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
  - Providing Regulatory Submissions in Electronic Format-Standardized Study Data (February 2014 Guidance)
  - EMA Public Disclosure of CT Rule
- Reviewer's Guides – Templates Available
- 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

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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.
  - FDA Guidance (February 2014) mandates this model for submission of data (binding).

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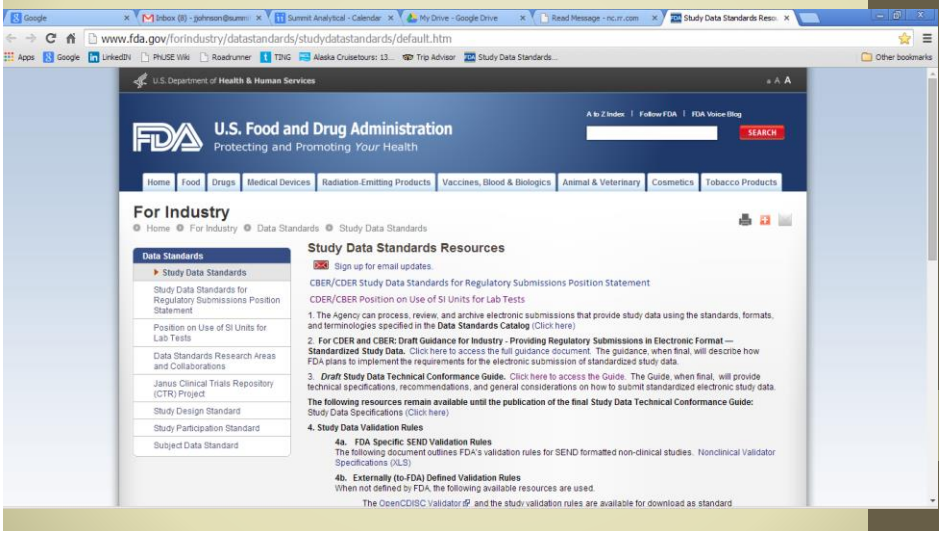
FDA Study Data Standards Resources Web Page



FDA Position Statement on Standards

Study Data Standards for Regulatory Submissions Position Statement
Position Statement

FDA recognizes the investment made by sponsors over the past decade to develop the expertise and infrastructure to utilize Clinical Data Interchange Standards Consortium (CDISC)[1] standards for study data. The submission of standardized study data enhances a reviewer's ability to more fully understand and characterize the efficacy and safety of a medical product.

The Prescription Drug User Fee Act (PDUFA V)[2] Performance Goals state that FDA will develop guidance for industry on the use of CDISC data standards for the electronic submission of study data in applications. In the near future, FDA will publish guidance that will require study data in conformance to CDISC standards.[3]

FDA envisions a semantically interoperable and sustainable submission environment that serves both regulated clinical research and health care. To this end, FDA will continue to research and evaluate, with its stakeholders, potential new approaches to current and emerging data standards. FDA does not foresee the replacement of CDISC standards for study data and will not implement new approaches without public input on the cost and utility of those approaches.

September 13, 2013

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.

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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.

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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

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FDA DRAFT Guidance - 2012

Guidance for Industry

Providing Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning

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Summary Level Site Data

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

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

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Summary Level Site Data

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

III. DESCRIPTION OF SUMMARY LEVEL CLINICAL SITE DATASET

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

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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.

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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 – Standardized Study Data (02/2014)
  - Study data Technical Conformance Guide (Technical Specifications Document: 02/2014)

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FDA DRAFT Guidance - 2014

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Standardized Study Data

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FDA DRAFT Guidance - 2014

STUDY DATA TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

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FDA DRAFT Guidance-2014

- Technical Conformance Guide - Purpose

1.2. Purpose

This Guide provides technical recommendations to sponsors[3] for the submission of animal and human study data and related information in a standardized electronic format in INDs, NDAs, ANDAs, and BLAs. The Guide is intended to complement and promote interactions between sponsors and FDA review divisions. However, it is not intended to replace the need for sponsors to communicate directly with review divisions regarding implementation approaches or issues relating to data standards.

FDA Guidance - 2014

- Study Data Standardization Plan – With the IND!

2. Planning and Providing Standardized Study Data

2.1. Study Data Standardization Plan

For clinical and nonclinical studies, sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. The Study Data Standardization Plan (Standardization Plan) assists FDA in identifying potential data standardization issues early in the development program. Sponsors may also initiate discussions at the pre-IND stage. For INDs, the Standardization Plan should be located in the general investigational plan. The Standardization Plan should include, but is not limited to the following:

1. List of the planned studies
2. Type of studies (e.g., phase I, II or III)
3. Study designs (e.g., parallel, cross-over, open-label extension)
4. Planned data standards, formats, and terminologies and their versions
5. List of and justification for studies that may not conform to the standards

EMA - 2013

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2013
EMA/240810/2013
Executive Director

Publication and access to clinical-trial data

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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.

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"Reviewer's Guides"

- Now required…listed in Draft Guidance 02/2014…..BUT….
  - Requests have been made by the reviewing divisions within the agency for a "Data Reviewer's Guide".
- Both Study Specific SDTM, ADaM data sets, as well as Integrated ADaM data sets.

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"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)
- Templates for SDRG and ADRG are available from the PhUSE Wiki
- PhUSE: Optimizing Data Standards Working Team

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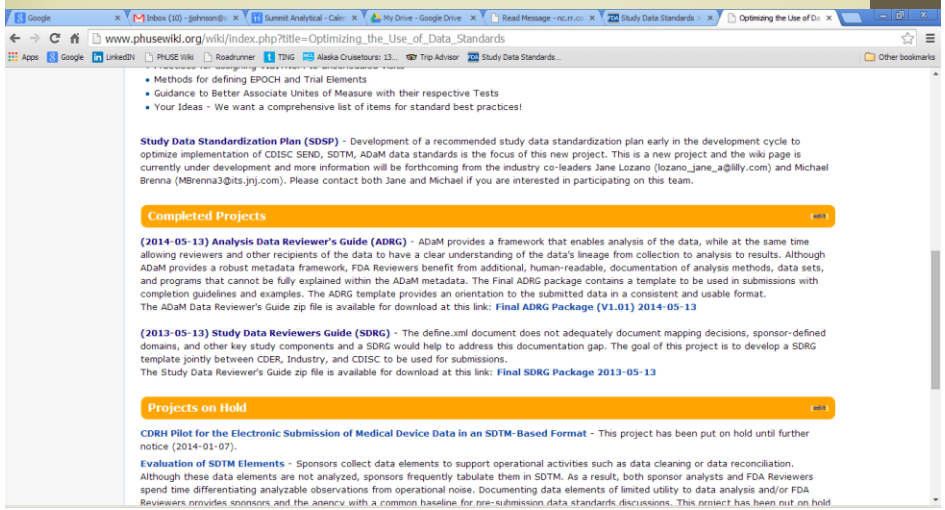
PhUSE Wiki

- Optimizing Data Standards – Completed Projects



www.phusewiki.org/wiki/index.php?title=Optimizing_the_Use_of_Data_Standards

- Methods for defining EPOCH and Trial Elements
- Guidance to Better Associate Unites of Measure with their respective Tests
- Your Ideas - We want a comprehensive list of items for standard best practices!

Study Data Standardization Plan (SDSP) - Development of a recommended study data standardization plan early in the development cycle to optimize implementation of CDISC SEND, SDTM, ADaM data standards is the focus of this new project. This is a new project and the wiki page is currently under development and more information will be forthcoming from the industry co-leaders Jane Lozano (lozano_jane_a@lilly.com) and Michael Brenna (MBrenna3@its.jnj.com). Please contact both Jane and Michael if you are interested in participating on this team.

Completed Projects

(2014-05-13) Analysis Data Reviewer's Guide (ADRG) - ADaM provides a framework that enables analysis of the data, while at the same time allowing reviewers and other recipients of the data to have a clear understanding of the data's lineage from collection to analysis to results. Although ADaM provides a robust metadata framework, FDA Reviewers benefit from additional, human-readable, documentation of analysis methods, data sets, and programs that cannot be fully explained within the ADaM metadata. The Final ADRG package contains a template to be used in submissions with completion guidelines and examples. The ADRG template provides an orientation to the submitted data in a consistent and usable format.
The ADaM Data Reviewer's Guide zip file is available for download at this link: **Final ADRG Package (V1.01) 2014-05-13**

(2013-05-13) Study Data Reviewers Guide (SDRG) - The define.xml document does not adequately document mapping decisions, sponsor-defined domains, and other key study components and a SDRG would help to address this documentation gap. The goal of this project is to develop a SDRG template jointly between CDER, Industry, and CDISC to be used for submissions.
The Study Data Reviewer's Guide zip file is available for download at this link: **Final SDRG Package 2013-05-13**

Projects on Hold

CDRH Pilot for the Electronic Submission of Medical Device Data in an SDTM-Based Format - This project has been put on hold until further notice (2014-01-07).

Evaluation of SDTM Elements - Sponsors collect data elements to support operational activities such as data cleaning or data reconciliation. Although these data elements are not analyzed, sponsors frequently tabulate them in SDTM. As a result, both sponsor analysts and FDA Reviewers spend time differentiating analyzable observations from operational noise. Documenting data elements of limited utility to data analysis and/or FDA Reviewers provides sponsors and the agency with a common baseline for pre-submission data standards discussions. This project has been put on hold

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. • Use the PhUSE template found on the PhUSE Wiki as a model.. • 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

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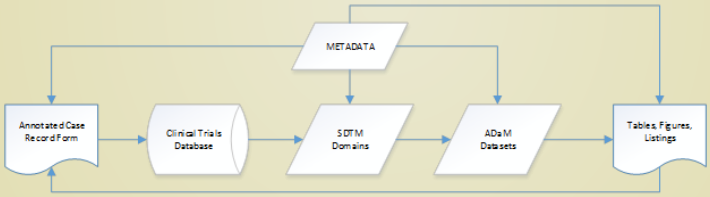
Traceability – Critically Important

- 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 <u>modifies subject level data eliminates the ability to trace data back to the source origin</u> and may result in a regulatory finding if found on audit.

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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.

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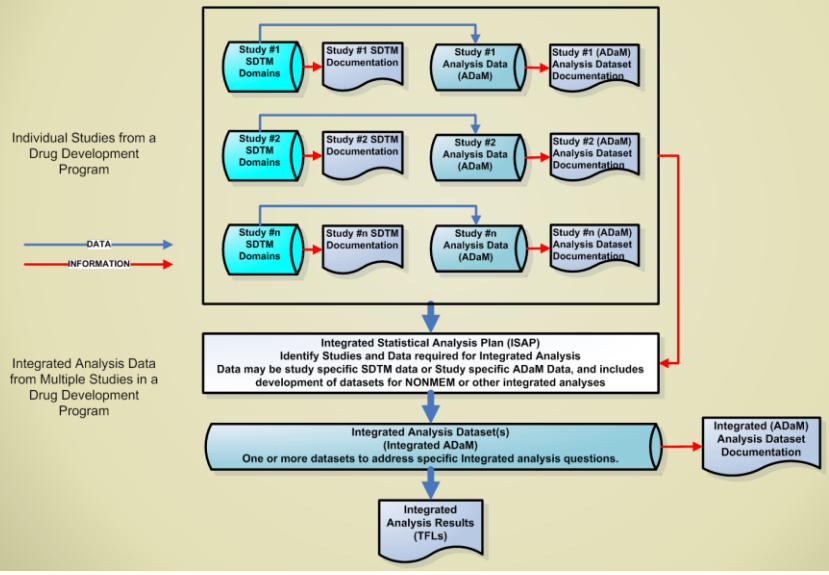
- **SPONSORS MUST BE EDUCATED ON THIS CONCEPT.**

Data Integration



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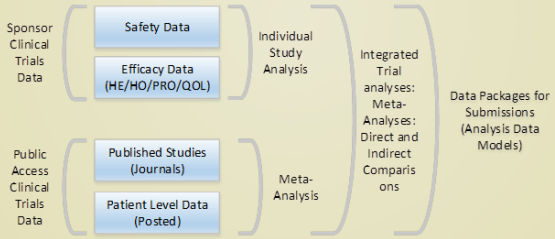
Evolving Landscape for Data Packages

- 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.



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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.

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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).
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Standardized Study Data (FDA Guidance: February 2014) (http://www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf).
- Study Data Technical Conformance Guide (FDA Technical Specifications Document: February 2014) (http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.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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SUMMIT ANALYTICAL

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