FDA eSubmission

What Programmers need to know?

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Agenda

1. eSubmission – Guidance for Industry
   a. eCTD Specification
   b. Datasets and Study Information
2. Statistical Programmer inputs to eCTD Components
3. Study Data Standardization Plan
4. Analysis Result Metadata
5. References

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FDA eSubmission

Guidance for Industry

Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product2 Applications and Related Submissions Using the eCTD Specifications

The Electronic Common Technical Document (eCTD) is the standard format for submitting application, amendments, supplements and reports to FDA

The two division in FDA reviewing this documents are

1. Center for Drug Evaluation and Research (CDER)
2. Center for Biologics Evaluation and Research (CBER)

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eCTD – What and Why ?

- electronic Common technical document (eCTD) consists of 5 modules:
  - Module 1: Region specific Information
  - Module 2: Summary Documents
  - Module 3: Quality
  - Module 4: Non-clinical Study Reports
  - **Module 5: Clinical Study Reports**

- This is applicable for
  - Investigational New Drug (IND)
  - New Drug Applications (NDAs)
  - Abbreviated New Drug Applications (ANDAs for generics)
  - Biologics License Applications (BLAs)

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eCTD Specification

- Details of current version of eCTD documents submitted to FDA is given in eCTD specification
- Provided by FDA
- eCTD specification is an excel document which has 4 sheets
  - Instructions
  - Data exchange standards
  - Terminology standards
  - Change history
- Link to eCTD Specification http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM340684.xls
- 
  Microsoft Excel Worksheet

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Components Provided by Programmers

- **Study Data Standardization plan**
- Pooled data
  - Summary of Clinical Safety (SCS) and Summary of Clinical Efficacy (SCE)
    - ADaM data
    - Define.xml
    - ADRG
    - **A**nalysis **R**esult **M**etadata

Contd...

- Individual Studies
  - SDTM
    - Data as XPT
    - Define.xml
    - Study Data Reviewers Guide (SDRG)
    - SDTM Annotated CRF
  - ADaM
    - Data as XPT
    - Define.xml
    - Analysis Data Reviewers Guide (ADRG)
    - **A**nalysis **R**esult **M**etadata

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Study Data Standardization Plan (SDSP) – What?

- It establishes and document a plan for describing the data standardization approach for planned studies within a specific submission.
- It is recommended to include as a part of regulatory submission.
- Informs about intended and/or current state of data standards.
- Used as communication tool with FDA to ensure reviewers understands the data standards.
- As this is a live document, can be used internally for business decisions (e.g. pooling, data conversion)

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Study data Standardization Plan (cont..)

- SDSP from Study Data Technical Conformance Guide – Nov 2016

  https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

  - This provides technical recommendations for the submission of animal and human study data in a standardized electronic format.
- FDA does not provide a specific template for an SDSP
- PhUSE provides an SDSP template

  http://www.phusewiki.org/wiki/images/7/7d/SDSP_Template.docx

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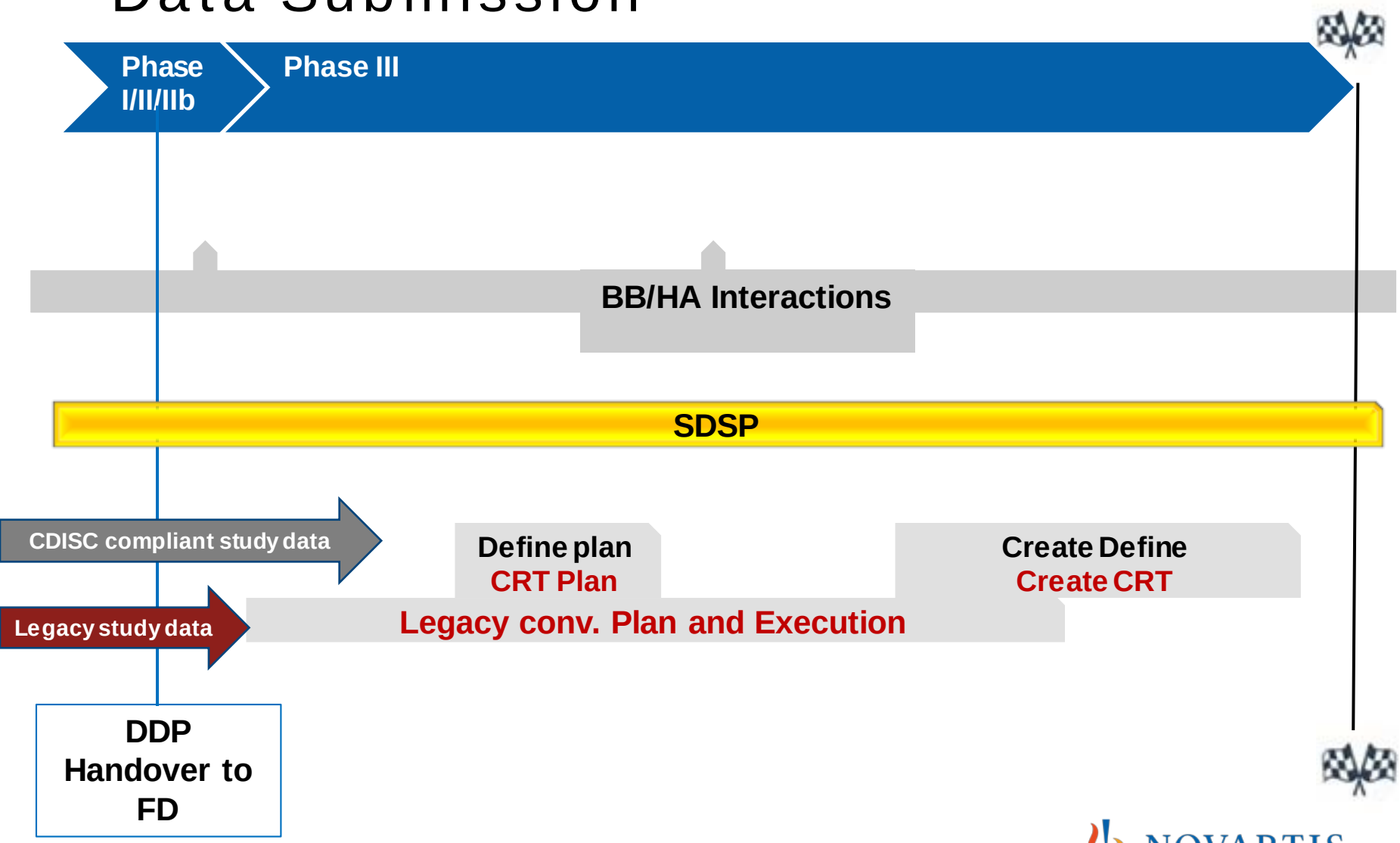
End-to-End – Electronic Standardized Data Submission



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Benefits of SDSP

- Brings internal focus and agreement to the standards throughout the project lifecycle
- Provides a means of tracking discussions and agreements with the FDA or other Health Authorities
- Drives decisions about legacy data conversion and up-versioning of data standards to allow for pooling of data across studies at a much earlier time than pre-NDA meetings.
- Provides an important reference for all stakeholders.

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Key point to keep in mind while SDSP update

- Ensure that the SDSP is available to the FDA at critical stage gate meetings.
- Update the SDSP prior to meetings or communications with the FDA where the SDSP will be discussed.
- Provide the SDSP in its formal form at submission including a statement in the cover letter describing the extent to which the latest version of the SDSP was executed.
- Ensure that critical changes or updates to the use of data standards are agreed upon with the FDA prior to submission
- Ensure that the SDSP that is being used to make critical decisions is current, complete, and accurate.
- Make sure to keep a clear change history for SDSP transparency

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Analysis Result Metadata (ARM)

- ARM describes the major attributes of a specified result found in submission
- It supports the review of analysis results and their relation to submitted clinical trial data
- Key components of ARM are:
  - Analysis Display metadata definitions
    - Analysis Result metadata definitions
      - Analysis parameter(s)
      - Analysis dataset(s)
        - Analysis variable(s)
        - Selection criteria
      - Documentation
      - Programming statements

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ARM – Why?

- Facilitates documentation and reproduction of analysis results.
- Not needed for every analysis which is included in submission
  - Sponsor determines which analyses should be included, e.g., primary efficacy analysis and secondary analysis.
- ARM can be provided for complex statistics.

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ARM for CDISC sample study

Table 14-3.01

Display	**Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)**
Analysis Result	**Dose response analysis for ADAS-Cog changes from baseline**
Analysis Parameter(s)	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)
Analysis Variable(s)	CHG (Change from Baseline)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADQSADAS [PARAMCD = "ACTOT" and AVISIT = "Week 24" and EFFFL = "Y" and ANL01FL = "Y"]
Documentation	Linear model analysis of CHG for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose). SAP Section 10.1.1

Programming Statements	[SAS version 9.2]
	`proc glm data = ADQSADAS;`
	`  where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT";`
	`  class SITEGR1;`
	`  model CHG = TRTPN SITEGR1;`
	`run;`

Useful links and References

1. Analysis Result Metadata (ARM) v1.0 guide:

https://www.cdisc.org/standards/foundational/analysis-data-model-adam/analysis-results-metadata-v10

2. FDA eSubmission latest updates – sign in for email updates using below link:

http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm#guides

http://www.lexjansen.com/pharmasug/2016/SS/PharmaSUG-2016-SS01-PPT.pdf

http://support.sas.com/documentation/cdl/en/clinstdtktug/69404/HTML/default/viewer.htm#n1r0huhk4td6xyn1iprj00nnsxdb.htm

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM511230.pdf

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Thank You!!

Q & A ?

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Back up

Timing of SDSP creation

Stage gate	Expectation
Pre-IND	**Provide all known studies and their data standards information.**
IND	**Ensure initiation of the SDSP at this time point if not earlier.**
End of Phase II	**Add more about the studies expected in the submission and the plan for possible integration of standards.**
Type C meeting to discuss data standards	**If not given time at other FDA meetings, communicate the SDSP to FDA to ensure their agreement to the SDSP.**
Pre-NDA meeting	**Provide SDSP as a confirmation of all prior agreements around data standards.**
Submission	**Include in eCTD.**

1. Start as early as possible, preferably at pre-IND meeting
2. Add as much data standards information that is known at this time point

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Briefing Book and SDSP

- A document prepared to facilitate the exchange of information with Health Authorities during formal meetings.
- If the SDSP is to be provided with the BB, it is recommended that it be an Appendix to the BB with a reference in the Data Standards section.
- The SDSP should be updated to match the studies discussed in the briefing book.
- The current proposal is to reference the SDSP whenever we want to identify the Data Standard of the study data.
  - Reference the SDSP in the Data Standards section of the Briefing Book.
  - Provide the SDSP under separate cover for the End-of-Phase 2 meeting.

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Triggers for SDSP updates

- New study added or planned
- Integrated analysis plan defined
- Study removed from a submission
- Upcoming regulatory interaction with FDA
- Agreements between FDA and sponsor

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