



An Introduction

From CDISC to PhUSE to Approval – A Statistical Reviewer's Experience and Thoughts

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FDA PhUSE Computational Science Symposium

Silver Spring, MD

March 20, 2017

Socializing the Deliverables

FDA/CDER/OTS/OB
Statistical Review Staff





“Socializing the Deliverables”*

OB Data Review Committee (DRC)

From the DRC Charter

- Assess OB practice -- handling of review data
- Evaluate compliance with CDER policies
- Collaborate with internal (i.e., CDER and FDA) data standards committees and working groups
- Liaise with outside organizations (e.g., CDISC, **PhUSE**, PharmaSUG, TransCelerate, CPath Institute, CFAST, DIA, HL7, SCDM, ASA, etc.)
- SOPs/guidelines
- Training

OB & DRC Involvement in PhUSE



- Mat Soukup – “Standard Scripts” Liaison
- Kate Dwyer – “Define v2.0 Implementation & Style Sheet Recommendations” and many others
- Weiya Zhang – Co-Chair of the OB DRC, Member: “Study Data Standardization Plan (SDSP),” “Legacy Data Conversion Plan & Report” and “Champion” for the ADRG
- Paul Schuette – “Standardizing data within the Inspection Site Selection Process” and others
- Jimmy Wong – R Shiny Poster (A new project, perhaps?)
- Huanyu (Jade) Chen – “Define v2.0 Implementation & Style Sheet Recommendations,” “Study Data Standardization Plan (SDSP),” “Legacy Data Conversion Plan & Report,” “SDTM ADaM Implementation FAQ” and others



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Disclosure Information

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies
- This presentation is mainly based on review experience for oncology products

CDER/OB/DB V Experience in 2016

- Approved Priority NDA/BLA/sNDA/sBLA: 82%
- A reviewer reviewed ~ 3-4 NDAs in 2016
- FDA: A reviewer +Team Leader + Division Director
- NDA/BLA submissions with
 - Good quality controlled data
 - Adequate documentations
 - Software codes
- Help to conduct review in a timely manner with fewer Information Requests (IRs)
- Response to IR needs 1-4 weeks

Timeline & Milestone for Statisticians in a 6-Month Priority Review

- Filing: check availability of essential components
- Internal mid-cycle: present major review issues
- Before Primary Review due: solve review issues and finalize product label
- Review clock is short under priority review:
 - 1-2 months review time from submission to mid-cycle
 - 1-2 months review time after mid-cycle to primary review due
- Sometime reviewer might have 3 months for expedited reviews

PhUSE Working Groups

- Optimizing the Use of Data Standards
 - Define file
 - Study Data Standardization Plan (SDSP)
 - SDTM ADaM Implementation FAQ
 - Legacy Data Conversion Plan & Report
 - Standardizing Data within the Inspection Site Selection Process
- Standard Analyses and Code Sharing
- ...

Pre-NDA Communication

- Provide an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG).
- Provide sufficient comments, adequate bookmarks, and hyperlinks in the define file(s).
- Provide executable SAS program(s), all necessary macro programs, and format library with adequate document(s) to
 - Duplicate the analysis datasets derivation from raw datasets
 - Duplicate efficacy and safety data analysis in the CSR and USPI



Data Format: CDISC vs. Legacy

- Study started before 12/17/2016
 - FDA Prefers to get CDISC data
 - Following FDA Data Standards Catalog
 - SDTM IG 3.1.1 or older: contact edata@fda.hhs.gov to get waiver
 - Legacy data is acceptable
- Study started after 12/17/2016
 - Following FDA Data Standards Catalog

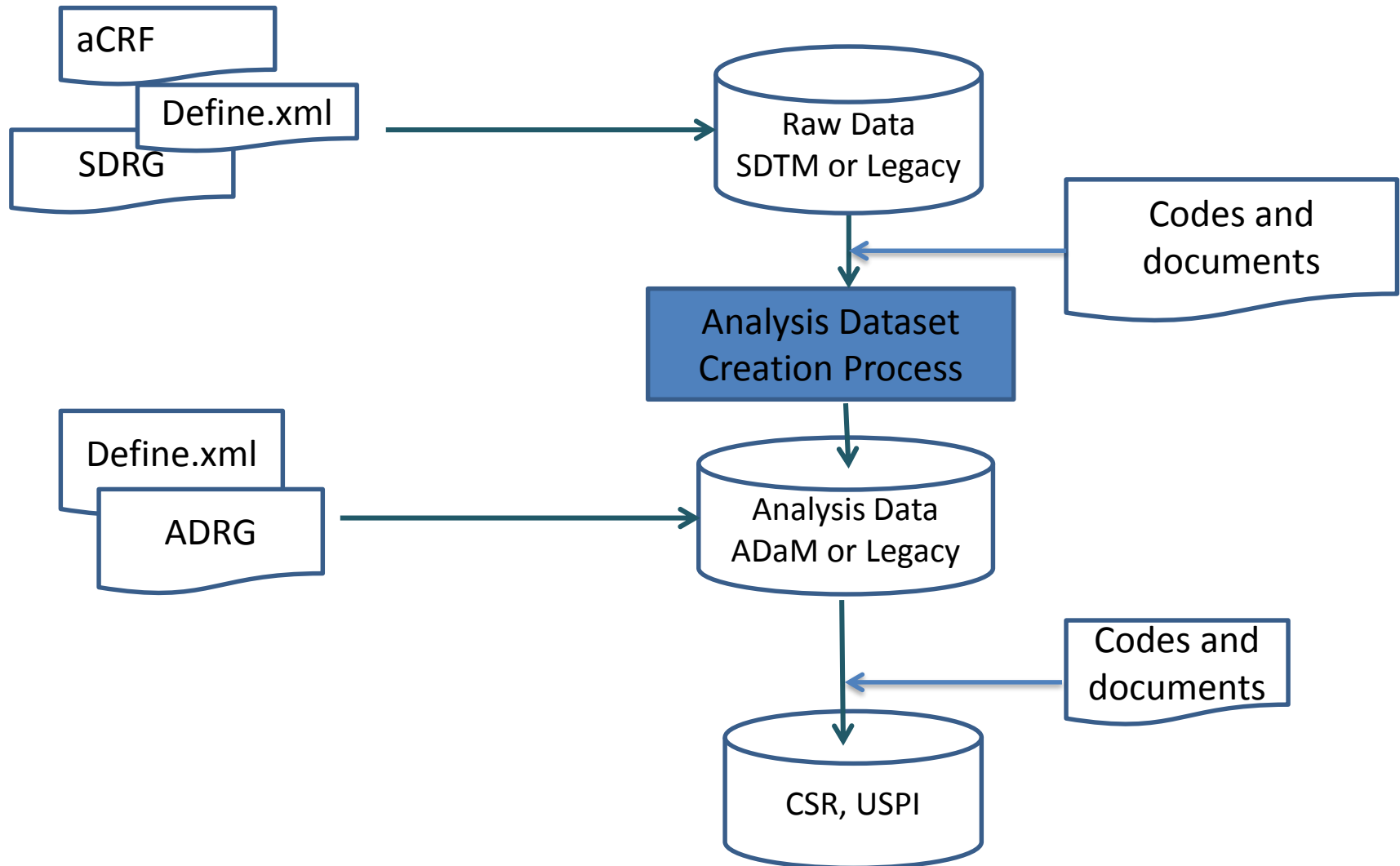
Data Format

- FDA Data Standards Catalog
 - Data: SAS Transport Format V5 (.XPT)
 - Documents: .PDF
 - Define file: .XML (V2) or .PDF
 - Statistical programs: ASC II

To do List for Data-Related Filing

- Data structure (Legacy, CDISC)
- Data location
- Define files sufficiently detailed
- Software code for CSR and USPI
- Pick sites for inspection
- Analysis datasets:
 - Randomly pick analysis variables to confirm the derivation from raw data
 - Sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation

Data Traceability



Define file – DM Domain

3.2.1 Table 3.2.1 SDTM Submission Dataset-Definition Metadata Example

Dataset	Description	Class	Structure	Purpose	Keys*	Location
DM	Demographics	Special Purpose Domains	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt
CO	Comments	Special Purpose Domains	One record per comment per subject	Tabulation	STUDYID, USUBJID, COSEQ	co.xpt

- Bookmarks and hyperlinks help to explore multiple documentations
- Contents in the define file help to understand data structure

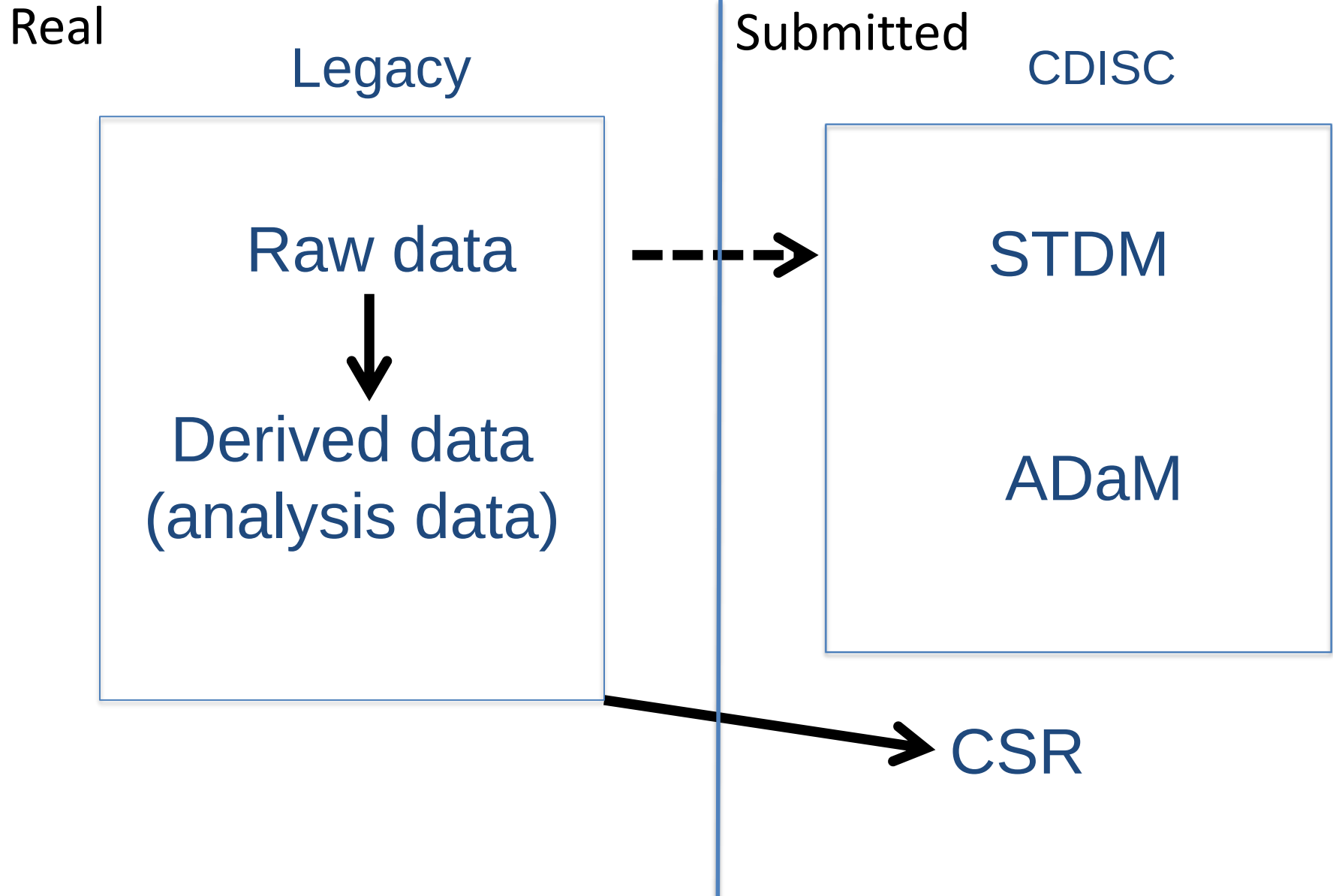
Potential Actions

- Before issuing filing letter
 - IR(s) will be sent to applicant for further clarification
 - During the applicant orientation meeting, review team shares issues with applicant face to face
 - Whether major issue can be solved before filing
 - Yes: issue filing letter
 - No:
 - Resubmit data
 - Extend PDUFA clock
 - Refuse to file

To do List for Data During Review

- Reproduce the primary analysis dataset, and in particular the primary endpoint and major secondary endpoint(s), from the raw data
- Verify the randomized treatment assignments
- Check the usability of the data
- Check documentation of data quality control/assurance procedures
- Check the blinding/unblinding procedures
- Additional exploratory analyses based on inconsistent results or clinical concerns

Issues During Review



Conclusions

- CDISC helps to standard data collection/ submission
- PHUSE helps to generate adequate documents for FDA's reviewer to understand submitted data
- Software codes from raw data to analysis data to CSR helps to save further information requests

Useful Documents Related to NDA/BLA Data submission

- CDER [Common Data Standards Issues Document](#)
- CDER: [Statistical NDA Reviewer template](#)
- ICH: Data quality control/assurance procedures ([ICH E3](#), section 9.6; [ICH E6](#), section 5.1)
- FDA Mapp 6025.4: [Good review practice: Refuse to file](#)
- FDA: [Data Standard Catalog](#)
- FDA: [Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products](#)
- FDA: [Guidance for Industry Providing Regulatory Submissions in Electronic Format — Standardized Study Data](#)
- FDA: [Regulatory Submissions in Electronic Format — Submissions Under Section 745A\(a\) of the Federal Food, Drug, and Cosmetic Act](#)
- FDA: [Guidance for Industry Providing Regulatory Submissions in Electronic Format — Standardized Study Data](#)
- CDISC: [Study Data Tabulation Model Metadata Submission Guidelines \(SDTM-MSG\)](#)
- CDISC: SDTM IG 3.2 and ADAM IG 2.1
- PHUSE: [SDRG](#) V1.2, [ADRG](#) V1.1

Acknowledgments

OTS/CDER/FDA

- Thomas Gwise, Ph.D., Deputy Director, DB V
- Rajeshwari Sridhara, Ph.D., Director, DB V
- Steve Wilson, Ph.D. , Director, DB III

