U.S. FOOD & DRUG ADMINISTRATION

Common Data Related Review Issues and Prevention:

A Statistical Reviewer's Thoughts

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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 2017

- Approved Priority NDA/BLA/sNDA/sBLA: 56%
- A reviewer reviewed ~ 3-4 NDAs in 2017
- FDA Statistical review: 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

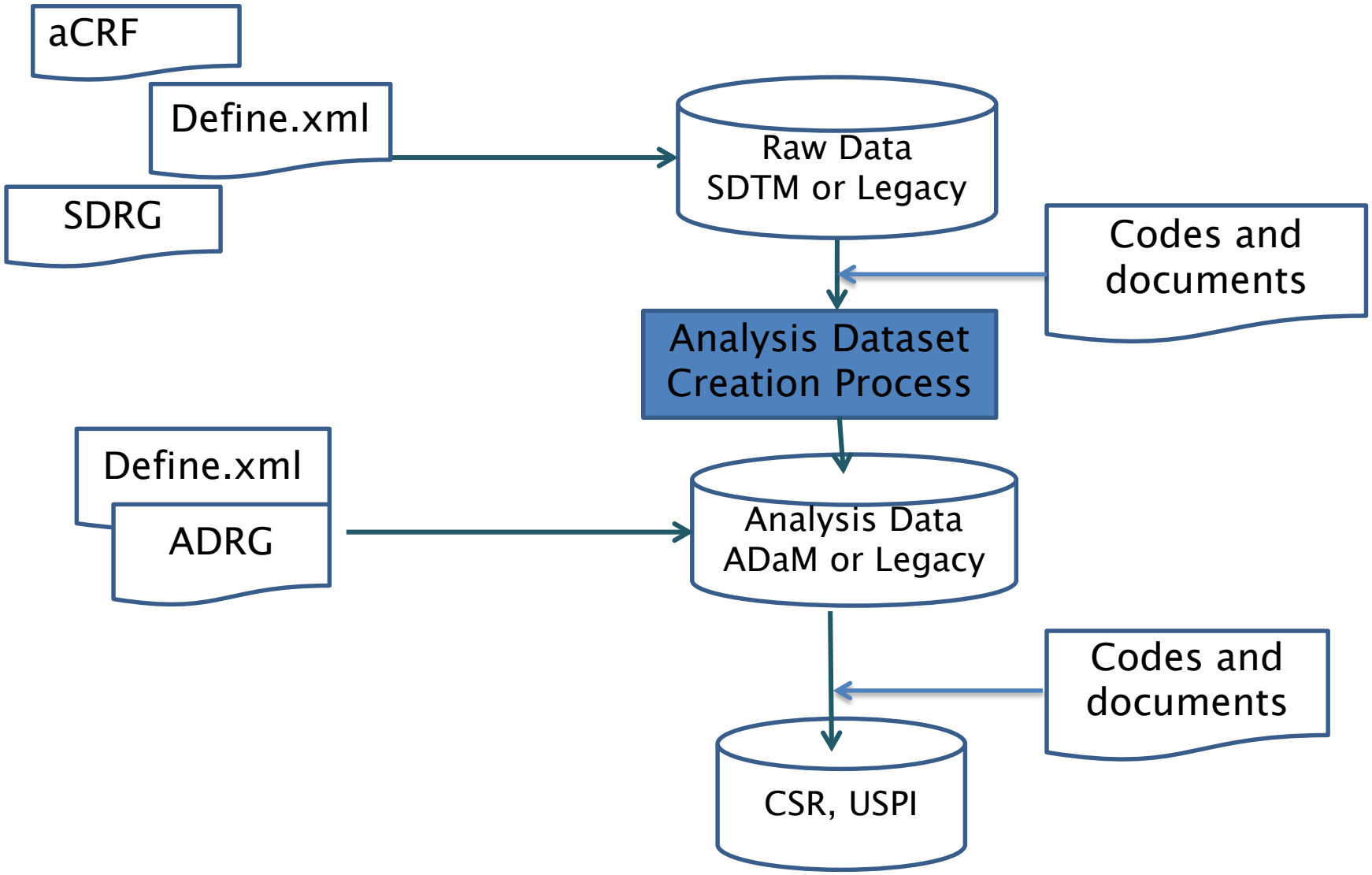
Timeline & Milestone for Statisticians in a 6-Month Priority Review

- 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

To do List for Data-Related Filing

- Data structure (Legacy vs. 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



Common Data Related Review Issues

- Data format
  - Failed to follow aspects of standardization
  - Organized inadequately
  - Lack of documentations
  - Incompatible with FDA tools
- Lack of required elements of a complete application
- Discordance among submitted datasets

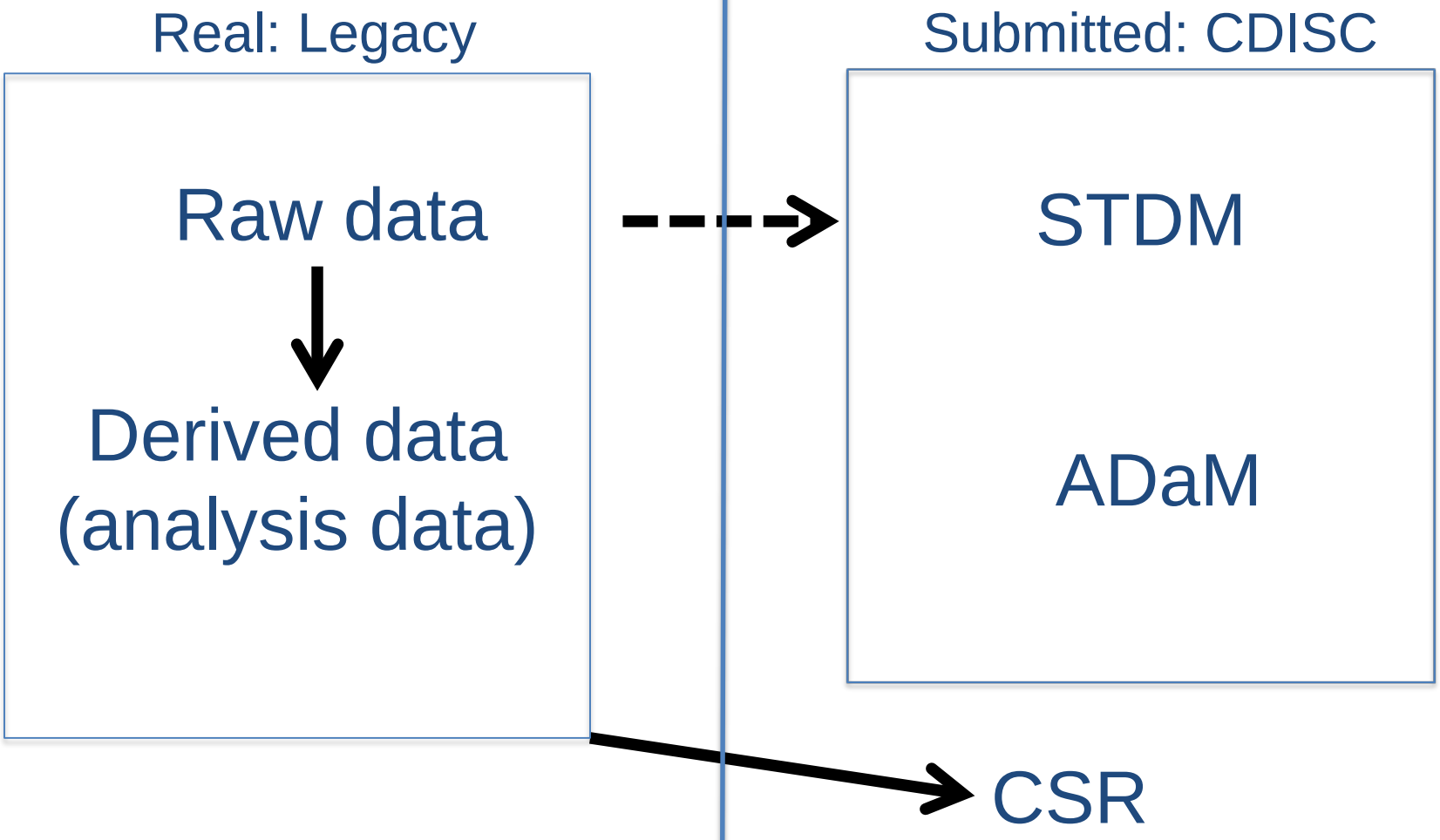
Data Format: CDISC vs. Legacy

- 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
  - DM and TS in CDISC format are mandatory
- 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

Issues – Standardization



Issues – Documentation

- ADRG & define files
  - Insufficient information to understand and navigate analysis datasets
  - Insufficient details to allow reviewers to understand the meaning, source, and derivation of each variable used in the safety and efficacy analyses
  - Inadequate comments, bookmarks and hyperlinks
- CSR: inadequate bookmark or hyperlink
- Reviewer's guide for submitted statistical programs

Issues – Essential Element

- **Data**
  - Lack of unique patient identifier
  - Lack of analysis population flags
  - Lack of treatment phase variables
  - Lack of important baseline disease characteristics
  - Lack of important variables in the efficacy or safety dataset
    - Treatment Phase, Worst AE grade
- **Statistical programs**
  - Insufficient information to understand and navigate programs
  - Insufficient comments
- **Missing all versions of SAPs, Protocols, and DMC meeting minutes**

Issues – Data Quality

- Missing value
  - Real missing, unknown, not collected, vs. systematic missing
- Discordant among different datasets
  - Inconsistent variable names across submission
  - Inconsistent results across submission
  - Lack of clarification between same contents among different dataset (CNMED and CNMEDP datasets have same columns but different number of rows)

Filing Issues

- Before planning meeting
  - Exchanged concerns within review team
  - Issued IR
- Before filling meeting
  - Discussed deficiencies identified during preliminary review in F2F meeting

    "deficiencies identified during our preliminary assessment of your application that preclude us from conducting a substantive and reasonable review of your BLA"
- Whether major issue can be solved before filing
  - Yes: Issue filing letter
  - No:
    - Resubmit data
    - Extend PDUFA clock
    - Refuse to file

Prevention

- Submit datasets using CDISC standards.
  - Otherwise, follow CDISC standards as much as possible
- Submit SDRG and ADRG
- Provide statistical programs used to
  - Derive analysis datasets from raw datasets
  - CSR and USPI
  - Conduct SAP pre-specified supportive analyses
- Define files with adequate comments, bookmarks, and hyperlinks

Useful Documents Related to NDA/BLA Data submission

- 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
- FDA: Providing Regulatory Submissions in Electronic Format – Standardized Study Data - STUDY DATA TECHNICAL CONFORMANCE GUIDE Technical Specifications Document"
- 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)
- 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

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