Common Data Related Review Issues and Prevention:

A Statistical Reviewer’s Thoughts

Huanyu Chen, Ph.D.
Statistical Reviewer, DB V/OTS/CDER/FDA

PharmaSUG 2018 Seattle, WA 5/1/2018
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

- aCRF
- Define.xml
- SDRG
- Define.xml
- ADRG

Raw Data
SDTM or Legacy

Analysis Dataset Creation Process

Analysis Data
ADaM or Legacy

CSR, USPI

Codes and documents

Codes and documents
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

Real: Legacy

Raw data

Derived data
(analysis data)

Submitted: CDISC

STDM

ADaM

CSR
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 filing 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 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
Acknowledgments

OTS/CDER/FDA

– Rajeshwari Sridhara, Ph.D., Director, DB V
– Weiya Zhang, Ph.D., DB III
– Data Review Committee