124 Framework for Real-World Data Used in Regulatory Submissions [888]

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Background & Rationale

- The use of real-world evidence (RWE) for regulatory bodies and health technology assessment (HTA) decision-making has grown over the past decade.
- Numerous guidelines have been put forth by regulators and HTA bodies on the use of RWE in such submissions.
- While best practice recommendations for RWE exist, there remains a lack of a clear, operational framework to guide the preparation and transformation of real-world data (RWD) for regulatory use.

Objective: to present a structured framework for the use and delivery of RWD in regulatory decision-making.

Methods

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- We conducted a review of Food and Drug Administration (FDA) [US] guidance documents on RWD/RWE to date, focusing on guidance documents on RWD.
- We conducted a targeted literature review of regulatory feedback on drug approvals containing RWE as supportive or substantial evidence in Marketing Authorization Applications (MAAs) from January 2021 - present.
- **Regulatory focus**: FDA was selected due to their significance in the regulatory landscape.

Case Study Selection

- We selected seven medicines for analysis based on RWE included in their MAA submissions.
- These were chosen to represent a range of therapeutic areas and evidence types based on RWE included in their MAA submissions:
  - Idecabtagene vicleucel (ide-cel)
  - Omburtamab
  - Sotorasib
  - Alpelisib
  - Palovarotene
  - Tacrolimus
  - Omaveloxolone

Analysis

- We collected publicly available regulatory reports from the FDA.
- Two independent reviewers extracted information on the use and evaluation of RWE.
- We analyzed Sponsor practices in the submissions and reviewed feedback from regulators regarding the RWD.
- A framework was developed that synthesized guidance documents and prior regulatory practice.

Results

Table 1. Approved Data Standards Used in Clinical Studies

	Raw Data	Source Data	Analysis Data
CDISC Data Standard	CDASH	SDTM	ADaM
Purpose	Used for collecting clinical raw data such as from electronic case report forms (eCRFs)	Creating source datasets from raw data. SDTM datasets contain standardized metadata (e.g., variable names, labels, formats).	Creating analysis datasets from SDTM datasets. ADaM datasets contain derived variables for analysis and reporting of results.
Mapping	Blank eCRF are annotated to create the aCRF (annotated CRF), which contains mapped CDASH variable names.	Raw data from the eCRF or CDASH is mapped to SDTM using the SDTM Implementation Guide (SDTMIG).	Source data, such as SDTM datasets, are extracted and transformed to create analytic datasets using the ADaM Implementation Guide (ADaMIG).
Example Datasets	CRF forms	DM: Demographics AE: Adverse Events	ADSL: subject-level analysis dataset ADAE: adverse events analysis dataset

aCRF = annotated CRF, SDTM = Study Data Tabulation Modell, ADaM = Analysis Data Model, CDASH = Clinical Data Acquisition Standards Harmonization, CDISC = Clinical Data Interchange Consortium, CRF = case report form, eCRF = electronic CRF.

Table 2. Elements of Data Submissions

Data Standard	Define Files	Data dictionary / Dataset specifications	Reviewer's Guide
Supported data standard	Specifications that describe metadata for datasets, e.g., variables, possible values, controlled terminologies & codes.	Data dictionary / dataset specifications that describe programming definitions for derived variables (i.e., logic).	Comprehensive documentation on study/analysis tables, conformance findings, and other helpful details for FDA review.
SDTM standardized source datasets	A define.xml file that contains metadata for each SDTM and ADaM dataset.	Data dictionary: • Variables names and labels • Formats • Variable definitions • Controlled terminology Dataset specifications: • Dataset overview • Dataset structure • Variable derivations • Flags	Reviewer's Guide (SDRG/ADRG): • Mapping information • Study objectives • Summary of datasets • Hardcodes implemented • Special data considerations • Summary of conformance findings
ADaM standardized analytic datasets			

ADaM= Analysis Data Model, FDA = Food and Drug Administration, SDTM = Study Data Tabulation Model, XML = Extensible Markup Language, XPT = SAS Transport File used to support data transfers.

Figure 1. Operational Framework Preparing Real-World Data for Regulatory Submissions

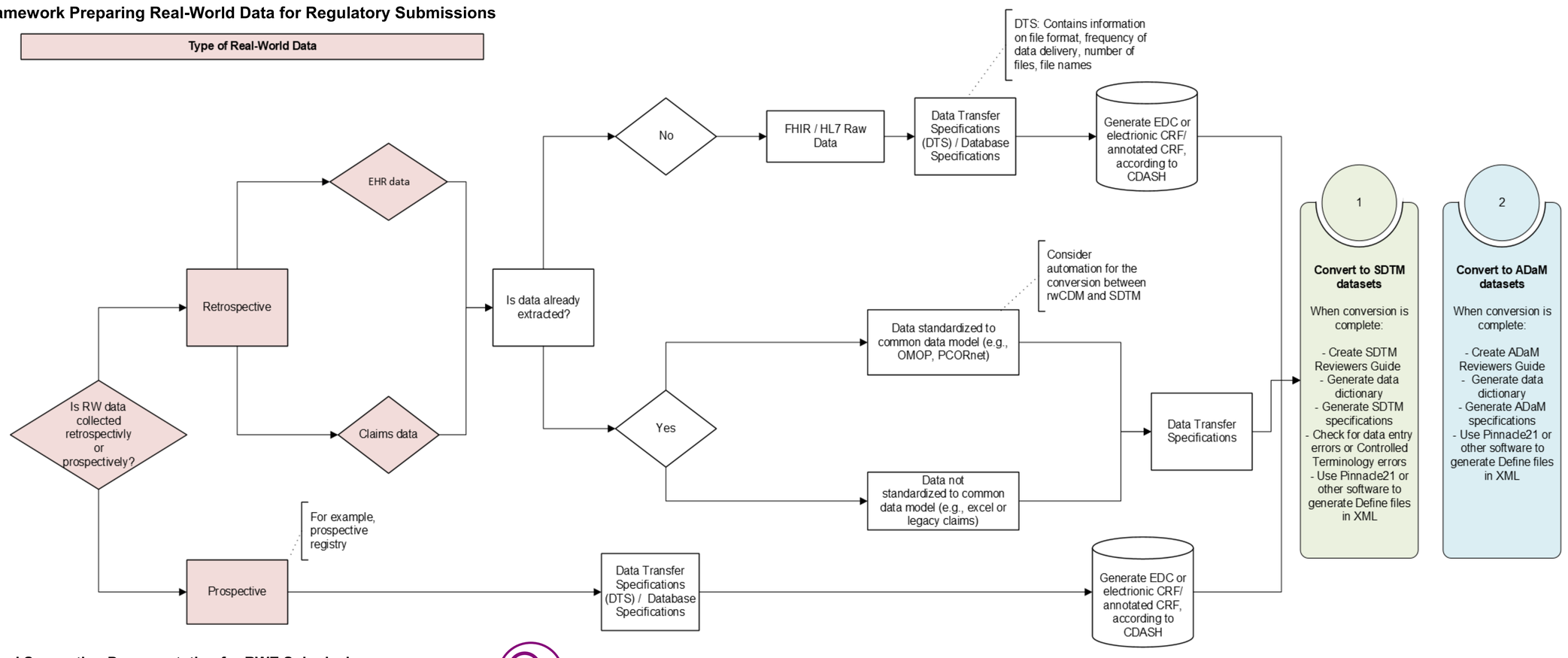
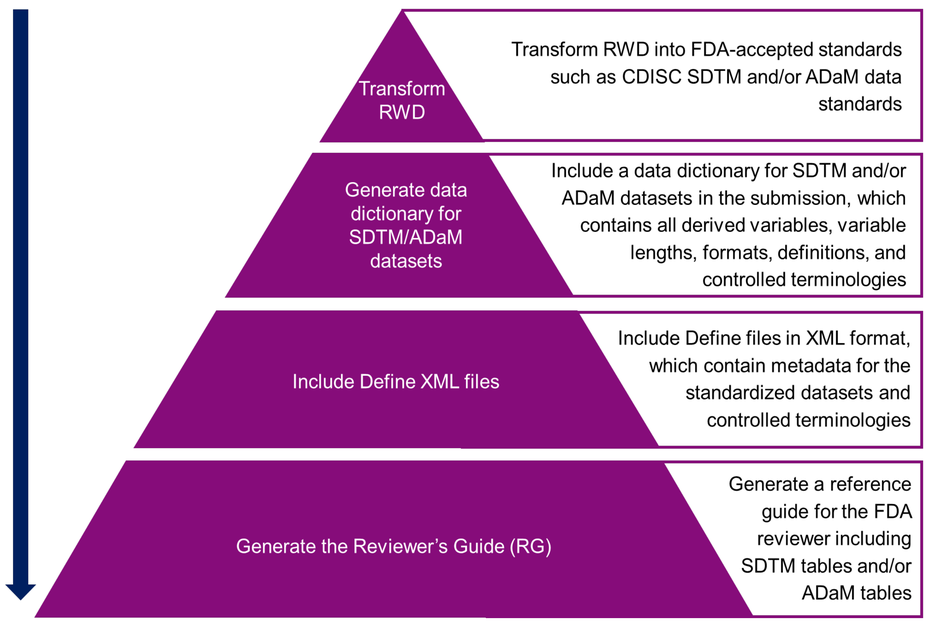


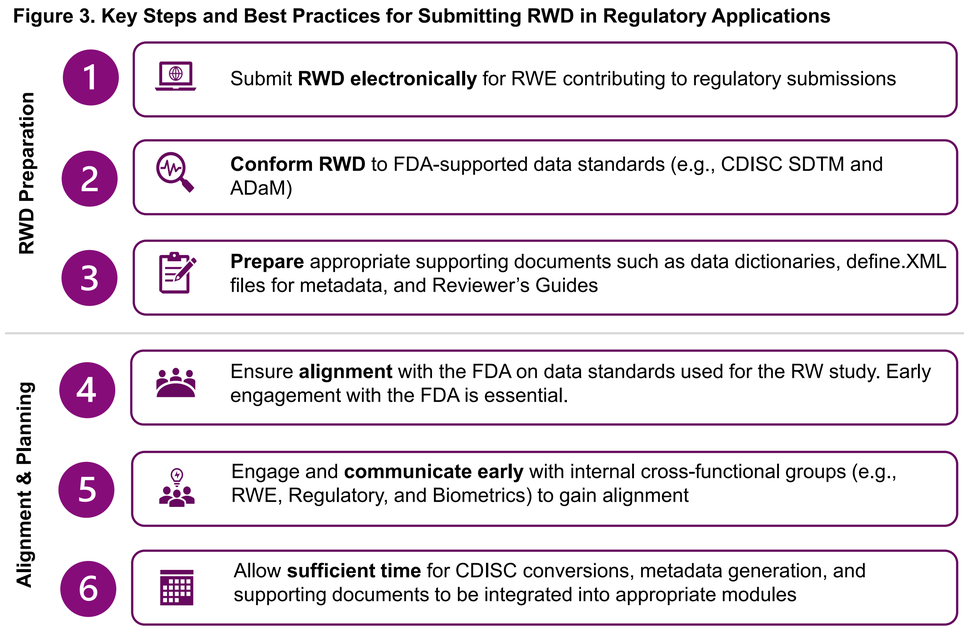
Figure 2. Hierarchy of Required Supporting Documentation for RWE Submissions



Reviewer's Guide: A Brief Primer

- The Reviewer's Guide (RG) is a *single summary document* that serves as a reference guide for the FDA reviewer.
- The RG should describe:
  - available datasets (e.g., tabulation or analytic);
  - special considerations or directions;
  - conformance issues identified;
  - hardcodes; and
  - any other items that may facilitate reviewers' use of the submitted data.
- The RG also assists reviewers in understanding the relationships between the study report and the data.
- Sponsors may use templates to complete the SDTM Reviewer's Guide and ADaM Reviewer's Guide.

Figure 3. Key Steps and Best Practices for Submitting RWD in Regulatory Applications



ADaM= Analysis Data Model, CDASH = Clinical Data Acquisition Standards Harmonization, CDISC = Clinical Data Interchange Consortium, CRF = Case Report Form, EDC = Electronic Data Capture, EHR = Electronic Health Record, FDA = Food & Drug Administration, FHIR/HL7 = Fast Health Interoperability Resources/Health Level 7, OMOP = Observational Medical Outcomes Partnership, PCORnet = Patient-Centered Outcomes Research Network, rwCDM = Real-World Common Data Model, RWD = Real-World Data, RWE = Real-World Evidence, SDTM = Study Data Tabulation Model, XPT = SAS Transport File used to support data transfers, XML = Extensible Markup Language.

Conclusions & Key Findings

What did the Literature Review of Marketing Applications containing RWE Show?

- In multiple submissions, RWD from prior studies was evaluated by regulators to support revised primary analyses and/or additional sensitivity analyses.
- Raw and source data should be available for regulatory audits, to the extent possible.

What are the Regulatory Requirements for Data in Submissions?

- Regulatory requirements apply to data submitted for Investigational New Drugs, New Drug Applications, and Biologics License Application.
- Data should be submitted in electronic format.
- Data should comply with formats supported by the FDA Data Standards Catalog, including SDTM and ADaM.

What are Recommended Practices for RWD in Regulatory Submissions?

- Sponsors should generate RWD in a manner that promotes transparency and reproducibility, to enable regulators to analyze source and analytic datasets.
- In addition to transforming datasets, Sponsors should generate supporting documentation such as data dictionaries, Define XML files, and Reviewers Guides.

Why Is This Research Important?

- This work offers a practical roadmap for aligning RWD with regulatory expectations - supporting transparency, reproducibility, and regulatory readiness.
- This framework provides a structured approach in delivering RWD.
- Implementing these practices also enables regulators to analyze sponsor-submitted data.
- This is intended for RWD used in regulatory submissions, although this may also be used as good practice for RWD/RWE used for other non-interventional observational studies.
- This framework offers recommendations and should not be interpreted as mandatory or prescriptive.

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References: References are available upon request to the corresponding author: Shivani@landmarkscience.com;
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