Abstract

Refuse-to-file (RTF) actions and technical rejection criteria (TRC) outcomes are often perceived by sponsors as last-minute crises arising during the 60-day filing review window. In reality, most filing failures are the predictable result of structural misalignment between strategy and programming teams centering on electronic submission requirements, and standardized study data implementation. While these issues typically arise years earlier in development they are frequently deferred past the point where it would be easy to address them. Typically, this is a structural problem of structure rather than scientific or regulatory issue. FDA law and associated guidance, including the RTF draft guidance, MAPP 6025.4, the Standardized Study Data Guidance, the Study Data Technical Conformance Guide, and eCTD guidance under section 745A(a) of the FD&C Act, clearly articulate expectations for completeness, organization, and technical conformity. However, all too frequently, these guidelines are referred to retrospectively, in the context of post hoc quality checks and "gap analysis" rather than prospectively at the design stage. As a result, these requirements frequently become sources of avoidable RTF and TRC risk. This paper examines why submissions fail, distinguishes filing issues from scientific review issues, and proposes a lifecycle framework that integrates regulatory and programming ownership to reduce structural filing risk.

Introduction: Why Submissions Fail:

The FDA's RTF draft guidance and MAPP 6025.4 spell out that filing decisions focus heavily on whether an application is complete and reviewable. Complex, significant deficiencies—like missing required sections, unreasonably disorganized applications, or inadequate information to support indication are classic grounds for RTF.

Both documents also highlight that electronic submission problems can themselves be filing issues for example, when required content is not submitted electronically in the specified format, or when datasets cannot be opened or interpreted using standard tools. MAPP 6025.4 explicitly notes that failures in dataset organization, format, coding, or readability can make an application unreviewable and justify RTF.

From the data standpoint, the Standardized Study Data guidance states that FDA may RTF/RTR if clinical or nonclinical study data do not conform to required standards listed in the Data Standards Catalog. The Study Data Technical Conformance Guide elaborates common pitfalls: non-unique USUBJID, missing baseline flags, poorly documented define.xml, and lack of alignment between TS, STF, and study identifiers—all of which can trigger technical rejection criteria before review begins.

Internally, these regulatory outcomes are often the end result of familiar operational issues: regulatory and programming running in parallel, late agreement on pooling and standards, and traceability that's retrofitted rather than designed.

MAPP 6025.4 makes a sharp distinction between filing issues–deficiencies that render an application unreviewable or administratively incomplete—and review issues that require deeper scientific judgment. Filing issues include missing sections, unreviewable electronic data, and failure to comply with electronic format requirements under section 745A(a).

Programming teams, however, are often incentivized around getting planned analyses done for the CSR, not around whether the resulting datasets satisfy Data Standards Catalog requirements, FDA business rules, and validator rules described in the Study Data Technical Conformance Guide. That's where we see mismatches: non-unique USUBJID across studies, missing required or expected SDTM variables, or incomplete metadata in define.xml—all flagged by FDA's automated validations.

At the same time, regulatory may assume "the data are there" if the CSR tables look right, but the Standardized Study Data guidance is clear that FDA can reject a submission if the underlying SDTM/ADaM/SEND don't conform, regardless of how polished the narrative appears.

Without a shared definition of "submission-ready", teams drift: regulatory optimizes narrative and structure; programming optimizes code and outputs. The result is often frantic rework inside the 60-day filing review window.

The RTF draft guidance and MAPP 6025.4 are written for FDA staff, but they are incredibly valuable for sponsors as design documents. They tell us exactly how reviewers think about completeness, what types of deficiencies are "potentially easily correctable" versus "complex and significant," and how RTF decisions are made by day 60.

In parallel, the Standardized Study Data guidance, the Study Data Technical Conformance Guide, and the eCTD guidance define what "technically acceptable" electronic submissions look like—from SDTM/ADaM/SEND implementation to eCTD module structure and validation.

Our initiative is to bring these worlds together by pairing regulatory and programming leads as co-architects of the submission. Instead of regulatory discovering conformance issues after the CSR is locked, or programming being asked to "make it standard" in the last 30 days, this model promotes shared ownership of RTF risk and data standards compliance from the outset.

The framework maps directly to how FDA's own processes work. For example, MAPP 6025.4 shows how review teams use discipline-specific filing checklists to identify deficiencies that might support an RTF action, while the Standardized Study Data guidance and Study Data Technical Conformance Guide describe when standards become mandatory based on study start dates and Catalog entries.

In Phase 1, we align on indication scope, endpoints, data standards, and eCTD expectations early—ideally at pre-IND and end-of-Phase 2 meetings, consistent with the meetings guidance referenced in the study data documents.

In Phase 2, as studies run, we treat SDTM and ADaM not just as reporting convenience, but as regulatory assets—ensuring USUBJID consistency, proper use of controlled terminology, and robust define.xml as data are created, following the technical details in the conformance guide.

In Phase 3, before we commit to the final eCTD, we run our own internal "filing review," mirroring FDA's distinction between filing and review issues, and proactively checking study data against FDA business and validator rules.

Finally, Phase 4 is about execution: structuring the eCTD in line with the eCTD guidance, managing ESG transmission, and having clean traceability so that information requests are fast and confident rather than scrambling.

The RTF draft guidance emphasizes that CDER expects applications to be complete at the time of submission, except for specifically agreed minor components delivered within 30 days for certain NME NDAs and BLAs. Missing entire sections—such as CMC, nonclinical pharmacology/toxicology, integrated summaries of safety and effectiveness, or statistical evaluations—are classic RTF triggers.

In parallel, the Standardized Study Data guidance makes standards mandatory for many studies based on start date and inclusion in the Data Standards Catalog, and the conformance guide stresses early planning of SDTM/ADaM/SEND, define.xml, and reviewer guides. This means that choosing standards and versions is a Phase 1 decision, not a programming afterthought.

Phase 1 is where regulatory and programming should sit together to sketch the **end-to-end submission package**: which studies will be pooled, which ADaM datasets will support primary and secondary endpoints, how traceability will be documented, and which controlled terminologies (e.g., MedDRA, CDISC CT, SNOMED CT, LOINC) will be used and documented in TS and LB domains as appropriate.

The Study Data Technical Conformance Guide gives very concrete expectations for implementation during study execution: ISO-8601 dates, CDISC naming conventions, consistent USUBJID across all studies, baseline flags, and robust define.xml describing variables, derivations, and controlled terminology. It explicitly notes that poorly documented or incomplete data definition files are a *common* deficiency

For ADaM, the guide expects subject-level analysis datasets (ADSL) with key covariates, clear core variables (e.g., analysis flags, demographics), and traceability from ADaM back to SDTM. For labs, it recommends both SI and conventional units in separate domains (ADLB / ADLC), and full documentation of reference ranges and imputation.

MAPP 6025.4 underscores that major dataset problems—like missing datasets, absent treatment codes, inconsistent subject IDs, or datasets so large or poorly structured that they can't be opened in common tools—can constitute complex significant deficiencies supporting an RTF action. Catching these issues while studies are still ongoing is far cheaper than repairing them in the filing window.

MAPP 6025.4 describes how FDA review teams use detailed filing checklists—by discipline—to decide whether an application is fileable. Parameters include whether indexes are sufficient to locate necessary data, whether ISS/ISE and complete study reports are present, whether datasets are accessible and of sufficient quality, and whether any deficiencies render the application unreviewable or inconsistent with regulatory requirements.

The Standardized Study Data guidance and Study Data Technical Conformance Guide describe Technical Rejection Criteria (TRC) for study data: automated validations that verify study start dates, the presence of TS and STF, and conformance to the standards in the Data Standards Catalog. Failure here can mean the submission is rejected before a reviewer is assigned.

In Phase 3, we mirror this logic internally. We ask: if CDER ran its MAPP checklists and TRC today, would we pass? Are there missing define.xml files, inconsistent TS/STF identifiers, or SDTM implementations that don't match the latest supported domains (e.g., lab and microbiology updates)? If not, this is the time to fix them—before day 60.

The eCTD guidance states that submissions not in an acceptable electronic format—consistent with supported eCTD versions and validation criteria—"will not be filed or received" unless a waiver or exemption is granted. It also clarifies that even amendments and supplements must be submitted in eCTD once the requirement applies, and that ESG is the required transmission channel for submissions ≤10 GB.

The Study Data Technical Conformance Guide describes how FDA's business and validator rules are applied at the beginning of review, and how technical rejection criteria are tied to specific eCTD validations (e.g., presence of TS, STF, correct study start date, acceptable file tags).

Because we've designed traceability from CSR → SDTM/ADaM/SEND → tables, we're able to answer information requests quickly and confidently, without re-deriving datasets under time pressure. And because we've separated **filing issues** from deeper scientific questions, we go into review with the reassurance that we're debating benefit–risk, not whether the application is even reviewable.

Looking across >50 submissions, one pattern is clear: teams that treat the RTF guidance, MAPP 6025.4, Standardized Study Data guidance, Study Data Technical Conformance Guide, and eCTD guidance as *design inputs*—not as QA documents—rarely run into filing crises. They've already aligned content, format, and standards before the clock starts.

Where we still see friction is when study data standards and pooling decisions are pushed late. For example, implementing new SDTM or ADaM versions after the final transition dates described in the standardized data guidance, or discovering after database lock that earlier studies used incompatible identifiers or controlled terms.

You don't need a reorg to start. One concrete step is to build joint regulatory–programming checkpoints into the same meetings FDA expects you to use for alignment—pre-IND, end-of-Phase 2, and pre-NDA/BLA. At those meetings, you can explicitly confirm RTF risk factors, study data standards, and eCTD strategy.

Next, move from a vague notion of being "ready" to a written submission-ready checklist that incorporates: all required 314.50/601.2 sections present; no obvious MAPP 6025.4 RTF triggers; SDTM/ADaM/SEND conformant to current Catalog entries; define.xml and reviewer guides complete; and electronic submissions aligned with the eCTD guidance

Finally, pilot the phased alignment framework on one NDA/BLA. Capture where it de-risks RTF or TRC issues, and then scale to the portfolio.

The core message from FDA's own documents is that the bar for fileability and standardized data isn't mysterious. The RTF guidance, MAPP 6025.4, Standardized Study Data guidance, Study Data Technical Conformance Guide, and eCTD guidance tell us exactly what's expected. Our job is to treat those expectations as design requirements, not as post-hoc troubleshooting aids.

When regulatory and programming own those requirements from Phase 1 onward, we stop thinking of submissions as a lastminute assembly activity and start treating them as a

lifecycle discipline. That shift is what separates teams that routinely clear filing decisions and TRC from those that are constantly surprised by preventable issues.-own those requirements from Phase 1 onward, we stop thinking of submissions as a last-minute assembly activity and start treating them as a