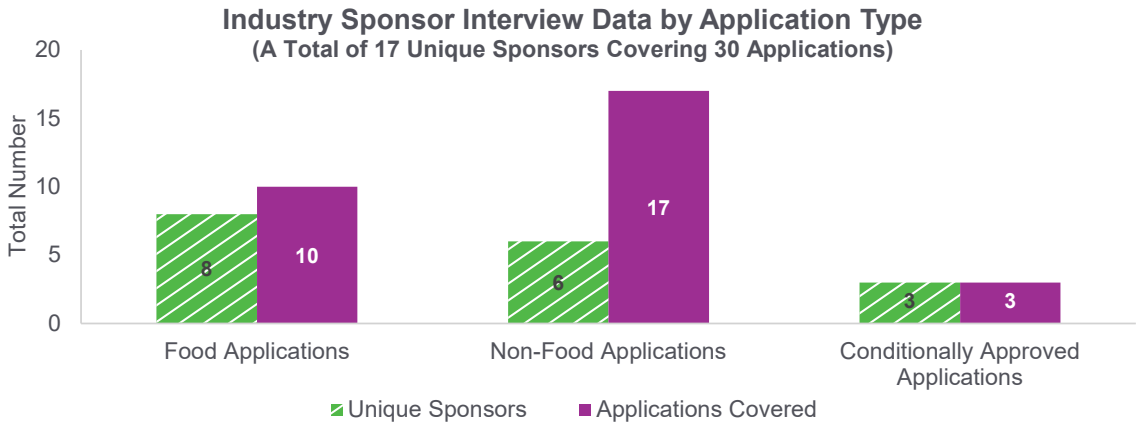



**Figure 32**. The unique sponsors and applications covered during, providing a clear view of sponsor involvement across interview rounds.

- **Round 1** included 16 interviews across the three categories of applications (i.e., Food, Non-Food, Conditional Approval)
- **Round 2** included 18 interviews, with one sponsor requiring three separate interviews to fully address different applications

The following breakdown of Industry demographics showcases the diverse range of sponsors included in the assessment (Figure 33). By including a variety of sponsors with different application histories and affiliations, the assessment reflects a range of perspectives and experiences.

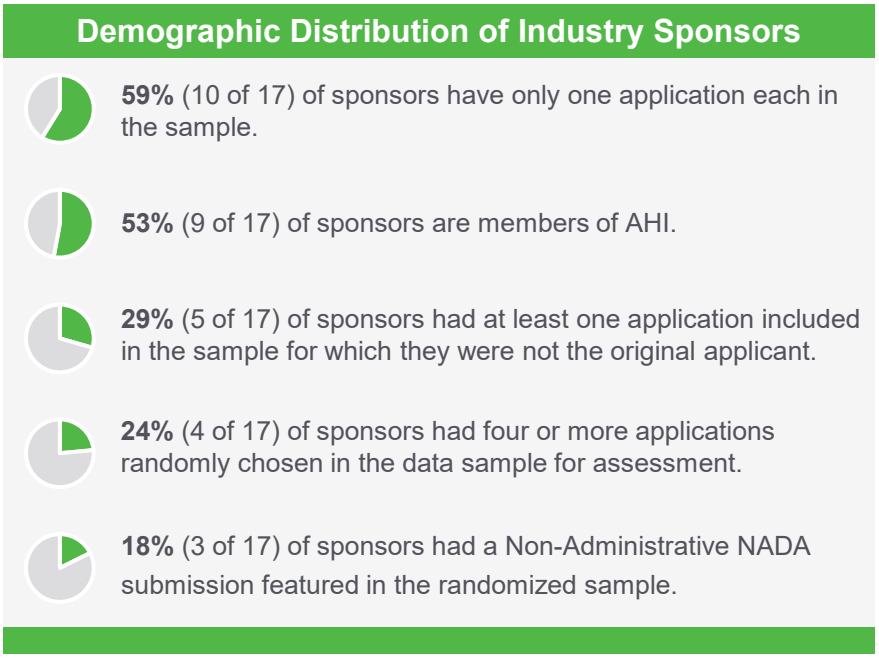



**Figure 33**. Additional breakdown of the demographics of sponsors that participated in interviews for the ADUFA V Assessment.

# Appendix III: CVM Systems Records Methodology and Data Collection

## *Approach*

An analysis of CVM's internal systems was conducted to evaluate submission processes, application timelines, and resource allocation for the 30 selected NADAs and their associated INAD submissions. Data were sourced from several key internal systems, including STARS, ATR, and Microsoft Project Plans. Together, these data provide details about submission timelines, application progression, and sponsor-specific actions, offering a complete view of how the NADAs and their major technical sections were managed. Additional key information such as submission codes, timelines, final action outcomes, and reviewer information were extracted and merged into a centralized database to serve as a master dataset. This dataset integrated unique data fields from CVM's internal systems, creating a more comprehensive and accurate administrative record of the end-to-end submission lifecycle. The coding of custom fields, explained further below, were also included in the master dataset. By eliminating data silos, created by disparate systems, this centralized dataset enabled the identification of patterns and inefficiencies that may have been overlooked in isolation.

## *Establishing Submission Data Linkages*

After consolidating submission data into a master dataset, data linkages were formed across systems to create a comprehensive view of the application. Since CVM's internal systems do not consistently record relationships between submissions, the assessment established a methodology to generate these connections. For each of the 30 NADAs, submission data linkages were created to follow chains of submissions within each major technical section, offering a clearer view into how protocols, data studies, and other supporting submissions relate to one another. The linkages include details on the total time spent in Industry and Agency, the number of associated submission review cycles, and the number of submission branches – a term defined as one or more submissions within a technical section that share a common purpose, such as study type or design, and a STC (Figure 34).

**Solution Construct**

INAD ➡ Technical Section
- Submission 1, Submission 2 ➡ Branch 1
- Submission 3 ➡ Branch 2 (Single-Cycle)

| Submission # | STARS Received Date | Final Action Date | Final Action Code | Predecessor ID | Branch |
|---|---|---|---|---|---|
| E-0001 | 7/6/2011 | 8/23/2011 | PROT NCONC | | Branch 1 |
| E-0002 | 5/26/2012 | 7/14/2012 | PROT CONC | E-0001 | Branch 1 |
| P-0003 | 8/31/2013 | 2/27/2014 | TS COMPLETE | | Branch 2 |

**Figure 34**. Example of a data linkage profile for one technical section.

Review cycles were identified by tracking submission sequences within each technical section, focusing on submissions received and final action dates to establish submission start and endpoints. For submissions that deviated from the routine technical section completion pathway (i.e., did not end in technical section completion), alternative endpoints were determined by examining CVM actions, sponsor responses, or review letters to identify appropriate conclusion points for each cycle. These cycles included multiple iterations where rework, additional data requests, or clarifications were required. This additional layer of data enabled a more accurate analysis of review cycles, capturing the progression and dependencies between submissions. Key data inputs for the submission linkages include:

- Submission Received Date
- Submission Final Action Date
- Predecessor Sequencing (manually coded to ensure sequential accuracy)
- E and P submission Alignment (manually coded for clarity in submissions)

The branch structure helped frame how individual submissions contributed to broader objectives and brought attention to inefficiencies, like overlapping submissions or extended resubmission timelines that slowed progress (Figure 35).

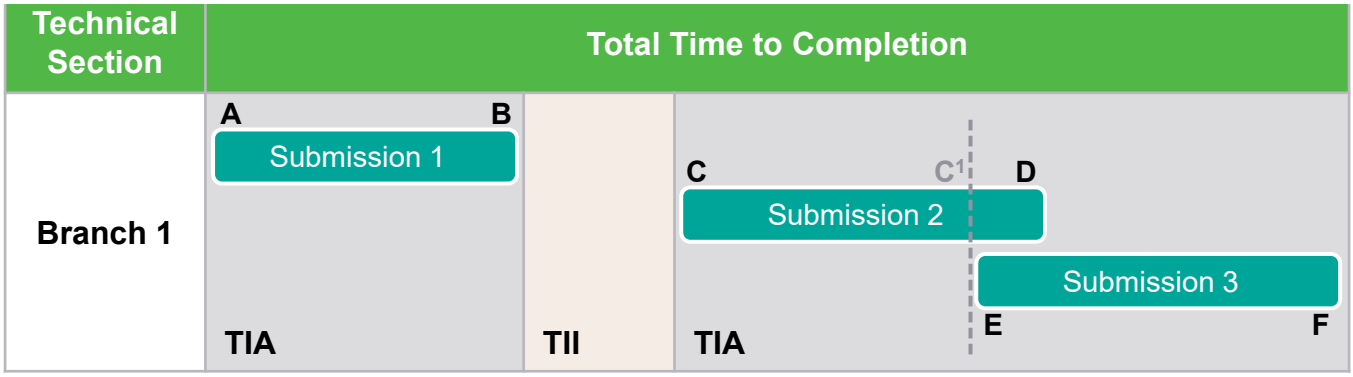



**Figure 35**. Example of multiple submissions within a branch, developed using manually established data linkages, with some overlapping submissions and TTC broken out into TIA and TII.

Ultimately, these linkages formed the backbone of the application and submission data analysis, connecting the dots between individual submissions to provide a complete and cohesive view of how CVM and Industry collaborate to advance drug approvals.

## *Key Components Analysis*

Each application was examined to assess factors influencing key components of the drug review process, including:

- **Application and Submission Timeliness**: Timelines for each submission and its associated review stage were analyzed to pinpoint delays. Factors such as sponsor readiness, submission quality, and response times from both CVM and sponsors were evaluated to identify trends in timeliness or bottlenecks.
- **First-Cycle Favorable Outcomes:** Success rates for achieving a first-cycle technical section complete were assessed to uncover common characteristics among favorably reviewed submissions.

- **Level of Rework:** Instances of rework were examined to determine the frequency and reasons for resubmissions or revisions. Rework often stemmed from incomplete submissions, unclear responses to reviewer comments, or misinterpretation of regulatory requirements. These insights highlighted areas for improving submission quality and clarity to minimize repeated reviews.
- **Enhancement Utilization and Impact**: Utilization of program enhancements and improvements, such as PSCs, H submissions, and minor amendments were analyzed with a focus on timing and intent to assess their impact on submission outcomes and timelines.

## *Data Collection*

Quantitative data were collected from multiple internal systems to capture empirical trends in INAD and NADA submissions, utilization rates of ADUFA enhancements, and allocation of CVM resources. The scope of data collection includes:

- **STARS Submissions:** Submission records were extracted from STARS, including over 1,600 submissions associated with the 30 randomly selected NADAs
- **Project Plans:** Data from 30 project plans were collected, providing detailed timelines and milestones for submissions
- **ATR Records:** The assessment evaluated time and attendance data from the past 20 years. For the 30 randomly selected NADAs, this included reviewing records covering time spent against 1,000+ submissions encompassing nearly 115,000 hours by 300+ personnel. Notably, the reported hours only reflect review-related activities and do not account for broader administrative or operational efforts, underscoring the intensive focus on submission evaluation
- **Corporate Document Management System (CDMS) Documentation:** Relevant documentation in CDMS offered additional contextual details regarding submission content, correspondence, and feedback

Within each of these systems, the following data fields were collected, contributing to the overall analysis and to creating linkages between data (Figure 36):

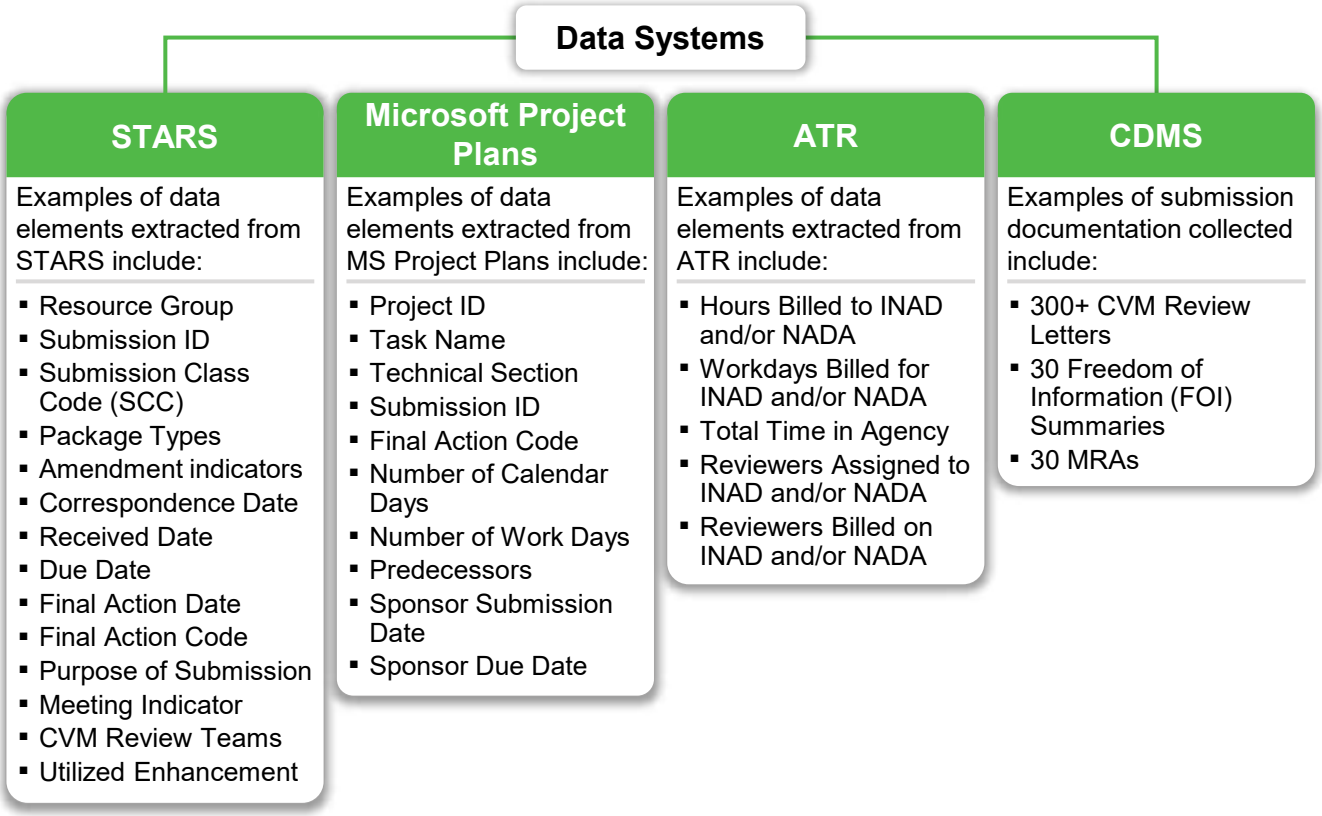



**Figure 36**. Representative list of the systems used to collect quantitative data, including example data elements extracted from each.

# Appendix IV: Process Documentation Methodology and Data Collection

## *Approach*

To support the data collection and mapping of CVM's current review processes, a thorough review of key documents was conducted. To gain a holistic view into each of the 30 sample applications, over 300 documents related to these submissions were gathered and reviewed. These included:

- **300+ CVM Review Letters:** Correspondence outlining feedback and required actions, providing context on common review issues and expectations
- **30 FOIA Summaries:** Summaries available to the public, highlighting the regulatory decisions made for each application
- **30 Major Review Actions:** Key documents summarizing major decisions and actions taken during the review process

In addition to submission-specific documents, a variety of process-related materials were collected to aid in the development of process maps, detailed below in Table 12.

**Table 12.** Description of the process-related materials gathered to support the development of comprehensive process maps.

| Process Documents Reviewed |
|---|
| **80 P&Ps:** Essential guidelines detailing the regulatory framework and operational standards within CVM, setting the foundational expectations for each review process |
| **58 SOPs:** Step-by-step instructions outlining the specific tasks and workflows required during application reviews, ensuring consistency across teams |
| **30 project plans:** Detailed timelines and task sequences from the 30 selected projects, providing insights into expected review durations and resource allocations |
| **15 policy documents:** Regulatory documents clarifying broader CVM policies that influence review decisions, especially for unique or complex cases |
| **14 miscellaneous reference documents:** Various additional procedural guidelines and reference materials for regulatory review, approval, and post-approval processes of animal drug submissions |
| **13 scientific reference documents:** Guidance materials created to supplement SOPs by providing additional context and specific technical guidance to ensure consistent evaluations |
| **11 previous CVM process maps:** Historical process maps that served as a reference point for understanding previous workflows and identifying areas for updates in the current state maps |

Details from these process documents were used to develop 14 end-to-end process maps that illustrate major review activities, roles, information flows, pain points, and areas for improvement in the process. Each process map details individual investigational submission review processes and sub-processes within the phased new animal drug review. These outline the entire review workflow, highlighting the intended sequence of activities and the documented order of operations

within each review stage. Additionally, they capture critical steps within the INAD and NADA processes, highlighting key responsibilities, information handoffs, supporting tools and systems, and additional attributes associated with each review activity. An example of these process maps is shown below in Figure 37.

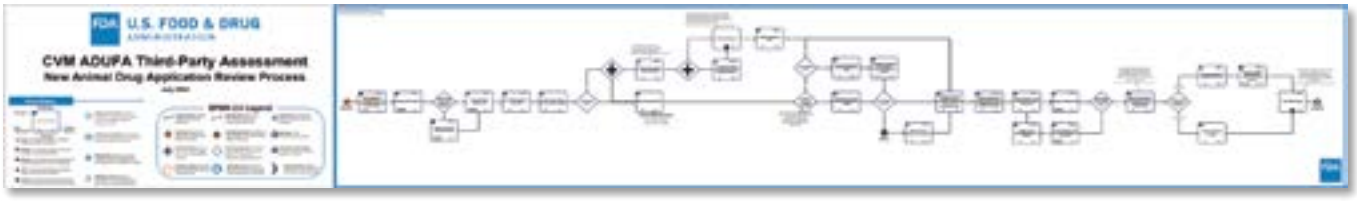



**Figure 37**. Visual sample of the process maps developed as part of this assessment.

After developing the process maps, they were converted into data points to provide quantifiable insights into process design and outputs. The activities in these process maps were further analyzed by submission type, activity type, IT system use, and other combinations of activity-level data. This approach allowed for a granular look at how different elements interact, where activities might experience delays, and how IT systems are integrated across the workflow.

Twenty validation sessions were held with CVM process SMEs to confirm that the process maps provided a true reflection of current procedures, activities, and operations within their specific areas of the review process. These sessions involved reviewing the maps in detail, identifying gaps, and addressing challenges. Key activities included walkthroughs of the process maps, SME review of the maps, and discussions on bottlenecks and known process challenges. Figure 38 below provides a breakdown of the total number of CVM validation sessions interviewees by division, categorized into staff and supervisory roles. This collaborative validation approach reinforced the reliability of the process maps as tools for understanding and improving the review process. Once revisions were made based on this input, the updated maps were shared with SMEs for further validation.

The questions during the validation sessions focused on ensuring the accuracy and completeness of the maps, identifying missing steps or outreach points, uncovering pain points or delays, and highlighting areas with frequent handoffs and/or touchpoints. Additionally, the questions explored whether certain steps were duplicative, unnecessary, or candidates for automation, and identified where additional instructions or templates could improve clarity and efficiency.

The result is a comprehensive set of process maps and detailed documentation that provide a transparent view of the review process for INAD and NADA submissions. These tools are instrumental in identifying areas for process improvement, enhancing workflow efficiency, and supporting informed decision-making within CVM's review process.

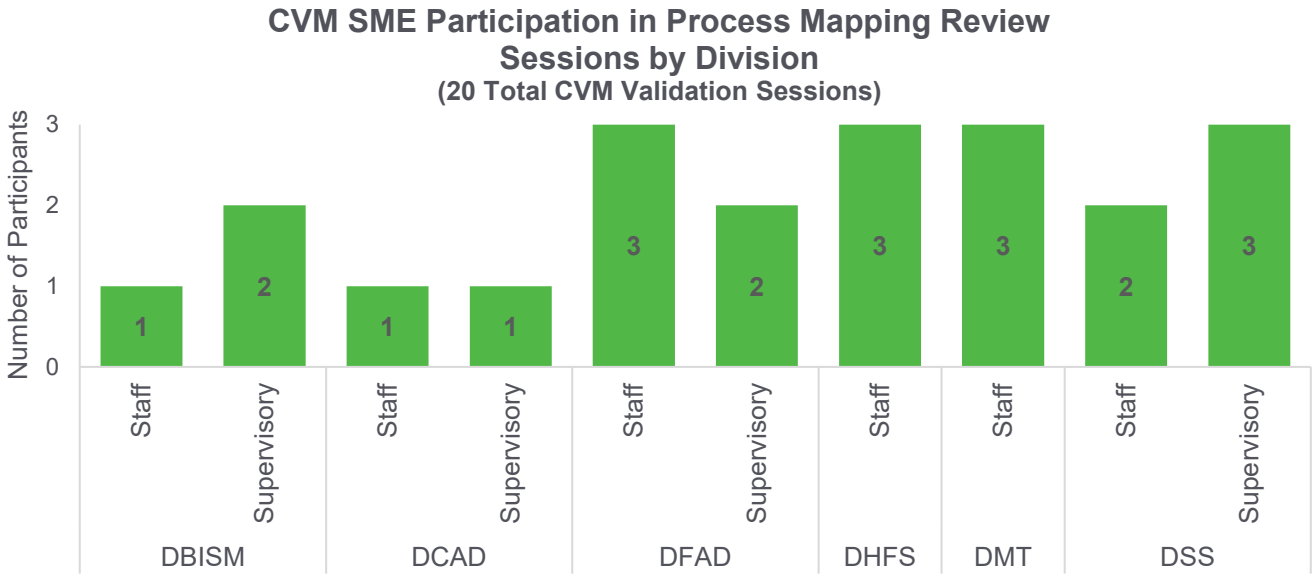



**Figure 38**. Twenty-one SMEs across CVM were engaged to validate all 14 current state process maps. See Appendix I: Acronyms for full division names.

# Appendix V: Interview Questions

This appendix includes the lists of interview questions utilized to inform the assessment. The questions are organized by round and audience type to facilitate understanding and reference.

### CVM Interview Questions – Round 1

1. How many years have you been working with the FDA? Working with the ADUFA program / animal drug review process?
2. What are your responsibilities as part of the ADUFA program / animal drug review process?
3. From your perspective, what are the top 1-3 biggest challenges, ranked in order, with the ADUFA program / animal drug review process internally?
4. From your perspective, what are the top 1-3 biggest challenges, ranked in order, with the ADUFA program / animal drug review process externally?
5. What have you seen as the top 1-3 biggest successes with the ADUFA program enhancements from ADUFA II to ADUFA IV?
    - How successful do you feel those enhancements have been?
6. What are the key responsibilities when reviewing the [technical section] portion of the animal drug approval process?
    - What are the challenges involved in this [technical section]?
7. What changes to the review process would you make for reviews to run more efficiently?
8. What are the most common factors that result in delays / take the most amount of time in the animal drug approval process?
9. What are the most common components of a quick and/or efficient application approval process?
10. Does your office/division have any communication challenges?
    - If yes, can you please describe?
11. How often does your office/division need to communicate with other offices/divisions either within or outside of CVM?
    - What challenges exist when cross-office/division communication is necessary?
    - How are review consultations different with staff within CVM compared to outside CVM consultations?
    - How can cross-office collaboration be improved?
12. Does your office/division personnel have the necessary resources to perform their duties?
    - Do you believe you have adequate staff, training, operational support, and/or technology to meet demand from of responsibility requirements? If not, where/what resources are needed?
13. Do you feel that your office/division has enough time/resources to successfully complete assigned reviews?
14. How does your office/division leverage technology to perform its work?
    - What IT systems does your office/division primarily use?
    - Are there any systems unique to your office/division that you rely on?
15. Are there any known challenges or user complaints with the IT systems and tools used in your office/division?

## CVM Interview Questions – Round 2

1. Can you provide a high-level walkthrough of the investigational drug submissions and approval process for the [Insert Technical Section(s)] of this drug? Our goal is to understand how the submissions within each technical section are related to one another.
    - What level of complexity was this drug application compared to the average submission?
    - Were there any general or technical section-specific presubmission conferences as a part of this application?
2. As identified under the "Submissions" section of the "Technical Sections" portion of the summary profile for this application, there were some unsuccessful submissions returned to the sponsor.
    - Were there any unsuccessful submissions that resulted in delays to the approval process?
    - Can you comment on what caused these submissions to be unsuccessful?
    - Were there any other major challenges that delayed approval? If so, what were those challenges?

      ***(Note: During these CVM Round 2 interviews, the following additional questions were posed if there were technical sections with zero unsuccessful E or P submissions.)***
    - If there are multiple E or P submissions for a technical section and none are unsuccessful, what is the relationship between the multiple "successful" submissions?
    - Given that there are no "unsuccessful" submissions listed in the profile, can you confirm that there was a single-cycle review for this technical section?
    - If yes, was there anything about this technical section that helped facilitate a single-cycle review?
3. As identified within the "Technical Sections" portion of the summary profile for this application, the sponsor submitted amendments to supplement some of their previous submission(s).
    - Can you comment on any major amendments that were submitted during the application process?
        - What additional data did CVM request?
    - Were there any amendments that impacted the approval timeframe? For example, did any amendments "stop or reset the clock" for any submissions?
4. Based on our analysis of the investigational submissions, we identified ADUFA process enhancements utilized during this application in the "ADUFA Enhancement" portion of the summary profile.
    - From your perspective, how did these enhancements affect the submission and review process?
    - Were there any early information submissions provided by the sponsor as part of this application?
    - ***(CMC technical section interview question):*** Did this application utilize a two-phased CMC technical section approach?
    - Were any of the other enhancements included in the "List of Enhancements" (PDF sent in advance) utilized during this application?
    - Moving forward, would you recommend FDA continue with these enhancements as part of the new animal drug review process?
5. What was the biggest challenge in the review process for this application and the associated investigational submissions?
6. Please describe your interactions with the sponsor during the investigation submissions and application review process.
    - Had you worked with the sponsor before? If so, was it new people or people with which you had existing relationships?
    - Are there any areas where communication with the sponsor could have been improved?

- Did the sponsor follow guidance and/or do anything out of the ordinary that hindered the review process?

### Industry Interview Questions – Round 1

1. What do you see as the top 1-3 biggest challenges with the ADUFA program / animal drug review process?
2. The application(s) from your company that was randomly selected (which we will discuss in more detail during a second-round interview) was/were a Food / Non-Food / Non-Food Conditional Approval[25] application. Were there any particular components of the process specific to your Food / Non-Food / Non-Food Conditional Approval application that made approval more or less difficult?
3. Referring to the list of ADUFA enhancements sent prior to this interview, what would you say have been the top 1-3 most beneficial enhancements made to the ADUFA program / animal drug review process from ADUFA II to ADUFA IV?
    - Can you describe how they have been beneficial?
    - Are there other improvements outside of those required by ADUFA renegotiations that you've noticed, which have also been beneficial?
4. What are the top 1-3 changes or improvements you think would be the most beneficial for the ADUFA program and review process?
    - If you could only fix one thing about the ADUFA program and the animal drug review process, without restrictions or limitations, what would it be?
5. Are there any metrics associated with the animal drug approval process that you would like captured to improve transparency into the review process?
6. Do you find the information and guidance provided by FDA to be clear regarding requirements and expectations for Industry to have a smooth and successful review and approval; to prevent initial rejection due to missing or incomplete data; to prevent re-submissions and amendments; and to prevent final denial of applications?
    - Is there one of these areas for which additional information and guidance from the FDA would be beneficial to Industry?
7. How would you describe the level of communication between your company and CVM throughout the animal drug investigational process and the approval process?
    - Are there any improvements that you would like made to the level or method of communication?
8. Are there any known challenges or user complaints with the IT systems and tools used within the new animal drug submission/review process?
    - What improvements would you make to the technology systems currently in place?

### Industry Interview Questions – Round 2

1. Can you walk through an overview of the drug investigational submissions and application for your randomly selected drug(s)?
    - What level of complexity was the drug application(s) compared to the average submission?
    - Did this drug application(s) originate from your current company?
2. Can you please comment, from your experience, on the cause for any delays in approval and any submissions that required multiple review cycles?
    - Were there any other major challenges that delayed approval? If so, what were those

25. The interview question was tailored to align with the specific application type being discussed during the interview.

challenges?

3. Based on our analysis of your investigational submissions, the review process incorporated the following ADUFA enhancement(s): [insert process enhancement(s) from analysis].From your perspective, how did the enhancement(s) affect the submission and review process?
    - Moving forward, would you recommend FDA continue with these enhancements as part of the new animal drug review process?
4. **(Food application interview question)** Can you please speak to the environmental impact and Human Food Safety sections (toxicology, residue chemistry, and microbial food safety if applicable) of your application?
    - How did the approval process go?
    - Were there any challenges associated with getting those sections approved?
5. **(Non-Food Conditional Approval application interview question)** Can you please speak to the Conditional Approval process and how that impacted your application?
    - Was it challenging to provide a reasonable expectation of effectiveness and seek approval every year for 5 years?
6. What was the biggest challenge in the review process for this application and the associated investigational submissions?
7. Did you find the information and guidance provided by CVM to be clear regarding the requirements and expectations from you to have a smooth and successful review and approval of the investigational submissions and application?
    - Were there points in this process that were challenging because it was unclear how to proceed?
8. Please describe your interactions with FDA personnel during the investigation submissions and application review process.
    - Are there any areas that could have been improved in those communications?

# Appendix VI: Time in Agency vs. Time in Industry Case Studies

As part of the ADUFA V commitment letter, CVM and Industry agreed to explore metrics regarding how review time of investigational submissions is distributed between TIA (i.e., time spent reviewing submissions) and TII (i.e., time spent developing submissions and responding to Agency feedback). During the assessment, case studies were developed to explore the application of the TIA/TII metrics for four Effectiveness technical section examples from Non-Food Animal applications.

The four case studies (Figures 39, 40, 41, and 42) include a visual depiction of the TIA vs. TII plotted on a normalized time scale[26] and a summary table including the TTC, TIA, and TII in days, along with the percentage split of TIA and TII. Relationships between submissions were manually identified for submissions within each technical section that were thematically related to one another (e.g., original unfavorable submissions and revised submissions responding to incomplete or non-concur letters). Additionally, TIA was calculated using the distinct count of days that a submission(s) was being reviewed by CVM to prevent double counting overlapping time when submissions were being reviewed concurrently.

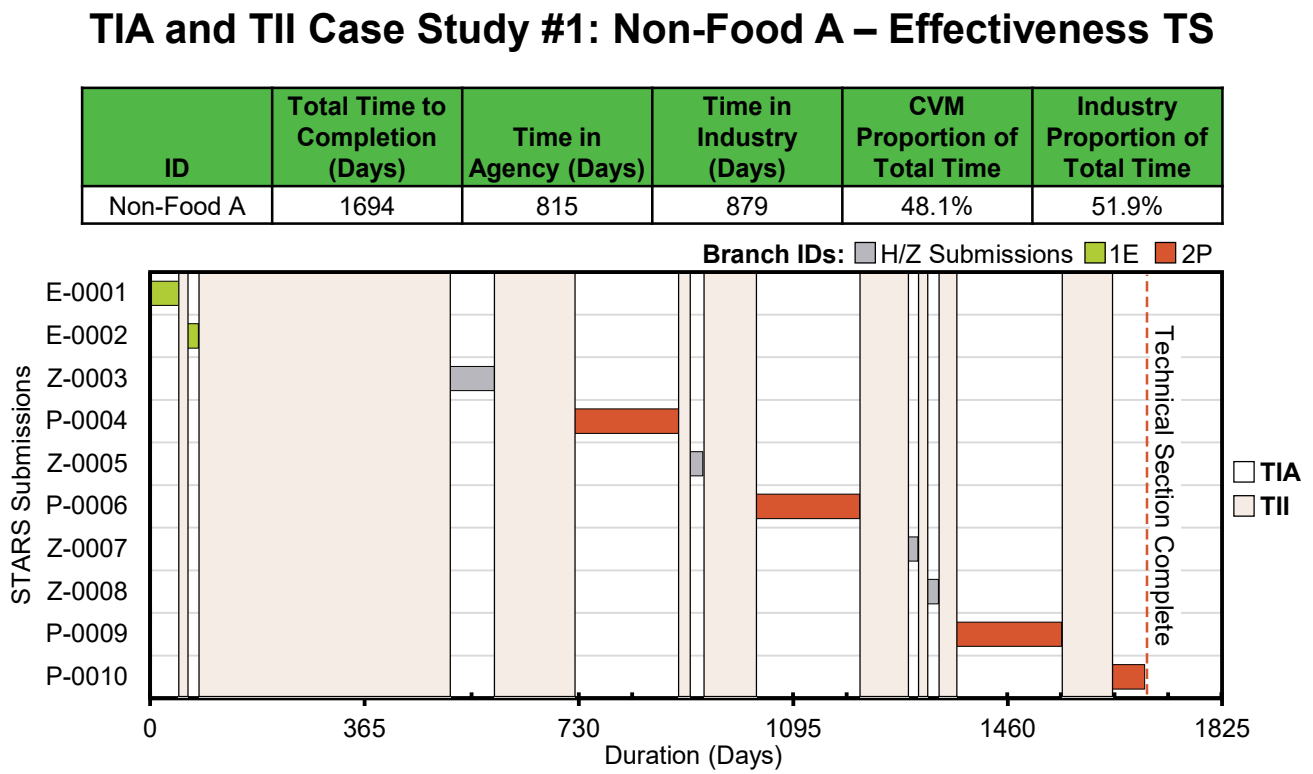



**Figure 39**. TIA vs. TII case study for the effectiveness technical section of Non-Food Application A.

26. The normalized timescale used the receipt date of the first submission as T0 and calculated received and final action dates for successive submissions from that point in time. The scale then plots these events in days from T0, allowing for the analysis of all associated applications, INADs, technical sections, and submissions on the same scale.

## TIA and TII Case Study #2: Non-Food B – Effectiveness TS

| ID | Total Time to Completion (Days) | Time in Agency (Days) | Time in Industry (Days) | CVM Proportion of Total Time | Industry Proportion of Total Time |
|---|---|---|---|---|---|
| Non-Food B | 876 | 447 | 429 | 51.0% | 49.0% |

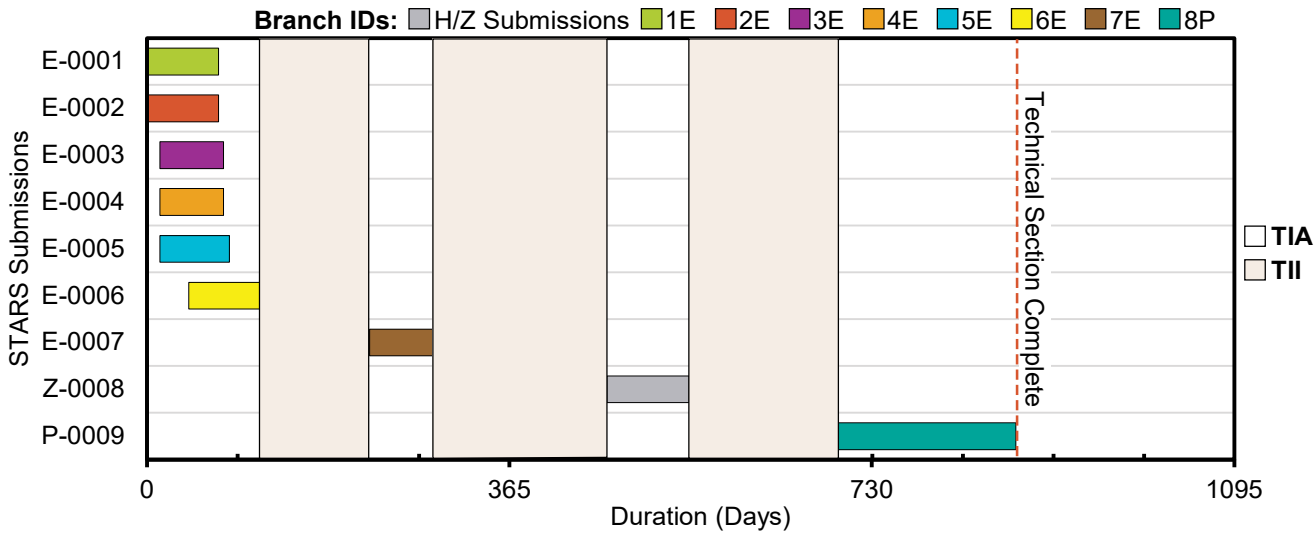



**Figure 40**. TIA vs. TII case study for the effectiveness technical section of Non-Food Application B.

## TIA and TII Case Study #3: Non-Food C – Effectiveness TS

| ID | Total Time to Completion (Days) | Time in Agency (Days) | Time in Industry (Days) | CVM Proportion of Total Time | Industry Proportion of Total Time |
|---|---|---|---|---|---|
| Non-Food C | 1644 | 778 | 866 | 47.3% | 52.7% |

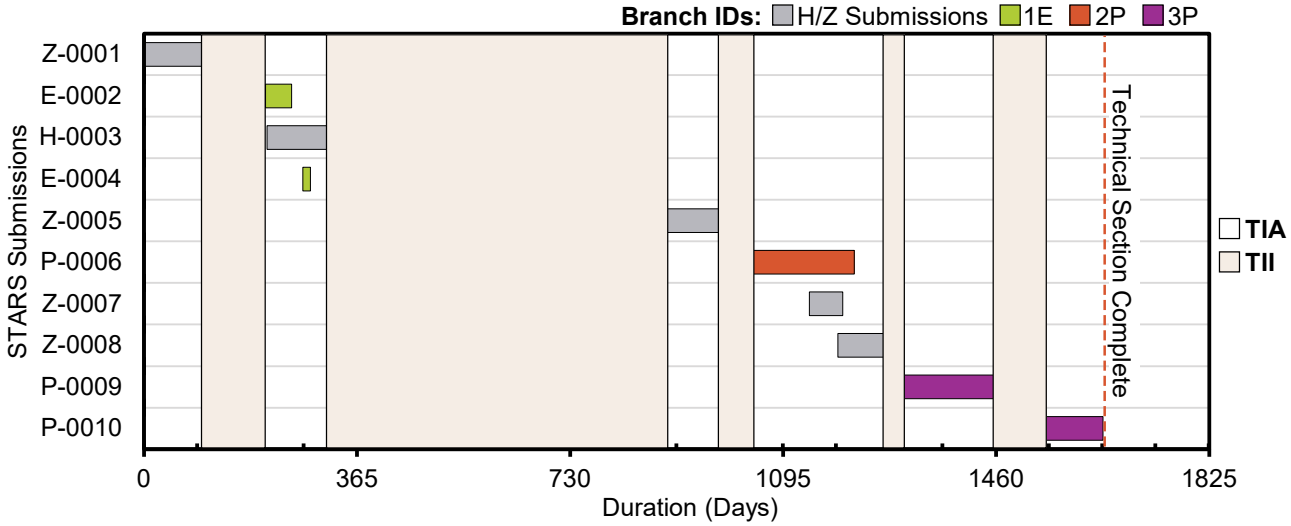



**Figure 41**. TIA vs. TII case study for the effectiveness technical section of Non-Food Application C.

## TIA and TII Case Study #4: Non-Food D – Effectiveness TS

| ID | Total Time to Completion (Days) | Time in Agency (Days) | Time in Industry (Days) | CVM Proportion of Total Time | Industry Proportion of Total Time |
|---|---|---|---|---|---|
| Non-Food D | 3474 | 1452 | 2022 | 41.8% | 58.2% |

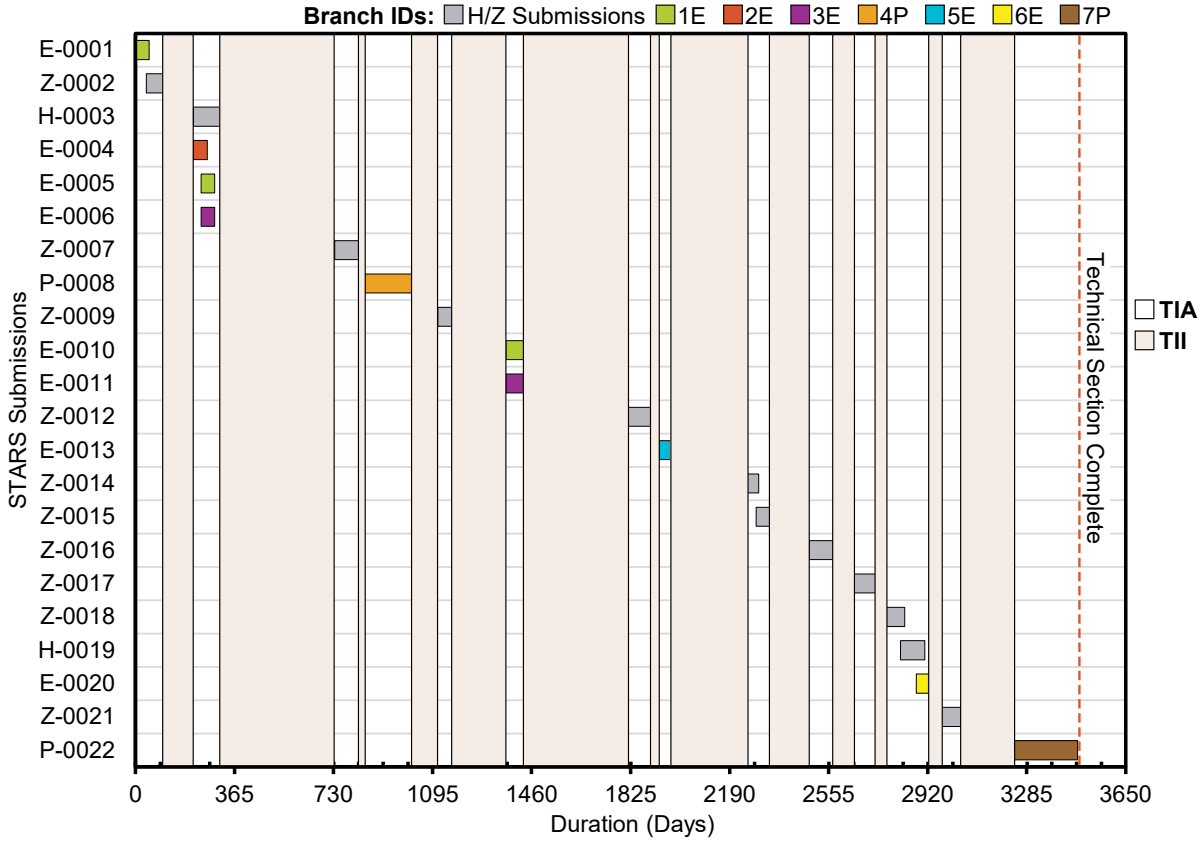



**Figure 42**. TIA vs. TII case study for the effectiveness technical section of Non-Food Application D.

# Appendix VII: Comment Analysis Case Study

To accompany **Recommendation 5: Improve Capture and Reporting of Reasons for Submission Failures**, an additional case study was undertaken to pilot a comment coding approach to examine example data outputs that could be developed from an analysis of CVM review comments. The pilot focused on protocol and data submissions that received unfavorable review outcomes as a part of the Effectiveness technical sections amongst the assessment sample.

To conduct the pilot analysis, all review comments from unsuccessful submissions in 25 Effectiveness technical sections were manually reviewed.[27] Each comment was assigned a broad category code describing the general domain of the comment, and a more specific subcategory code to identify the specific issue addressed by the comment.

The category codes include:
- Statistics
- Study Design
- Technical/Procedural
- Insufficient Evidence
- Other

The subcategory codes include:
- Corrective Language
- Typos, Grammatical Errors, and Formatting
- Failure to Follow Guidance
- Disagreement on Approach
- Failure to Follow Instructions
- Included Extraneous Information
- Improper Inclusion/Exclusion Criteria
- Missing Information
- Other

The category and subcategory fields were determined using the methodology of CVM's 2021 Audit of Protocol Letters as a guide. Categories and subcategories were added or adjusted to account for the inclusion of both protocol and data submissions in the comment analysis. Results of the comment analysis were aggregated to assess potential trends in comments across applications (Figures 43 and 44).

| Protocol Submissions (n=72) | Category | | | | |
|---|---|---|---|---|---|
| Subcategory | Statistics | Study Design | Technical or Procedural | Insufficient Evidence | Other |
| Corrective Language | 34 | 75 | 76 | | |
| Typos, Grammatical Errors, and Formatting | 3 | 2 | 51 | | |
| Failure to Follow Guidance | 3 | 2 | 1 | 2 | 2 |
| Disagreement on Approach | 80 | 169 | 39 | 8 | |
| Failure to Follow Instructions | 10 | 5 | 8 | 3 | |
| Included Extraneous Information | 2 | 4 | 9 | | 1 |
| Improper Inclusion/Exclusion Criteria | 2 | 58 | | 2 | |
| Missing Information | 28 | 77 | 94 | 3 | 2 |
| Other | | | 1 | 2 | |

**Figure 43**. Sample output of the comment analysis completed on 25 Effectiveness technical sections for protocol review letters.

27. Five applications from the assessment sample were not included in the comment analysis pilot because they either did not include an Effectiveness technical section or did not have any unsuccessful submissions to an Effectiveness technical section.

| Data Submissions (n=27) | Category | | | | |
|---|---|---|---|---|---|
| Subcategory | Statistics | Study Design | Technical or Procedural | Insufficient Evidence | Other |
| Corrective Language | | | 16 | 8 | |
| Typos, Grammatical Errors, and Formatting | | | 14 | | |
| Failure to Follow Guidance | | 1 | 2 | | 1 |
| Disagreement on Approach | 13 | 7 | 4 | 13 | 5 |
| Failure to Follow Instructions | 8 | | 3 | 2 | |
| Included Extraneous Information | | | 2 | | |
| Improper Inclusion/Exclusion Criteria | 1 | 5 | | | |
| Missing Information | 8 | 19 | 38 | 19 | |
| Other | | | | | 4 |

**Figure 44**. Sample output of the comment analysis completed on 25 Effectiveness technical sections for data submission review letters.

From the pilot dataset of review letters of protocols and data submissions from 25 Effectiveness technical sections, this assessment uncovered findings that could be indicative of larger challenges faced across the animal drug review process. These include the following:

### Protocol Submissions

- Comments related to study design were the most common amongst protocol submissions, with 46% of all protocol comments categorized as being related to study design
- 90% (65) of the protocol submissions received comments related to study design, 83% (60) received comments related to statistics, 81% (58) received comments related to technical or procedural aspects of the submission
- 100% (22 of 22) of applications with an unsuccessful protocol submission had at least one comment related to study design

### Data Submissions

- Only 16% of all data submission comments were categorized as being related to study design
- Of the 27 data submissions included in our pilot, 56% (15) received comments related to technical or procedural aspects of the submission, 52% (14) received comments related to statistics, and 41% (11) received comments related to study design.
- 50% (9 of 18) of applications with an unsuccessful data submission had at least one comment related to study design.

While these data points may provide insight into areas for improvement, Recommendation 5 can be implemented into CVM's review practices to fully realize the benefits of conducting a thorough analysis of review comments. This will allow CVM to better understand the common areas in which sponsors experience challenges during the animal drug review process, and ideally inform future revisions to guidance and policy.

# Appendix VIII: Assumptions

The CVM ADUFA Assessment was grounded in the following assumptions:

### Stakeholder Interview Assumptions

1. Interviewees were knowledgeable and authorized to speak to the selected application and associated submissions within the sample
2. Interviewees provided honest and accurate information
3. Interviewees not directly involved in the original drug development process could leverage historical documents and records to provide accurate information and current experience to contextualize challenges

### Data Analysis Assumptions

1. For undefined milestones, the team identified consistent and standardized fields and/or methods that were used to benchmark review activities
2. Technical sections were assigned to ADUFA reauthorization periods based on the received date of the earliest submission in the technical section
3. Referenced submissions from INADs outside of the sample were excluded from all calculations
4. Submissions that were referenced from other project plans within the same INAD were manually added to the submission dataset and included in analyses
5. Relationships between submissions were manually associated to conduct analysis on review cycles and impact of any predecessor of the submission
    - Project Managers manually tracked submission relationships and technical section submissions in MS Project plans, which were heavily used to inform the manual tagging of submission relationships
6. Data fields from CVM's time reporting and submission tracking systems were cross-referenced to the closest attributes to conduct analysis on resource time allocation associated with submissions

### Process Mapping Assumptions

1. Current state process maps accurately reflect normal operations and current enhancements based on the information provided by CVM SMEs during validation sessions. Information regarding enhancements no longer in use were discussed but not included in the documented workflow and activity analysis
2. Process maps do not capture every nuance or variance and/or workarounds for different technical section reviews or office-specific differences; however, this information did inform the logged challenges and assessment findings

# Appendix IX: Areas for Further Exploration

Throughout the course of this assessment, some topics areas arose that fell outside the scope of the review; however, they are clear factors in the effectiveness and efficiency of the animal drug approval process. While no conclusions can be made from these points, below is a list of topic areas for CVM to explore for their potential impact on the animal drug review process:

**Table 13**. Areas for further exploration, including descriptions and recommendations.

| Topic Area for Further Exploration | Description | Recommendation |
|---|---|---|
| **Multiple Projects Contained in INAD Folders** | INAD folders often contain multiple projects and exist in perpetuity, making it difficult to track the lifecycle of projects and report accurate TTA and TTC metrics. CVM's data files are not structured to easily determine which submissions contribute to which projects. | Explore the feasibility of tracking standalone projects rather than including multiple projects within INAD folders. This could mean restructuring the way INADs are structured and coded. |
| **Complexity of Animal Products and Study Designs** | The complexity of new animal products is a major factor contributing to the number of review cycles and TTA. However, CVM does not currently have a method to categorize the complexity of individual submissions, applications, or products. This makes it difficult to identify leading causes for delays and extended TTA metrics. | Explore a standardized method to categorize the complexity of INAD submissions and NADAs to improve reporting. This could also inform an updated triage process to evenly distribute overly complex submissions across reviewers. |
| **Abandoned Projects** | This assessment only evaluated projects that reached a successful conclusion. CVM spends resources on projects that are eventually abandoned by industry sponsors (see above under Multiple Projects Contained in INAD Folders), resulting in sunk costs of FTE hours. | Explore the revenue and cost of resource hours on abandoned projects to identify best practices to minimize wasted resources. |
| **Order of Operations Within Phased Review Process** | Interviews with CVM and Industry suggested that there may be a preferred order of operations for technical sections to be submitted to ease the phased review process. Initial analysis found that, among the 20 Companion Animal applications in the assessment sample, the four major technical sections were completed in 15 unique orders. | Explore the optimal paths to complete the phased review process and consider standardizing guidance and incentives to guide sponsors along the optimal path during the project's PSC. |
| **Review Activity Time Study** | An LVA analysis was conducted on the distinct activities performed throughout the animal drug review process; however, a time study at the activity level was not conducted. A time study would capture the amount of time spent on individual activities in the current state process maps developed during this assessment. | Explore conducting a time study of review activities within the animal drug review process, especially for activities deemed as LVA. This could include a cost benefit analysis of resources spent per sponsor against fees paid. |

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