Paper SA10

From Legacy to ISS/ISE: Real-World Lessons in Module 5 Submissions

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ABSTRACT

Packaging submission components into the eCTD Module 5 (m5) folder structure may seem like a straightforward technical task. It demands a deep understanding of regulatory requirements, therapeutic context, and extensive prior experience. The complexity multiplies when projects include legacy studies, remediated deliverables, and integrated submission packages such as ISS and ISE. Each of these adds unique challenges, ranging from harmonizing metadata across inconsistent datasets to managing updated define.xml files, ADRGs, and cSDRGs, while ensuring compliance with the latest CDISC standards and agency expectations. This presentation will share practical learnings, key challenges, and strategies to efficiently organize SDTM, ADaM, TLFs, and associated submission documents within m5. We will highlight common pitfalls, risk mitigation approaches, and best practices to streamline packaging while maintaining submission quality and integrity. Attendees will gain actionable insights to improve efficiency and reduce surprises when preparing complex submissions.

INTRODUCTION

Module 5 is the most data-intensive section of an eCTD submission and plays a critical role in regulatory review. Although regulatory guidance defines the required folder structure, sponsors retain flexibility in how datasets, analysis outputs, and supporting documentation are organized. Reviewer understanding depends not only on technical compliance, but also on logical organization, traceability, and clarity of documentation.

Recent submissions increasingly involve legacy studies conducted under older CDISC standards, dataset remediation to support pooling, and integrated analyses such as ISS and ISE. These factors introduce additional complexity and increase the risk of inconsistencies across datasets, metadata, and analysis outputs. This paper focuses on practical considerations for packaging ISS and ISE content into Module 5, based on common submission experience.

Although the high-level Module 5 folder hierarchy is consistent across submissions, the complexity of organizing content varies substantially based on therapeutic context, study design, and the degree of data integration required.

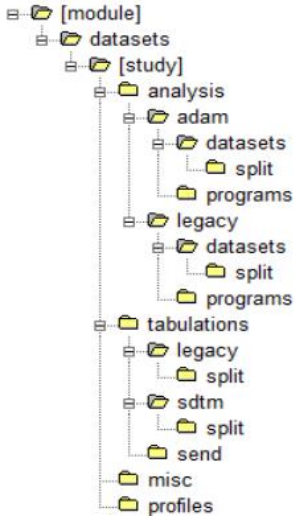
OVERVIEW OF MODULE 5 CONTENT

Module 5 typically contains:

- Clinical Study Reports (CSRs)
- SDTM and ADaM datasets
- Tables, listings, and figures (TLFs)
- Supporting metadata (define.xml, ADRG, cSDRG)

While the high-level structure is well defined, reviewer clarity depends on alignment between these components.

Figure 1: Example High-Level Module 5 Structure



For integrated submissions, additional care is required to distinguish study-level content from ISS and ISE deliverables.

COMMON CHALLENGES IN ISS AND ISE PACKAGING

LEGACY STUDIES AND REMEDIATION

Legacy studies may use:

- Earlier SDTM or ADaM versions
- Non-standard variables
- Different dictionary versions

To support integrated analyses, such studies are often remediated. A common issue is that datasets are updated without corresponding updates to metadata or documentation, resulting in inconsistencies within Module 5.

INTEGRATED ANALYSIS COMPLEXITY

ISS and ISE analyses require harmonization of:

- Analysis populations
- Treatment variables
- Endpoints and visit definitions

Without clear documentation and logical folder organization, reviewers may struggle to understand how pooled results were derived.

REGULATORY PERSPECTIVE ON MODULE 5 ORGANIZATION

Aspect	FDA	EMA	PMDA
Primary Focus	Filing readiness and reviewer traceability	Technical validation and structural consistency	Review clarity and completeness
Validation Sensitivity	Moderate; issues may lead to RTF	High; structural issues often block validation	Moderate–high; clarification or resubmission common
Dataset Placement	Expected in standard m5 locations	Strictly enforced hierarchy	Expected with emphasis on completeness
ISS / ISE Separation	Critical for filing and review clarity	Explicit separation expected	Clear differentiation strongly expected
define.xml Expectations	Link integrity and traceability	Scope clarity and correct placement	Comprehensive alignment with reviewer guides
Reviewer Guides (ADRG / cSDRG)	Strongly relied upon	Essential for assessment	Often highly detailed and explanatory
Tolerance for Naming Variance	Limited tolerance	Very low tolerance	Low tolerance
Impact of Poor Organization	RTF risk, filing delays, IRs	Validation failure, resubmission, List of Questions	Review delays, clarification requests
Optimization Strategy	Traceability and navigation	Validation success and consistency	Clarity and documentation

CASE EXAMPLE: INTEGRATED SUMMARY OF SAFETY (ISS) AND INTEGRATED SUMMARY OF EFFICACY

SCENARIOS

An ISS submission pools safety data from five Phase 2 and Phase 3 studies conducted over approximately ten years. Studies used multiple SDTM versions and different MedDRA releases.

Similarly, ISE submission pools data from the same five studies with differing visit schedules but a common primary efficacy endpoint.

COMMON ISSUES OBSERVED FOR ISS

Typical issues identified during Module 5 preparation include:

- Inconsistent derivation of safety population flags (e.g., SAFFL)
- Treatment variables not harmonized across studies
- AE seriousness derived using different rules
- Reuse of study-level define.xml files for pooled ISS datasets

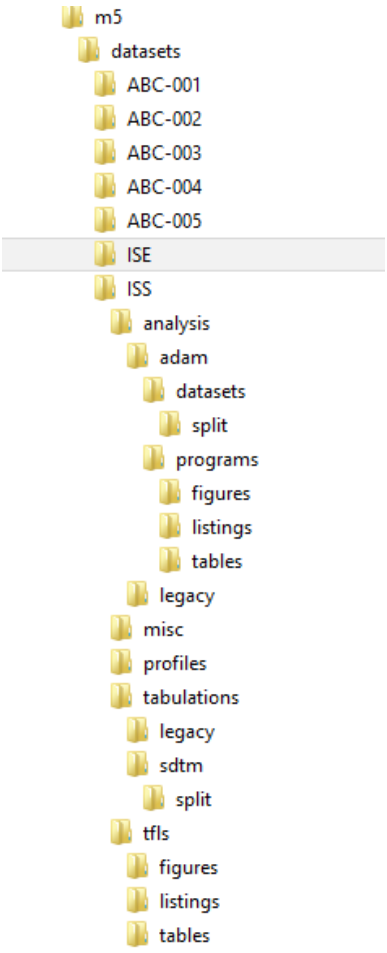
COMMON CHALLENGES INCLUDE

- Non-comparable visit definitions across studies
- Inconsistent baseline derivations
- Endpoint variables with similar names but different logic

Without harmonization, pooled efficacy results are difficult to interpret and defend.

RECOMMENDED ISS/ISE FOLDER ORGANIZATION

Figure 2: Example ISS/ISE Module 5 Structure



LESSONS LEARNED:

- Create ISS and ISE specific ADaM datasets
- Use a single define.xml for ISS and ISE
- Explicitly document harmonization rules and clearly justify visit windowing decisions in the ADRG
- Harmonize visit windowing using standard ADaM variables (AWTARGET, AWRANGE, AWTDIFF)

For example, if AE seriousness was derived differently across studies, the ADRG should clearly describe how it was re-derived for the ISS and why this approach was chosen.

METADATA ALIGNMENT

Metadata plays a critical role in reviewer understanding of ISS and ISE submissions. The define.xml file must accurately reflect the final datasets included in Module 5, including variable attributes, controlled terminology, and derivation descriptions. Reuse of study-level define.xml files for ISS or ISE datasets frequently leads to inconsistencies and should be avoided. The Analysis Data Reviewer's Guide (ADRG) should clearly describe analysis intent, pooling logic, harmonization rules, and any deviations from standards, while the Clinical Study Data Reviewer's Guide (cSDRG) should document SDTM structure and compliance decisions. Clear, submission-level metadata that aligns with remediated datasets and integrated analyses significantly improves traceability from datasets to TLFs and reduces the likelihood of regulatory questions.

COMMON PITFALLS AND RISK MITIGATION

Several recurring pitfalls were observed during ISS and ISE Module 5 preparation, most of which stemmed from misalignment between datasets, metadata, and analysis outputs. Metadata inconsistencies following dataset remediation were a frequent issue, particularly when define.xml and ADRG files were not updated to reflect final dataset structures. Traceability gaps between ADaM datasets and TLFs also posed challenges, often requiring additional explanation during submission review. The presence of multiple dictionary versions without clear documentation further increased reviewer uncertainty. Although folder structures were technically compliant, logical organization did not always align with reviewer workflows, making navigation more difficult. These risks were mitigated by conducting early mock Module 5 builds, maintaining a clear traceability path from CSR to SDTM, ADaM, TLFs, and metadata, and ensuring early and continuous alignment between programming, biostatistics, and regulatory teams. Together, these measures improved submission consistency and reduced late-stage rework.

REGULATORY IMPACT

While incorrect Module 5 folder structures are rarely cited as the sole basis for application rejection, FDA filing experience indicates that deficiencies in dataset placement, metadata linkage, and integrated analysis organization can materially affect filing decisions and early review efficiency. Refusal-to-File determinations and filing delays have occurred when datasets are not submitted in expected locations, define.xml hyperlinks are broken, or the distinction between study-level and integrated analyses such as ISS and ISE is unclear. Even when applications proceed to review, inadequate logical organization can result in extensive information requests and reduced reviewer confidence. Structuring Module 5 to support traceability and efficient navigation is therefore critical to facilitating FDA review and minimizing avoidable delays.

CONCLUSION

Packaging ISS and ISE content into eCTD Module 5 is not a purely technical exercise. Legacy data, remediation, and integrated analyses introduce complexity that must be actively managed through thoughtful folder organization and robust metadata. Applying the practical lessons described in this paper can improve reviewer usability, reduce regulatory risk, and support high-quality submissions.

KEY TAKEAWAYS AND LESSONS FOR FUTURE SUBMISSIONS

Experience from preparing ISS and ISE submissions demonstrates that packaging content into eCTD Module 5 requires more than technical adherence to folder structures. Several practical lessons were identified that would directly inform future submissions.

ISS and ISE should be planned and executed as standalone submission deliverables rather than extensions of study-level analyses. Reuse of study-level datasets and metadata frequently resulted in documentation gaps and late rework. Defining ISS- and ISE-specific datasets, define.xml files, ADRGs, and folder structures earlier would have improved consistency and reduced downstream effort.

Dataset remediation decisions must be aligned with the overall submission strategy. In several cases, datasets were remediated without fully considering the impact on Module 5 organization and metadata, leading to avoidable inconsistencies. Earlier coordination between programming, biostatistics, and regulatory teams would have reduced rework and improved alignment.

Standardization of key analysis variables prior to pooling proved critical. Inconsistent definitions of population flags, treatment variables, visit windowing, and endpoint derivations required retrospective harmonization. Establishing submission-level rules for these elements earlier would have simplified integration and improved traceability.

Metadata planning was equally important. Developing ISS- and ISE-specific define.xml and ADRG templates upfront would have reduced reliance on study-level documentation and ensured clearer explanations of pooling logic, deviations, and known limitations.

Early mock Module 5 builds were an effective risk mitigation strategy. Conducting dry runs earlier would have highlighted navigation, traceability, and documentation issues before submission-critical milestones.

Finally, reviewing Module 5 content from a regulatory reviewer's perspective proved valuable. Walking through the submission as a reviewer helped identify logical gaps that are not apparent through technical validation alone. Assigning clear ownership for Module 5 integration further improved consistency across datasets, TLFs, and metadata.

Overall, applying these lessons in future submissions is expected to improve efficiency, reduce regulatory risk, and enhance the quality and usability of ISS and ISE submissions.

CONTACT INFORMATION

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