U.S. FOOD & DRUG ADMINISTRATION

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Presentation Developed By…

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FDA/CDER/Office of Biostatistics (OB)/

Division of Analytics and Informatics (DAI)

Brief Bio:

- Joined FDA in 2018
- NDA/BLA submissions
- CDISC data standards
  - ADaM ADQRS
  - SDTM QRS

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Experiences of CDER Statistical Analysts with NDA/BLA reviews: Some Helpful Tips for Sponsors

–contributed by all the analysts from DAI

Disclaimer

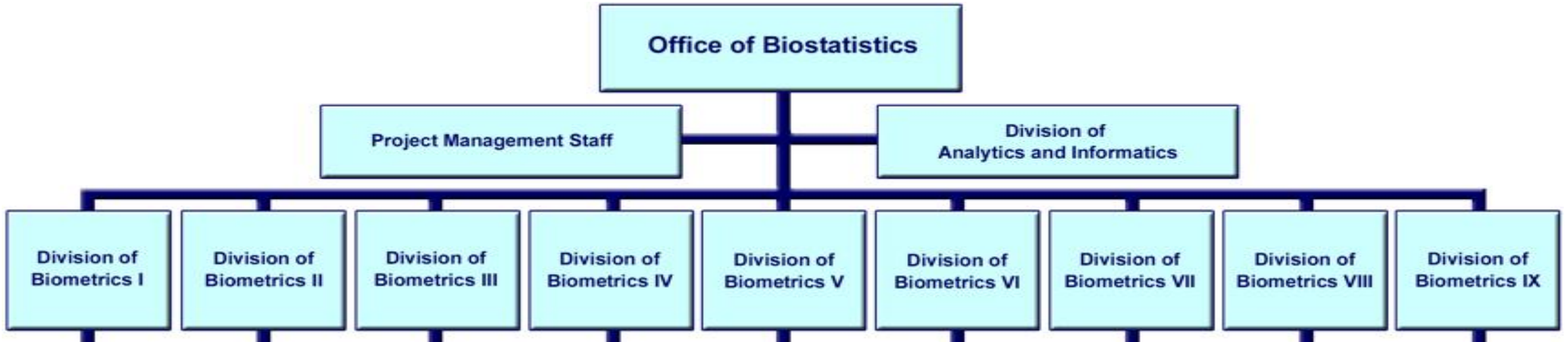
The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Outline

- Division of Analytics and Informatics (DAI) Overview
- Challenges to review the submissions
- Examples from our real work
- Summary

DAI – Who we are

- Analytics and Informatics Staff (AIS) - Established in November 2019
- Division of Analytics and Informatics (DAI) – Reorganized in 2022
  - ➢ One of the ten divisions of the Office of Biostatistics
  - ➢ We continue to grow and hire to meet the increasing demand for our services



DAI – What we do

- Works jointly with all 9 Divisions of Biometrics (DB)
  - To support computational and programming needs of NDA/BLA reviews
- Provides leadership in the areas of:
  - Data Standards
  - Data Integrity and Data Quality
  - Data Visualization and other Data Tools
  - Scientific Computing and Statistical Programming
  - IT Tools Development and Support

DAI – How we work

Collaborate closely with statistical reviewers to

- Conduct site selection analyses
- Perform data quality checks
- Replicate sponsor's results
- Conduct additional statistical analyses as needed
- Draft Information Request (IR)
- Prepare tables and figures for Advisory Committee (AC) meetings

Challenges with Submissions

- Define xml files
- SAS Programs
- Clinical Study Reports (CSR)
- Study Data Reviewer's Guide (SDRG)/ Analysis Data Reviewer's Guide (ADRG)
- ……

Define xml-1

Issue

The variable definitions are not complete

- No information available regarding the derived parameter and how the parameters were calculated
- Request sponsor to send original data from which these variables could be derived

Recommendations

- Provide a thorough and detailed define file
- Provide the logic or algorithms used to derive these variables

Analysis Dataset for Bowel Movement Parameter [CL.ADBM.PARAM]

Permitted Value (Code)
Average Number of BM per Day
BM Daily Average by Week
Loose/Water stool days per week
Bowel Movement Daily Report
Loose/watery stool on the Day (Y/N)
Daily BM Number

Define xml-2

Issue

The variable definitions are not complete

- The variable definitions are not meaningful
- May end up having to send an IR

Recommendations

- Provide explicit definition in DEFINE document, particularly for key variables such as PARAMCD. If numbers used, please indicate clearly what the numbers mean

PDCRSLT	Protocol Defined Central RSV LRTI
PDCRSLT1	Protocol Defined Central RSV LRTI 1
PDCRSLT2	Protocol Defined Central RSV LRTI 2
PDCRSLT5	Protocol Defined Central RSV LRTI 5

SAS Program-1

Issue

Lack of sufficient comments

- SAS programs/R scripts do not follow good programming practices

Recommendations

Having well-commented code to explain what it is doing

- Describing the purpose of the code in the header of the program
- Separating the code into chunks with a one-line description at the beginning of each chunk
- Adding comments is a simple action sponsors could take to make our work easier

SAS Program-2

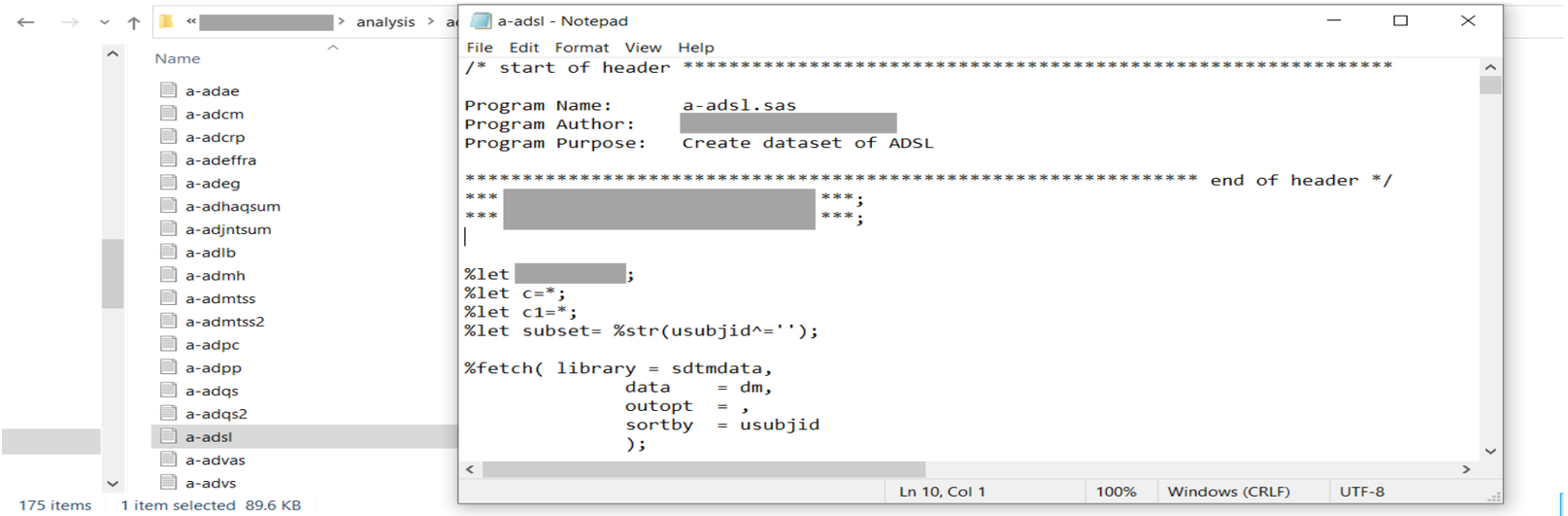
Issue

Lack of necessary information in the program header

- Missing SAS macro dependency

Recommendations

- Provide comprehensive information in the program header, such as the datasets used and the names of all macros called in the program
- Ensure the program's structure and dependencies are easy to understand



SAS Program-3

Issue

- Not all macros called in the program have been submitted

Recommendations

- Please ensure it is complete and submit all the macros called in the program in the package, particularly for the primary efficacy analyses

```
%macro eff_mi(uri=, pop=, data=,basetype=,testcd=, testnum=,pmnfmt=,anlfl=,visn=120,endeffvis=,type=,anlyvar=,dec=0, meandata=,showparam=N
              ,nimpute=50
              ,mincutoff=N
              ,maxcutoff=N
              ,subgrp=,subgrplbl=,tf=TABLE,savedata=%str( )
              ,mi_datalib=MI_DATA,midata=%str()
              ,covid19=N,covid_wocf_locf_anlfl=anl06fl,cond=%str(1)
              ,tnum= , tt1= , tt2= , tt3= , tt4= , tt5= , tt6= , ft1= , ft2= , ft3= , ft4= , ft5= , ft6= , ft7= , ft8=
              );
```

SAS Program-4

Issue

ALL analyses performed in ONE program

- All aspects of the analysis are in one program, including primary, secondary, exploratory, subgroup, and sensitivity analyses, etc. This makes it difficult to review the code and locate necessary information

Recommendations

- Separate programs based on the purpose of each analysis

SAS program-5

Issue

Lack of usefulness

- Multiple layers of macros for one table
- Hard to locate key information
- May end up having to send an IR

Recommendations

- Simplify programs
- Easy to find key information on
  - how key variables were derived
  - how the efficacy analyses were performed

Please provide the following:

1) Step-by-step procedure for how to calculate the average weekly dose and the number AEs for each dose category using the ADaM data sets submitted with the NDA and relevant variables. For example, if ADSL.xpt and ADEX.xpt were used to derive another data set for analysis, the step-by-step procedure should describe how variables in ADSL.xpt and ADEX.xpt were manipulated and analyzed to allow us to replicate calculation of average weekly dose and number of AEs.

2) Simplified SAS code that will allow us to generate tables.

If the SAS code is repetitive, you can provide one sample code and clearly specify relevant datasets and variables. Your SAS code should not use any macros and only read in datasets that were submitted with the NDA.

Clinical Study Report-1

Issue

Lack of meaningful information in the footnotes

- Necessary information about how the tables were generated is absent

Recommendations

It would be very helpful to provide as much as information in the footnotes

- Inclusion/exclusion criteria
- Source datasets
- Statistical models
- Programs
- Key variables

Clinical Study Report-2

Issue

Missing files referred to in the footnotes

- SAS programs referenced in the footnotes were not submitted.
- Not consistent with names for datasets, programs and footnotes throughout the submission

Recommendations

- If a program is cited in the footnote, then that program should be submitted as part of the submission package

Study Data Reviewer's Guide (SDRG)/ Analysis Data Reviewer's Guide (ADRG)

- The SDRG and ADRG are usually the first documents we read before working on the data
- Provide essential information to understand the submission
- Recommend providing more information
  - For datasets: core variables/flag variables/parameters
  - To specify the statistical models for efficacy
  - To explicitly specify any multiple imputation methods used
- Provide illustrative snippets of SAS code

Summary

- The FDA requires complete and accurate information in submissions to ensure the safety and efficacy of drugs and other medical products.
- Sponsors can improve the review process by following best practices which will enable efficient and effective FDA reviews
  - Use clear and concise programming to facilitate the review process
  - Simplify complex programming when possible to reduce the risk of errors and save review time
  - Provide complete information from the package, including define.xml, programs, CSR, and SDRG/ADRG
  - Ensure that key information is easily accessible and well-organized to streamline the review process and avoid information requests

Thank you for your attention.

Questions?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