



Evolving Regulatory Guidance on Submission of Standardized Data

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Topics:

- Data Standards Environment and Management
- Evolving Regulations:
 - PUDUFA V
 - Submission of Site Level Summary Data
 - Technical Specifications for Site Level Summary Data
 - EMA Public Disclosure of CT Rule
- Reviewer's Guides
- Clinical Data Submitted with Applications
- Analysis data Submitted with Applications
- Traceability / Data Integration
- Evolving landscape for data packages
- New Skills for Statisticians and Statistical Programmers

Data Standards Environment and Management

- Data Standardization is becoming increasingly important as Regulatory Agencies Worldwide (e.g. FDA, MHRA, PMDA, EMA, etc.) all are requesting that clinical data be migrated to a standardized format to support for review, approval, and disclosure of these data.
- CDISC Data Standards are the *de-facto* model for this data standard

Data Standards Environment and Management

- Changing Regulatory Environment:
 - August 27, 2012: A Pharmaceutical company issued a press release stating that it had received a Refuse to File letter from the FDA in response to its supplemental Biologics License Application (sBLA), revealing that *“after collaborative consultations with the FDA, the agency requested that the company modify the presentation of the data sets to enable the agency to better navigate the application.”*
 - Translation: Provide standardized data sets that comply with CDISC Standards so the agency can adequately review your data.

Evolving Regulations

- FDA Guidance related to the Statistical Sciences are evolving as a result of PDUFA-V Legislation promulgated in 2012.
 - FDA Guidance for Industry: Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning
 - Request for “Reviewer's Guides” with regulatory submissions
 - PDUFA-V has performance goals identified in the legislation.

PDUFA V Performance Goals

- Enhancing Regulatory Science and Expediting Drug Development
 - Advancing the science of meta-analysis methodologies
 - Advancing the development of Patient Reported Outcome (PRO) and other endpoint assessment tools.
- Enhancing Benefit-Risk Assessment in Regulatory Decision-Making
- Improving the Efficiency of Human Drug Review through the required Electronic Submissions and Standardization of Electronic Drug Application Data

FDA DRAFT Guidance - 2012

Guidance for Industry

Providing Submissions in
Electronic Format —

Summary Level Clinical Site Data for
CDER's Inspection Planning

Summary Level Site Data

- Summary level Clinical dataset (SDTM, ADaM, and Metadata) to be used to facilitate site level inspections.

26 The purpose of this guidance is to assist applicants in the submission of a clinical dataset that
27 describes and summarizes the characteristics and outcomes of clinical investigations at the level
28 of the individual study site (summary level clinical site data). The summary level clinical site
29 dataset is intended to facilitate use of a risk-based approach for the timely identification of
30 clinical investigator sites for on-site inspection by CDER during the review of marketing
31 applications. This guidance refers to a number of technical specification documents and other
32 resources. These technical specification documents and resources are available online to make
33 them more accessible to applicants.

Summary Level Site Data

- Combination of multiple studies integrated into a single dataset that allows for interrogation of investigational sites.

95 **III. DESCRIPTION OF SUMMARY LEVEL CLINICAL SITE DATASET**

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97 A summary level clinical site dataset contains data from all relevant studies used to support
98 evaluation of the application, including studies that support various treatment indications. The
99 summary level clinical site dataset is intended to (1) characterize individual clinical investigator
100 sites, (2) describe aspects of the studies with which those clinical investigator sites are
101 associated, and (3) present the characteristics and outcomes of the study at the site level. The
102 summary level clinical site dataset provides critical information in a usable format to assist in
103 site selection.

Technical Specifications

- Efficacy Parameters: ADaM Dataset Variables

For each study and investigator site, use the following variables associated with efficacy and their variable names:

- **Treatment Efficacy Endpoint (TRTEFFE)** – the summary statistic for each primary efficacy endpoint, by treatment arm (see below for examples of summary statistics according to different types of efficacy endpoints)
- **Treatment Efficacy Endpoint Standard Deviation (TRTEFFS)** – the standard deviation of the summary statistic (TRTEFFE) for each primary endpoint, by treatment arm
- **Site-specific Treatment Effect (SITEEFFE)** – the treatment effect should be reported using the same representation as reported for the primary efficacy analysis
- **Site-specific Treatment Effect Standard Deviation (SITEEFFS)** – the standard deviation of the site-specific treatment effect (SITEEFFE)
- **Endpoint (endpoint)** – a plain text label that describes the primary endpoint as described in the data definition file data dictionary included with each application.
- **Treatment Arm (ARM)** – a plain text label for the treatment arm that is used in the Clinical Study Report

Technical Specifications

- **Summary Level Data Categories:**
 - **Study Level Metadata Information:** STUDY, STUDYTL, DOMAIN, SPONNO, SPONNAME, IND, UNDERIND, NDA, BLA, SUPPNUM.
 - **Study / Site Specific Identification Information:** SITEID, ARM, ENROLL, SCREEN, DISCONT.
 - **Study / Site Specific Efficacy Information:** ENDPOINT, ENDPTYPE, TRTEFFE, TRTEFFS, SITEEFFE, SITEEFFS, CENSOR.
 - **Study / Site Specific Safety Information:** NSAE, SAE, DEATH, PROTVIOL.
 - **Site Specific Metadata Information:** FINLMAX, FINLDISC, LASTNAME, FRSTNAME, MINITIAL, PHONE, FAX, EMAIL, COUNTRY, STATE, CITY, POSTAL, STREET
- Multiple sources of origin: Regulatory affairs databases, clinical trials management system databases, SDTM and ADaM datasets.

EMA - 2013



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2013
EMA/240810/2013
Executive Director

Publication and access to clinical-trial data

Public Disclosure of CT Data

- Allows for both direct and indirect comparisons between medicines.
- Allows for independent replication, and further exploration of CT data.

Enabling public scrutiny and secondary analysis of CTs: Access to CT data in an analysable format will benefit public health in future. It will make drug development more efficient by establishing a level playing field that allows all drug developers to learn from past successes and failures, and it will enable the wider scientific community to make use of detailed and high-quality CT data to develop new knowledge in the interest of public health. The Agency also takes the view that a high degree of transparency will take regulatory decision-making one step closer to EU citizens and patients, and promote better-informed use of medicines. Independent replication of CT data analysis is a legitimate

- Will require sponsors to plan better studies, with fewer, focused endpoints: Knowing that data will be publically available.

“Reviewer’s Guides”

- Not yet required...but coming, and requests have been made by the agency for a “Data Reviewer’s Guide”.
- Both Study Specific SDTM, ADaM data sets, as well as Integrated ADaM data sets.

“Reviewer’s Guides”

- Reviewer’s Guides for the Data Submitted with submissions are designed to enhance and focus the Reviewer on the data submitted and includes:
 - Content of all data submitted with a submission
 - Data Architecture
 - Study Data Tabulation Model (SDTM)
 - Analysis Data Model (ADaM)
 - Algorithms and Derivations at study and program level
 - Data Handling Rules
 - Interpretation

Clinical Data Submitted with Applications

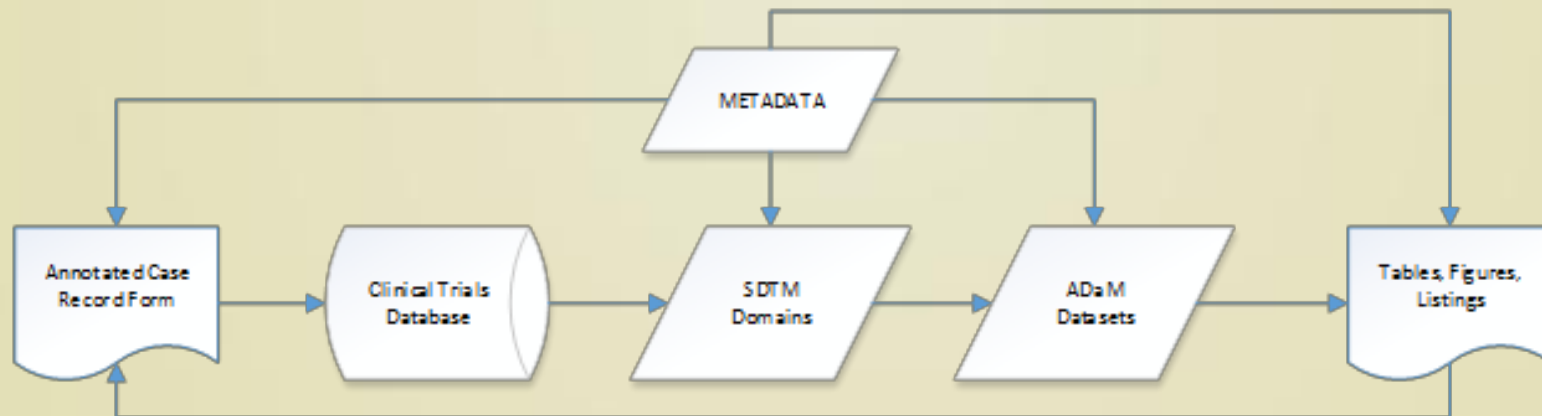
Category	Description of Materials
Phase I and Phase IIa Trials (Early Development trials)	- Recommend converting all data into SDTM domain (Version 3.1.2 or higher) - Map datasets to use controlled terminology - Use as basis for integration into ISS Adam datasets
Phase IIb and Phase III (Registration Trials)	- All clinical data should be stored in SDTM domains (Version 3.1.2 or higher), with minimal use of custom domains and SUPPxx domains - Apply all controlled terminology
SDTM Data Sets	- Submitted as XPT files - Validate SDTM datasets using OPENCDISC Validator, explaining any error or warning messages not addressed. - Compliance with SDTM Metadata requires is essential for homogeneity across individual studies submitted.
Programs	- Generally not required to be submitted for SDTM domains. - Should have available and ready to submit if requested, - Should be available for audit and inspection.
Case Record Forms	All CRFs must be annotated with SDTM domains, including xxCAT and code lists for each study. This aids in review
DEFINE.XML	- Follow the CDISC ODM Model, including all links to the Annotated CRF. - May also include a DEFINE.PDF rendition if requested by agency.
SDTM Reviewers Guide	- New requirement. - Use the PhUSE template found on the PhUSE Wiki as a model. - Derivations are not generally included in SDTM domains. If any derivations are included in SDTM then explain in detail in reviewers guide. - Reviewer guides are essential for presenting data issues encountered and any deviations from expected CDISC compliance. - Include in the reviewers guide any validation issues encountered.

Analysis Data Submitted with Applications

Category	Description of Materials
Phase I and Phase IIa Trials (Early Development Trials)	ADaM datasets may be required if key analysis information for labeling is used from early development trials.
Phase IIb and Phase III (Registration Trials)	- ADaM datasets required for submission for registration trials. - EMA, PMDA, MHRA does not currently require submission of datasets. Should have available for inspection. - FDA requires submission of datasets.
Data Integration (ISS/ISE)	- ADaM datasets recommended for all integrated data. - Should submit integrated ADaM datasets with application
ADaM Datasets	- ADaM dataset standard is ideal for all analysis data. - Can apply ADaM principles for Clinical data not collected in SDTM. - Compliance with Metadata for ADaM essential to ensure traceability between SDTM and ADaM.
Programs	- Programs for efficacy ADaM dataset creation should be submitted with application. Does not have to be executable, but should be able to read program and understand code for program. - Recommend liberal use of comments in programs to explain steps and all derivations. - Can apply ADaM principles for Clinical data not collected in SDTM.
DEFINE.XML	Needed to provide hyperlink for datasets and mapping to source data (SDTM, or other clinical data sources)
ADaM Reviewers Guide	- New requirement. - Template currently under development. Check the PhUSE Wiki for a template. - The ADaM reviewers guide is not the Statistical Analysis Plan. The Analysis Datasets Reviewers Guide can be used to explain deviations from the SAP or other changes and enhancements to the planned analysis derivations. - Reviewer's guides are essential for presenting analysis data issues encountered and any deviations from expected CDISC compliance. - Include in the reviewers guide any validation issues encountered, or, any issues that may affect traceability from clinical data to the planned displays

Traceability – Critically Important

- Clinical Trials data MUST be traced to their respective source documents. This GCP criteria is identified in ICH as well as FDA regulations.
- CDISC principles define “Traceability” as one of the key components of trial data in both SDTM and ADaM domains.

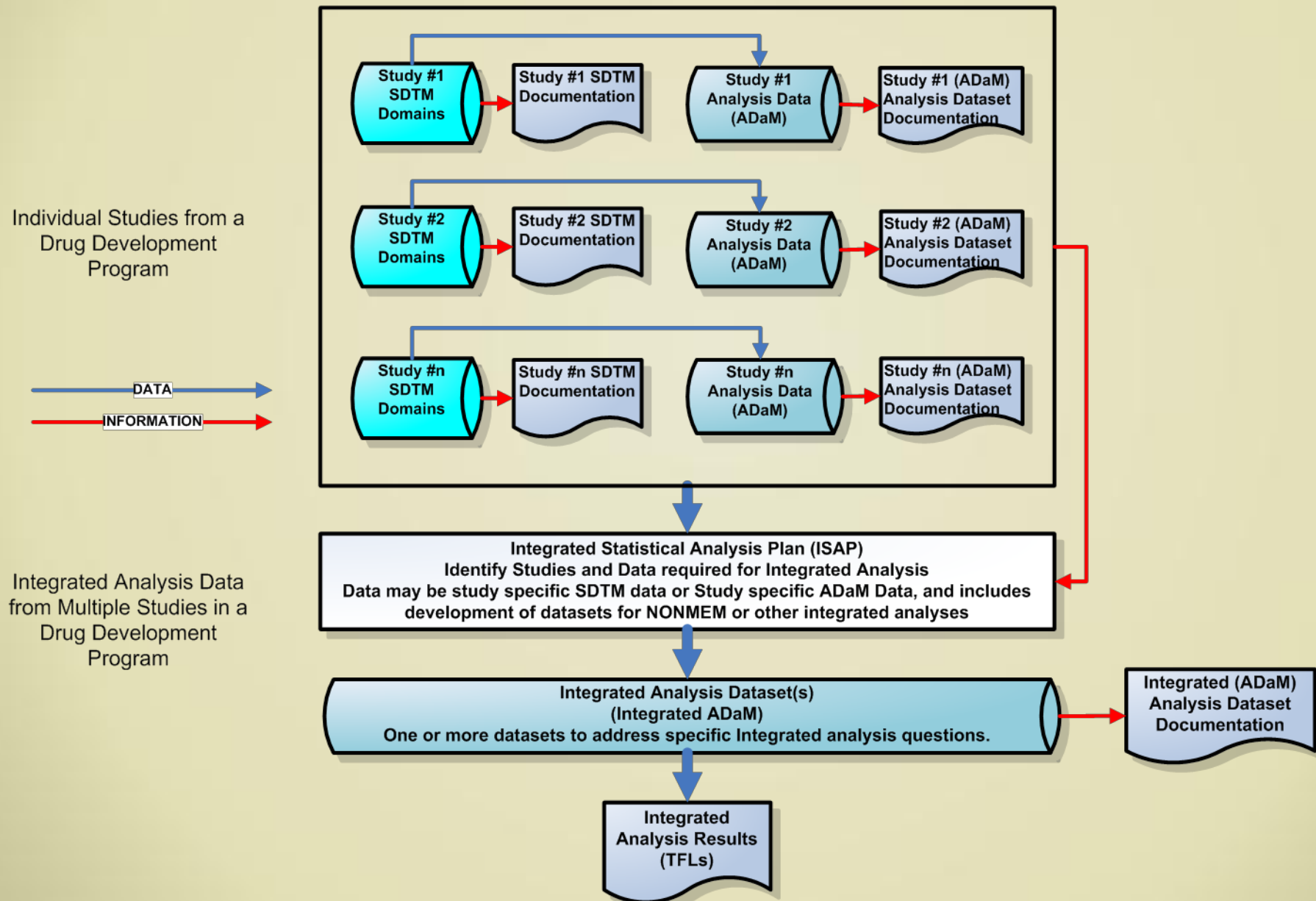


- Any process that modifies subject level data eliminates the ability to trace data back to the source origin and may result in a regulatory finding if found on audit.

Traceability

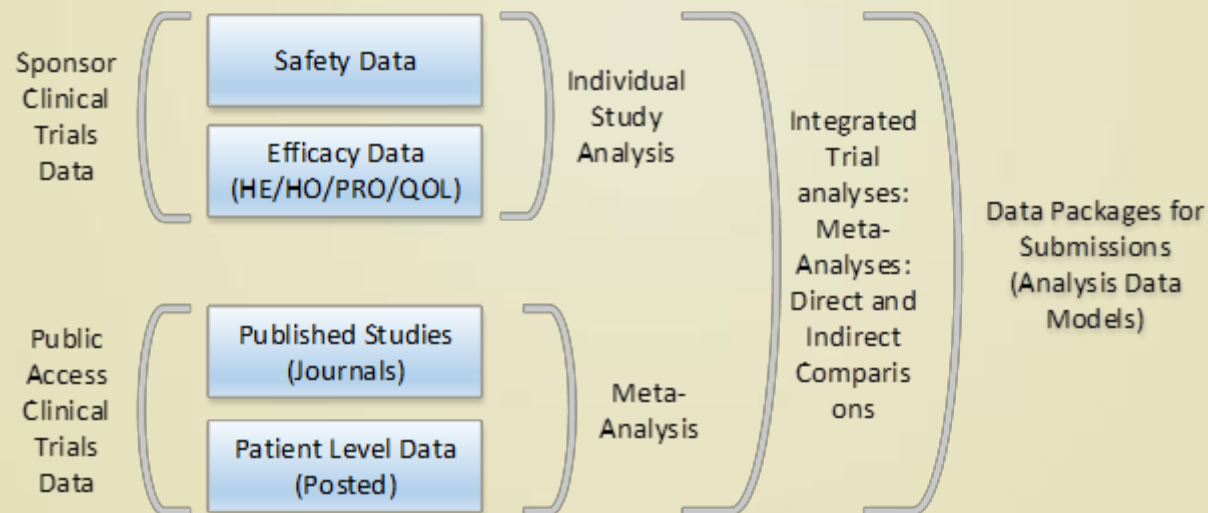
- Permits and enables understanding of the relationship between the analysis results, the analysis datasets, and the SDTM datasets and the source.
- Is built by clearly establishing the path between an element and its immediate predecessor(s).
- Establishes across-dataset relationships, as well as within-dataset relationships.
- Equals Transparency.
- Regulatory Authorities expect that any given data element can be traced from the reported result back to its source in any trial.
- DEFINE.XML (CRT-DDS V1.0) is the basis for Traceability.

Data Integration



Evolving Landscape for Data Packages

- The landscape of a data package is evolving to include not only trial level data but also meta-analyses, site summary level data, and more robust integrated analysis datasets.



Skills for the Future

Three specific areas for development of new skills are identified.

1. Enhanced skills with meta-analyses, integration of published results, and interrogation of public access data to complete secondary research,
2. Enhanced communications skills to support meetings and regulatory agency interactions to explain the data packages delivered with applications, and
3. Skills for the assessment of data quality and risk-based monitoring.

All of this in addition to those skills currently required to work effectively on a drug development team.

References

- Prescription Drug User Fee Act, PDUFA V: Fiscal Years 2013-2017.
(<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>)
- Guidance for Industry: Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning (FDA DRAFT Guidance: December 2012)
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>).
- Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDERs Inspection Planning (FDA DRAFT Guidance: Technical Specifications, November 2012).
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ucm332466.pdf>).
- EMA Draft Policy 70: Publication and access to clinical trial data.
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500144730&mid=WC0b01ac058009a3dc).



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