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One Study, Many Regulators: Submission-Ready Data Package for Multi-Region Filings

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ABSTRACT

Global clinical trials are routinely submitted to multiple health regulatory authorities, including the FDA (US), EMA (EU), PMDA (Japan), and NMPA (China). While CDISC® standards provide a unified technical framework, differences in regional regulatory requirements, such as eCTD structure, data expectations, validation requirements, and review-tool sensitivities, can create significant challenges during submission preparation. This paper presents a practical, programmer-led framework for building a submission-ready data package that supports multi-region filings with minimal region-specific changes. Using oncology studies as an example, the paper discusses strategies for designing region-agnostic datasets, managing region-specific requirements through metadata and documentation, and maintaining robust traceability from raw → SDTM → ADaM → Tables, Listings, and Figures (TLFs). Additionally, it includes recommendations for folder structures, quality checklists, validation workflows, traceability artifacts commonly expected during regulatory reviews or inspections, and common mistakes and how to prevent them. By shifting the mindset from "analysis-ready" to "submission-ready" early in the study lifecycle, programmers can significantly reduce downstream regulatory risk, improve submission efficiency, and support parallel global filings.

INTRODUCTION

The globalization of clinical trial development has changed how clinical trials are designed, conducted, and submitted for regulatory approval. A single pivotal study can now support submissions to multiple health authorities, including the FDA, EMA, PMDA, and NMPA. These agencies generally accept CDISC standards, but each have their own regulatory approach, leading to differences in expectations for data structure, traceability, and documentation.

For programmers, there has been a fundamental shift in responsibilities. Programming is no longer limited to producing analysis datasets, tables, listings, and figures (TLFs); it now plays a critical role in ensuring that datasets are ready for submission, understandable to various regulators, and acceptable across different regions. Decisions made during dataset development (e.g., variable inclusion, derivation logic, controlled terminology management, and metadata consistency) can have significant implications, especially when multiple regulatory agencies review the same datasets with different review practices.

This paper demonstrates that a "one study, many regulators" approach is achievable through targeted, submission-focused programming strategies. By designing datasets based on a global core standard and utilizing metadata-driven programming, programmers can develop reusable submission packages. It outlines practical techniques, common pitfalls, and best practices that help programmers to efficiently support high-quality multi-region regulatory submissions while ensuring compliance and traceability.

MULTI-REGION REGULATORY LANDSCAPE

There are four major regulatory agencies for drug approval or marketing authorization: the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and China's National Medical Products Administration (NMPA). All four are members of, or engaged with, CDISC, and all formally accept or prefer CDISC-formatted electronic submissions. Understanding the differences in mandate and operational requirements is crucial for designing a submission-ready data package.

The FDA has required SDTM and ADaM for all NDA and BLA submissions for studies starting on or after December 17, 2016, as specified in the FDA Data Standards Catalog. PMDA requires CDISC standards and uses the same Pinnacle 21® (P21) validation engine as the FDA, but with different configurations, rules, and severity levels. China's NMPA formally committed to SDTM and ADaM as the preferred standards in late 2019, with the commitment effective for eCTD submissions in the early 2020s. The EMA has not

formally mandated CDISC for marketing applications but has strongly encouraged it through its pilot programs and its Clinical Trial Information System (CTIS).

The following table compares and summarizes the key regulatory differences relevant to submission package design.

Requirements	FDA (US)	EMA (EU)	PMDA (Japan)	NMPA (China)
SDTM Mandatory	Yes (Studies started on or after Dec 17, 2016)	Encouraged	Yes (submissions on or after April 1, 2020)	Preferred
ADaM Mandatory	Yes	Not Mandated	Yes	Preferred
Define-XML Version	v2.0 / v2.1	v2.0 / v2.1	v2.0 / v2.1	v2.0+
eCTD Version	v3.2.2 or v4.0	v3.2.2	v3.2.2 or v4.0	v3.2.2
Reviewer's Guide (cSDRG/ADRG)	Required	Recommended	Required (specific PMDA sections)	Encouraged
Controlled Terminology	CDISC CT (Latest supported version)	CDISC CT	CDISC CT	CDISC CT + Local Terms
Oncology Domains (TR/TU/RS)	Required (for oncology review)	Recommended	Required (for pivotal studies)	Recommended / Expected
Module 1 Language	English	English / EU Languages	Japanese	Chinese/English
Note: *Requirements are subject to change. Always verify against the current FDA Data Standards Catalog, PMDA guidance, and agency-specific technical conformance guides prior to submission.*				

Table 1. Regional Regulatory Requirements Summary

Despite regional differences, all major agencies align with the CDISC standards framework. The Study Data Tabulation Model (SDTM) organizes raw clinical trial data into defined domains, and the Analysis Data Model (ADaM) builds analysis-ready datasets on top of SDTM with explicit traceability. Define-XML contains machine-readable metadata that describes every variable, codelists, and derivations included in the submission package. Together, these standards establish the "global core" upon which a multi-region data package strategy can be developed.

A critical yet often overlooked standard is the CDISC Controlled Terminology (CT). CT provides standardized values, known as codelists, for variables such as sex, race, adverse event severity, and tumor response categories. Using the appropriate and consistent CT version across SDTM and ADaM datasets is essential for successful validation and helping regulatory reviewers interpret the data clearly. Programmers must document the CT version used in the Study Data Standardization Plan (SDSP) and ensure it is maintained consistently throughout the study lifecycle.

DESIGNING REGION-AGNOSTIC DATASETS

THE STUDY DATA STANDARDIZATION PLAN (SDSP)

The most important early-phase action a programming team can take is to update the SDSP document that is submitted with the IND submission or, at the latest, with the first protocol amendment. The SDSP documents the sponsor's intentions for SDTM and ADaM implementation, specifying:

- The SDTMIG and ADaMIG versions to be used
- The CDISC Controlled Terminology versions
- Any planned deviations from CDISC standards, with justification

- The define.xml version

The FDA uses the SDSP as a reference during review to understand the sponsor's standards approach. A well-written SDSP reduces the likelihood of a Refuse-to-File (RTF) action and sets clear expectations for later Reviewer's Guide content.

GLOBAL CORE DATASET DESIGN

The "global core" strategy is the most efficient path for multi-region oncology submissions, ensuring that datasets created for one agency are inherently compatible with those of other agencies. This approach shifts the burden of regional compliance from data restructuring to metadata and documentation. A few examples are:

- Select the highest common version supported by all target agencies. For 2025–2026 submissions, SDTMIG v3.3 is a stable "global core" choice, as it is widely accepted across the agencies.
- Include the most stringent variables required by any single agency, even if other agencies do not require them. For example, an FDA-mandated variable that NMPA does not explicitly require will not cause a problem with NMPA, but its absence would cause an FDA validation error.
- Apply CDISC Controlled Terminology consistently, using the same CT version referenced in the SDSP. For extensible codelists where sponsor-specific values are needed, document all extensions in define.xml and in the cSDRG
- Ensure a consistent USUBJID format (e.g., STUDYID-SITEID-SUBJID) across all datasets. This ensures perfect traceability when agencies perform independent pooled analysis or cross-study reviews.
- Implement TR (Tumor Results), TU (Tumor Identification), and RS (Disease Response) domains for oncology studies regardless of region (applicable for studies using SDTMIG v3.2 or later). These domains are required by FDA and PMDA for oncology submissions and are recognized by all other agencies.

The concept of a "global core" does not mean that a single, static dataset is submitted to all agencies without modification. Instead, it means that the datasets are structured so that any required regional adaptations are limited to Module 1 (administrative) documents and, at most, supplemental metadata documentation, not the datasets themselves.

ONCOLOGY-SPECIFIC CONSIDERATIONS

Oncology studies require three specialized SDTM domains beyond the general observation class domains:

Domain	Class	Structure	Key Variables
TU (Tumor Identification)	Findings	One record per identified tumor per subject per assessor	STUDYID, USUBJID, TUGRPID, TUSPID, TULNKID, TUTEST, TUORRES, TUCAT, TULOC, TUMETHOD, TUBLFL, TUEVAL, TUDTC, VISIT
TR (Tumor Results)	Findings	One record per tumor measurement/assessment per visit per subject per assessor	STUDYID, USUBJID, TRTESTCD, TRLNKID, TREVAL, VISITNUM, TRGRPID, TRSPID, TRDTC

Domain	Class	Structure	Key Variables
RS (Disease Response)	Findings	One record per response assessment per visit per subject per assessor	STUDYID, USUBJID, RSGRPID, RSSPID, RSLNKGRP, RSTESTCD, RSEVAL, RSTEST, RSORRES, RSCAT, VISIT, RSDTC

Table 2. Oncology-specific SDTM Domains

A common oncology-specific error is incomplete RELREC linkage. Regulatory reviewers use RELREC to trace the basis for every response determination. Missing links are flagged by P21 and can trigger queries during review. Programmers should create a complete RELREC population as part of the checklist.

MedDRA coding of adverse events is universally required. AETERM must be coded to the current MedDRA version, and the complete hierarchy (AELLT, AELLTCD, AEDECOD, AEPTCD, AEHLT, AEHLTCD, AEHLGT, AEHLGTCD, AEBODSYS, AEBDSYCD, AESOC, AESOCCD) must be populated.

SUBMISSION-READY PROGRAMMING STRATEGY

Preparing a submission-ready clinical data package requires more than producing datasets that support statistical analysis. It requires a programming strategy that ensures consistency, traceability, validation readiness, and transparency across the entire data lifecycle. In a multi-region regulatory environment, programmers must design programming workflows that support both analysis needs and regulatory review expectations. The following foundational principles, folder structure, naming conventions, and early adoption of a submission-ready mindset help achieve this goal.

METADATA-DRIVEN PROGRAMMING

Metadata-driven programming minimizes manual effort, enhances consistency, and simplifies the adaptation of a submission package for multiple regions. By using the same metadata to generate both the define.xml and the Reviewer's Guide, we can eliminate common risks associated with reviewers' findings and reduce regulatory delays caused by inconsistencies between datasets, the define.xml, and the Reviewer's Guide. At a minimum, a metadata repository should track:

- Dataset name, label, class, and structure (e.g., one record per subject, one record per subject per timepoint, etc.)
- Variable names, labels, types, lengths, and codelist assignments
- Derivation rules and SDTM mapping logic from source CRF or raw data
- Origin (CRF, derived, assigned), with page references for CRF-collected variables
- Comments on any non-standard variable or deviation from the SDTMIG

An important metadata-driven technique is the creation of a controlled terminology mapping table that maps raw CRF values to CDISC CT values for each domain. This table should be version-controlled alongside the programming code and reviewed whenever a new CT version is released prior to submission.

TRACEABILITY FROM RAW → SDTM → ADAM → TLFS

Regulatory reviewers expect clear traceability across all stages of clinical data processing. Each variable in ADaM datasets should be traceable back to its source data in SDTM or raw datasets, with derivation logic clearly documented. Similarly, analysis outputs, including tables, listings, and figures, must be reproducible from ADaM datasets. Maintaining this traceability requires consistent programming efforts:

- **Stable identifiers:** Subject IDs, visit variables, and sequence numbers must remain consistent across datasets to preserve relationships.

- **Transparent derivations:** Derivation algorithms should be well-documented, transparent, and reproducible.
- **Comprehensive documentation:** Metadata, reviewer's guide, and program comments should clearly describe how analysis variables are derived and how they link back to source data.

When implemented effectively, this traceability enables regulators to follow the data flow from collection to analysis, facilitating efficient and confident review.

SUBMISSION PACKAGE FOLDER STRUCTURE

The eCTD (electronic Common Technical Document) is the standard format accepted by all major agencies. The study data package is structured into five modules, with the majority of the data residing in Module 5 (Clinical Study Reports). The FDA is accepting eCTD v4.0 for new applications beginning September 16, 2024, while eCTD v3.2.2 remains supported. Most sponsors continue to use v3.2.2 for existing submissions; v4.0 adoption is encouraged and is expected to become mandatory in phases, likely around 2029. PMDA, EMA, and NMPA continue to use v3.2.2.

The following folder structure aligns with FDA Technical Conformance Guide requirements and is compatible with PMDA and NMPA submission standards. Variations may be required for specific agency-level requirements, but this structure provides the recommended global baseline.

Folder / File	Contents / Notes
m5/datasets/<studyid>	Root study data folder (Module 5)
tabulations/sdtm/	SDTM datasets (.xpt), define.xml, stylesheet, csdrg.pdf, acrf.pdf
analysis/adam/datasets/	ADaM datasets (.xpt), define.xml, stylesheet, adrg.pdf, analysis-results-metadata.pdf
analysis/adam/programs/	SAS/R programs for ADaM datasets and TLF (.txt)
analysis/legacy/	Legacy datasets if applicable, with conversion notes
suppinfo.pdf	Supplemental information / documents (e.g., external data required technical explanation, coding or legacy data documentation)
m1/sdsp.pdf	Study Data Standardization Plan (submitted with IND/protocol)

Table 3. Recommended Folder Structure and Content for Data Package

FILE FORMAT AND NAMING REQUIREMENTS

All SDTM and ADaM datasets must be submitted in SAS Transport (.XPT) format. File names must use lowercase characters and numbers only, with no special characters except hyphens and underscores. Domain or dataset names must follow the SDTMIG or ADaMIG naming conventions (e.g., ae.xpt, lb.xpt, adsl.xpt). Dataset name lengths must not exceed 8 characters.

All datasets listed in define.xml must be present in the datasets folder, and all datasets in the folder must be documented in define.xml. Variable metadata, codelist assignments, and origins must be complete and consistent with the actual dataset contents. Automated generation of define.xml from a metadata repository is strongly recommended to maintain this consistency.

ANALYSIS-READY VS. SUBMISSION-READY MINDSET

A common challenge in clinical programming is the distinction between datasets that are analysis-ready and those that are submission-ready. Analysis-ready datasets are optimized for statistical modeling and analysis efficiency, whereas submission-ready datasets must also meet strict regulatory standards for structure, documentation, and traceability.

While these goals are closely related, they are not identical. Submission-ready datasets must adhere strictly to CDISC standards, pass validation checks, and include comprehensive metadata and documentation. Programs must be reproducible, and derivations must be transparent to allow reviewers to follow the analysis.

Adopting a submission-ready mindset early in the study lifecycle helps minimize rework during the submission phase. By designing datasets, metadata, and programming workflows with regulatory review in mind, programmers can ensure that analysis datasets seamlessly transition into submission-ready deliverables that support global regulatory filings.

The table below summarizes the key differences between analysis-ready and submission-ready datasets:

Analysis-Ready Dataset	**Submission-Ready Dataset**
Optimized for statistical modelling	Compliant with CDISC SDTM/ADaM standards
Efficient for internal team use	Passes P21 Enterprise validation
May use study-specific variable structures	Strictly follows controlled terminology and naming convention
Documentation suited for analysis	Define-XML, ADRG, cSDRG required
Reproducibility expected by team	Reproducibility required by regulators globally
Flexible derivation logic permissible	Transparent and traceable derivation algorithms

Table 4. Differences Between Analysis-Ready and Submission-Ready Datasets

A submission-ready programming strategy is not a final-mile activity but a foundational design principle that must be integrated into every stage of programming. The submission-ready strategies outlined in this section provide a clear framework for developing clinical data packages that meet the regulatory standards of the global regulatory environment.

VALIDATION WORKFLOWS

Ensuring validation and compliance readiness is a critical part of preparing a regulatory submission package. Regulatory agencies rely on automated validation tools and standardized metadata to evaluate the quality and consistency of submitted datasets. For programmers, this means that validation should not be viewed as a final step done just before submission. Instead, validation should be integrated throughout the entire dataset development lifecycle. This approach ensures that SDTM and ADaM datasets meet regulatory expectations across multiple regions.

PINNACLE 21 AS THE STANDARD VALIDATION TOOL

Pinnacle 21 is widely used by regulatory authorities to validate SDTM and ADaM datasets against CDISC standards. P21 validates SDTM, ADaM, and define.xml against CDISC conformance rules, SDTMIG/ADaMIG conformance rules, and FDA/PMDA/NMPA business rules. Although the tool itself is standardized, the interpretation of validation findings can vary across agencies. For example, the FDA generally expects datasets to pass P21 validation with minimal unresolved issues, particularly for rules classified as errors or significant warnings. Reviewers often examine unresolved findings to determine whether they represent true compliance problems, affect analysis results/interpretations, or acceptable deviations supported by documentation.

Other agencies, such as PMDA and NMPA, also rely on CDISC validation, but their interpretation of findings may differ slightly depending on review practices and submission guidance. As a result, programmers should focus on resolving validation issues whenever possible and clearly documenting any unavoidable warnings in submission documentation.

Adopting a proactive validation approach and running P21 checks throughout dataset development helps identify structural or terminology issues early and reduces the risk of last-minute corrections. The current production engines for P21 as of March 2026 are listed below:

Engine ID	Agency	Status
P21 2508.1	All	Current (Official FDA and PMDA, beta NMPA, custom standards and CT rules)
FDA 2508.1	FDA	Current at FDA
PMDA 2411.0	PMDA	Current (Valid for initial submissions starting 2025-04-01)
NMPA 2405.2	NMPA	Beta (Supports Chinese-language datasets, Displays rule messages and descriptions in Chinese)

Table 5. Pinnacle 21 Enterprise Engines for Multiple Regions

THREE-TIER VALIDATION FRAMEWORK

A robust pre-submission validation framework is divided into three tiers:

- **CDISC Conformance Checks:** Validate dataset structure, variable names, types, lengths, and codelist values against SDTMIG/ADaMIG specifications. P21 performs these automatically.
- **FDA/PMDA Business Rules:** Validate cross-domain consistency, treatment-emergent flags, date relationships, and other regulatory-specific quality checks. P21 applies these as a second layer.
- **Sponsor Quality Checks:** Study-specific edit checks that validate protocol compliance, population flags, and analysis parameter derivations against the SAP. These are implemented as custom P21 rules or as independent SAS/R QC programs.

For multi-region submissions, during dataset development, use the P21 engine for region-agnostic checks to ensure comprehensive coverage of all agency requirements; as the submission date approaches, switch to an agency-specific engine. Document all findings from all tiers and their explanation in the cSDRG and ADRG document before submission.

TRACEABILITY ARTIFACTS

Traceability from raw source data through SDTM to ADaM to TLF outputs is a core expectation at regulatory inspections. The following traceability artifacts should be maintained as part of every submission package:

- **Annotated CRF (aCRF):** Maps each CRF field to its corresponding SDTM variable. Must be kept current with the final CRF version.
- **SDTM Mapping Specifications:** Document the derivation logic from raw/CRF data to SDTM. Should include source variable names, transformation rules, and codelist mappings.
- **ADaM Derivation Documentation:** Captured in the define and ADRG document. Must align with the SAP.
- **TLF Output Traceability:** Each table, listing, and figure program header should reference the ADaM dataset, population flag, and analysis variable used.

SUBMISSION QUALITY CHECKLIST

The following checklist (Table 6) presents a minimum set of quality checks that should be cleared before the study data package is finalized for any multi-region regulatory submission. It is recommended to complete this checklist at three key points: before the database lock, at the time of database lock, and 30 days before submission. This approach allows sufficient time for any necessary remediation.

Check Item	Applies To	Risk if Missing
All SDTM datasets pass P21 with no Errors; Warnings documented in cSDRG	FDA, PMDA	FDA: Review Delay PMDA: “Reject” is not accepted and required correction of data
ADaM datasets pass P21; all issues explained in ADRG Section 6	FDA, PMDA	Review delay
Define-XML present for both SDTM and ADaM; all datasets cross-referenced	FDA, PMDA	Technical rejection
CDISC Controlled Terminology version declared and consistent across datasets	All regions	CT2002 warnings; reviewer confusion
SDTM datasets in XPORT v5 format; filenames lowercase, no special characters	All regions	File rejection
USUBJID consistent across all SDTM and ADaM domains	All regions	Data integrity failure
Oncology domains TR, TU, RS populated and linked via RELREC; response variables BESTRESP, OVRLRESP, TRGRESP present	FDA, PMDA (oncology)	Efficacy review issues
AE terms coded to current MedDRA version; AETERM → AEDECOD hierarchy complete	All regions	Safety review delays
SDSP filed with IND/protocol and updated if significant changes occurred	FDA	Reviewer query
Region-specific Module 1 documents prepared in required language (English/Japanese/Chinese)	PMDA, NMPA	Refusal to file
All TLF programs submitted; program header includes input dataset name and run date	FDA, PMDA	Reproducibility failure
Traceability map: raw data → SDTM → ADaM → TLF available or documented in ADRG	All regions	Inspection finding

Table 6. Submission Quality Checklist for Multi-Region Filings

COMMON MISTAKES AND HOW TO PREVENT THEM

Despite the widespread adoption of CDISC standards and increasing experience with global submissions, preparing a single study for multiple regulatory authorities remains complex. Programmers encounter many challenges during submission package preparation, and these can be avoided with proper planning defined early in the study life cycle. Understanding common mistakes can help programmers design more robust and scalable strategies that support efficient multi-region submissions.

Common Mistake	Root Cause	Prevention Strategy
Study Data Standards not determined early	Standards planning deferred to submission phase	File SDSP with IND; align on SDTM/ADaMIG versions at study start
Inconsistent USUBJID format across domains	Multiple programming teams or systems	Define USUBJID macro globally; enforce in SDTM programming conventions
Using outdated CDISC Controlled Terminology	CT not updated after study lock	Define CT version in SDSP; run validation with same CT version throughout
P21 validation only at submission	Validation treated as submission-phase only task	Integrate P21 validation in QC cycles from SDTM first draft
Missing or incomplete oncology domains (TR/TU/RS)	Oncology-specific SDTMIG requirements not reviewed	Use SDTMIG Oncology supplement; link RS, TU, TR via RELREC
Define-XML not updated to match final datasets	Dataset changes made post-lock without updating metadata	Treat define.xml as a living document; automate via P21 Enterprise or metadata repository
Programs not reproducible or not submitted	Programs stored locally or not submitted with the package	Submit all ADaM and required TLF programs in Section 7 of the ADRG document

Table 7. Common Mistakes in Multi-Region Submissions and Prevention Strategies

CONCLUSION

Building a submission-ready data package for multi-region regulatory filings is achievable with a disciplined, submission-focused programming strategy applied consistently from study initiation through database lock. The key principles are: (1) establish an SDSP early and commit to a global core dataset standard; (2) design datasets to the most stringent requirements across all target agencies; (3) implement metadata-driven programming to ensure consistency across datasets, define.xml, and Reviewer's Guide; (4) integrate P21 validation continuously, not only at submission; (5) maintain complete traceability from raw → SDTM → ADaM → TLFs; and (6) follow the submission quality checklist at the database lock and 30 days before submission. In oncology studies, it is required to fully implement the TR, TU, and RS domains along with their RELREC linkages. Additionally, coding all adverse events according to the complete MedDRA hierarchy is important to meet the expectations of major agencies.

By shifting the programmer's mindset from "analysis-ready" to "submission-ready" at the beginning of the study, sponsors can significantly reduce regulatory risk down the line. This approach also supports simultaneous global filings without extensive rework and helps accelerate the regulatory review process.

REFERENCES AND RECOMMENDED READING

- U.S. Food and Drug Administration (FDA)
  - *"Study Data Technical Conformance Guide, v6.1"* Retrieved from https://www.fda.gov/media/153632/download
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