

Three blue, glossy spheres are arranged vertically on the left side of the slide, each reflecting light and showing a distorted view of the other spheres.

An FDA Submission Experience Using the CDISC Standards

RG04

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PhUSE2017



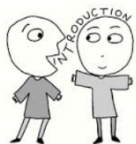
October 8th – 11th, 2017 | Edinburgh, Scotland | Join us at booth 31

Disclaimer

The content of this presentation represents my personal experience with this particular submission with this specific sponsor on a specific indication

Although some of the slides contain information coming from existing requirements, such as CDISC standards and FDA guidances, they represent our experience of applying standards and interacting with the FDA

Topic and timing of submission, as well as reviewer 'preferences', are important factors to consider when submitting data to FDA



A Recent Submission (1)

- Indication: Pain in a « specific » indication
- Scope of Work: FDA NDA submission
 - ISS: Integrated Summary of Safety
 - ISE: Integrated Summary of Efficacy
- Nr. Of studies: 6
 - 3 only ISE: 1018 Randomized patients
 - 6 ISS: 1155 Randomized patients
 - Screening Failure Patients not included in the SDTM packages → **FDA Requested later « some » SF data for pivotal studies only**
- **Cytel** involved in SDTM Migration, Phase II/III pivotal studies analysis, ISS/ISE Pooling and Analysis, Data Submission Package, Gives advices
- **Sponsor** Interact with FDA and responsible for final package preparation, Takes Decisions

A Recent Submission

The Data Package

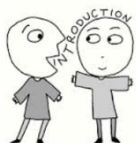
Interaction with FDA

SDTM

ADaM Pooling

Validation

Conclusions



A Recent Submission (2)

A Recent Submission

The Data Package

Interaction with FDA

SDTM

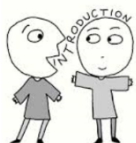
ADaM Pooling

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Standards Used

- SDTM Ig 3.2
 - + cSDRG (Study Data Reviewer Guide) as per latest PhUSE template
- ADAM Ig 1.0
 - + ADRG (Analysis Data Reviewer Guide) as per latest PhUSE template
- Define.xml 2.0 (without results metadata)
 - + Output program details provided in the ADRG
 - i.e. SAS proc used, source ADAM dataset, selection (i.e. PARAMCD to be used, way of selecting correct records to be analysed, etc.)



A Recent Submission (3)

A Recent Submission

The Data Package

Interaction with FDA

SDTM

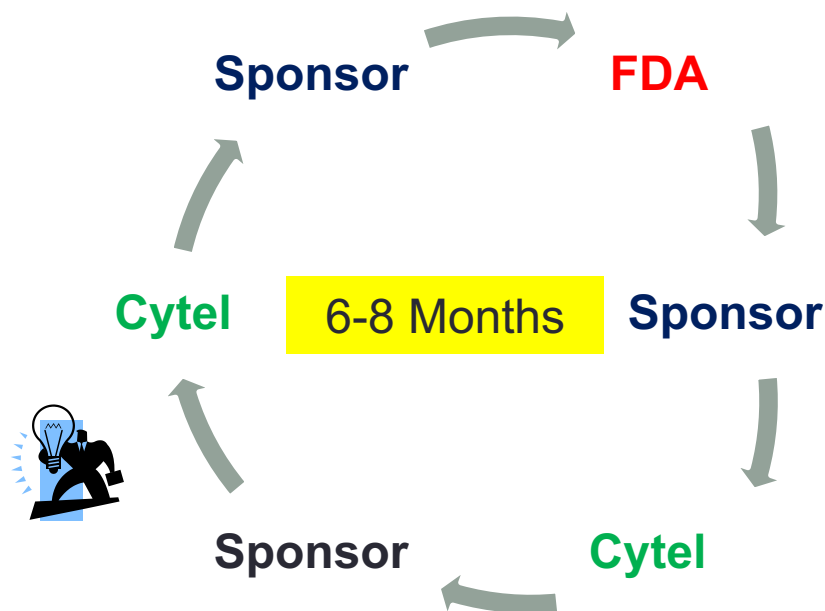
ADaM Pooling

Validation

Conclusions

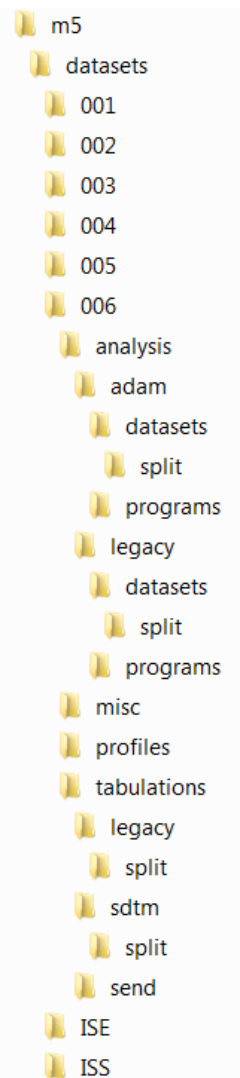
Current Status

- Submitted in October 2016
- 1st set of FDA Feedback in January 2017
- « Looping » through sponsor exploratory analyses and FDA additional requests





The Submission Data Package



ADaM Analysis Datasets and Programs

Non ADaM Analysis Datasets and Programs

Other datasets i.e. look-up datasets

Non-SDTM Tabulation Datasets

SDTM Tabulation Datasets

ISS/ISE Pooling Folders

A Recent Submission

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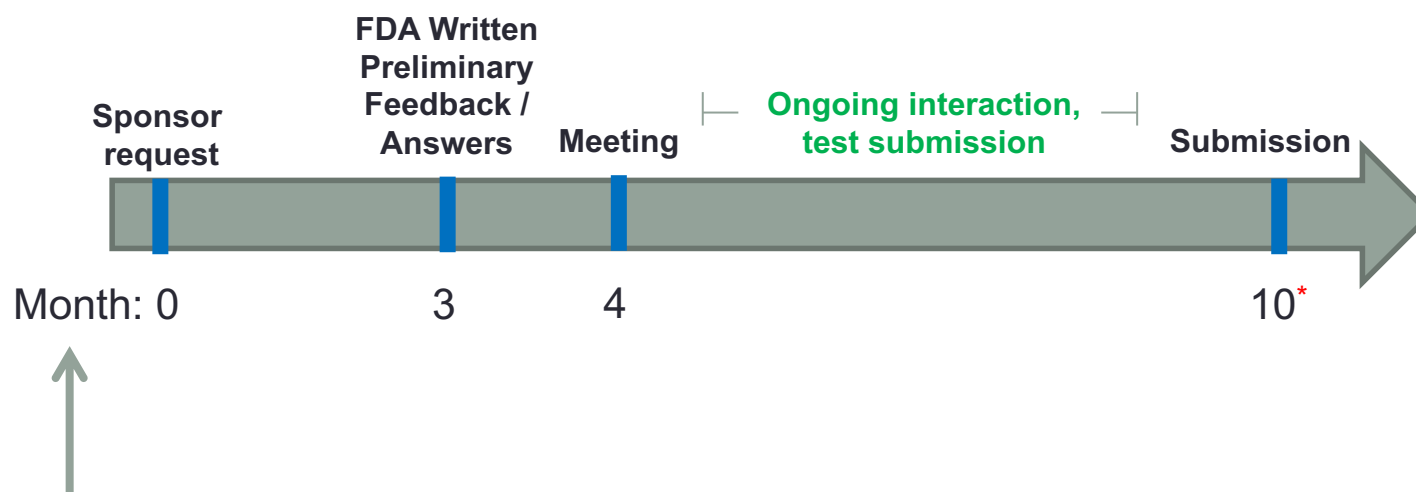
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FDA Interaction with FDA – Pre (1)

Pre-NDA meeting



Anticipate Items / Questions you would like to discuss during the meeting with regards to the application

* These are from our experience i.e. they are not standard FDA timeline

Formal Meetings Between the FDA and Sponsors or Applicants

<https://www.fda.gov/downloads/drugs/guidances/ucm153222.pdf>

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Interaction with FDA – Pre (2)

Pre-NDA Meeting

Data Submission Strategy FDA Feedback

1. **The integrated safety dataset must include the following fields/variables:**
 - a. unique patient identifier,
 - b. study/protocol number,
 - c. patient's treatment assignment, demographic characteristics, including gender, chronological age (not date of birth), and race,
 - d. dosing at time of adverse event,
 - e. dosing prior to event (if different),
 - f. duration of event (or start and stop dates),
 - g. days on study drug at time of event,
 - h. outcome of event (e.g., ongoing, resolved, led to discontinuation),
 - i. **flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment**
 - j. marker for serious adverse events
 - k. verbatim term

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Interaction with FDA – Pre (3)

Pre-NDA Meeting

Data Submission Strategy FDA Feedback (cont)

- Replication of potential covariates / subgroup variables in all ADaM datasets i.e. RACE, SEX
→ make a clear plan in the SAP
- MedDRA Version to be used in the pooled ISS
- SMQ Proposal for further safety investigation

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FDA Interaction with FDA – Pre (4)

Pre-NDA Meeting

By site investigator listings for investigator on-sites inspections

For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:

- a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
- b. Subject listing for treatment assignment (randomization)
- c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
- d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
- e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
- f. By subject listing, of AEs, SAEs, deaths and dates
- g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
- h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
- i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
- j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

FDA OSI Webinar: Overview of information Requested by CDER OSI.....

<https://collaboration.fda.gov/p44198603>

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FDA Interaction with FDA – Pre (5)

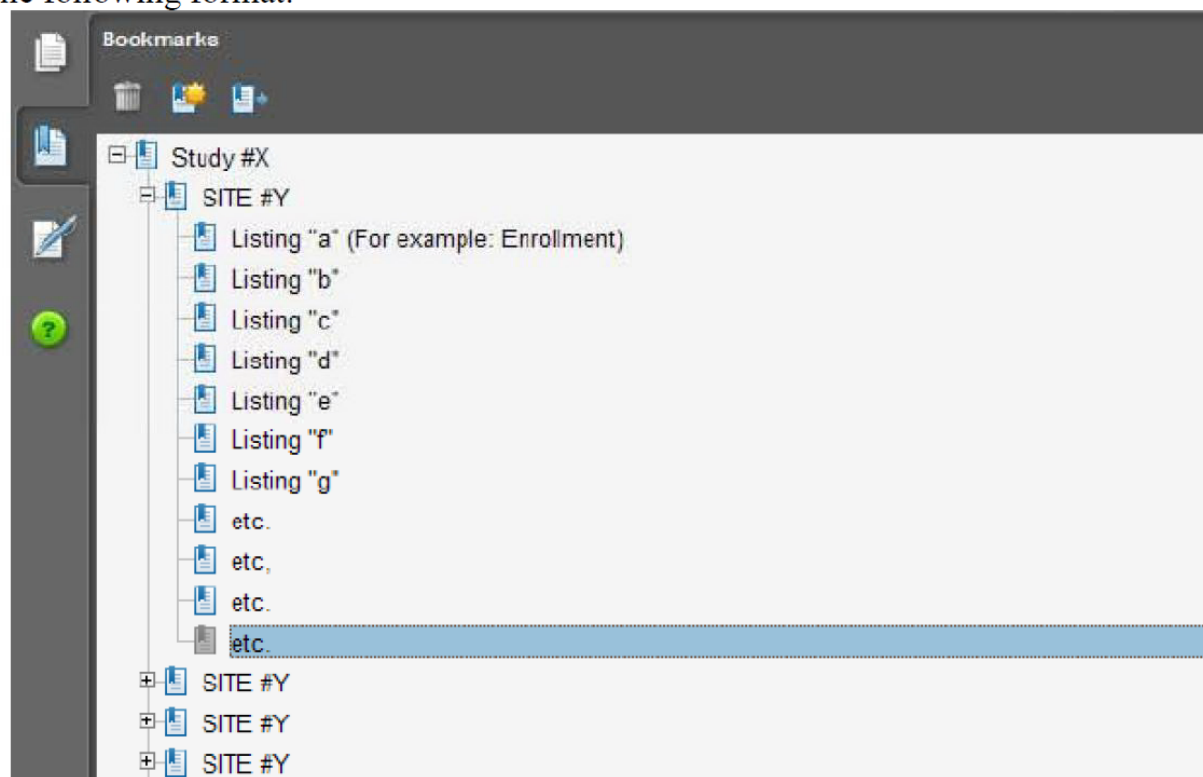
Pre-NDA Meeting

By site investigator listings for investigator on-sites inspections (cont)

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2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



OSI Packages. What you need to know for your next NDA or BLS Submission
PharmaSUG 2015

Interaction with FDA – During (1)

Data Submission Test with one Study SDTM

→ Sent by the sponsor to edata@fda.hhs.gov

XXXXX sample submission

Summary of evaluation findings

XXXXXX sample submission includes tabulation data for 1 clinical study.

The open, publically available Pinnacle 21 Community v2.2.0 tool was used for validation of datasets and a define.xml file.

Validation specifications were used according information provided in Reviewer's Guide documents. The following configurations were used for validation.

- Define-XML v2.0 (automated selection)
- SDTM IG 3.2
- MedDRA 18.0
- SDTM CDISC CT 2015-12-18

The summary of evaluation findings includes examples only. See validation reports for details.

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Interaction with FDA – During (2)

- FDA runs the Pinnacle21 Community tool
- At this stage they made use of the Reviewer Guide 'only' to check for standards used i.e. SDTM Ig Version
- Some good suggestions for define.xml
 - Supplemental Qualifier and Value Level Metadata (VLM) Origin Mismatch

« When origins for all VLM items within one variable are not the same an Origin for Variable should have a missing value with all details provided on VLM »

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Interaction with FDA – During (3)

- Suggestions on SDTM Content

i.e. RACE='OTHER' in DM domain

- « *CAMBODIAN* » should be represented as « *ASIAN* »
- « *NATIVE CANADIAN* » should be represented as
« *AMERICAN INDIAN OR ALASKA NATIVE* »
- « *MIDDLE EAST* » and « *PALESTINIAN* » should be
represented as « *WHITE* »

NO ACTION **Sponsor decision**

OTHER Races also correctly grouped in pooled ISS/ISE ADaM
for subgroup analyses

White

Asian

Non White / Non Asian

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Interaction with FDA – During (4)

- Other technical issues
 - Some SDTM discrepancies. Most of them corrected meanwhile
 - i.e. Use of YN terminology vs Y terminology
 - Advices on *"Permissible variable with missing value for all records"* NO ACTION variables kept for output programming purpose and explained in the cSDRG

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SDTM Mapping

Adverse Events

Issue with seriousness criteria not properly collected in old studies → FDA « wants » that → re-collected retrospectively from safety surveillance dept and integrated in SDTM

NOT ALWAYS RECCOMENDED AND FEASIBLE

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Pooling for ISS and ISE

- Done in ADaM from single study SDTMs
- Adverse Events Medical Coding Up-versioning Required
 - Ref FDA Study Data Technical Conformance Guidance
 - In SDTM (no guidance in Ig) vs ADaM (examples of multiple versions handling in OCCDS)

FDA Feedback ***“If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data”***

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Pooling Issues – Differences with CSR (1)

Be Transparent make use of Reviewer Guide

Analysis Data Reviewer's Guide			
Analysis Data Reviewer's Guide Final Work Package			
Version	Release Date	Downloadable Work Package	Changes from Previous Version
v1.1	26-Jan-2015	ADRG Package v1.1 2015-01-26	- Added ADSL Header to Section 5.2 - Improved ADRG Template usability - Minor revisions to instructions in ADRG Completion Guidelines - ADRG Examples updated to match revised SDRG Template
v1.01	13-May-2014	ADRG Package v1.01 2014-05-13	Initial Version

http://www.phusewiki.org/wiki/index.php?title=Analysis_Data_Reviewer%27s_Guide

http://www.phusewiki.org/wiki/index.php?title=Study_Data_Reviewer%27s_Guide

Study Data Reviewer's Guide			
Study Data Reviewer's Guide Final Work Package			
Version	Release Date	Downloadable Work Package	Changes from Previous Version
Clinical Study Data Reviewer's Guide			
v1.2	26-Jan-2015	SDRG Package v1.2 2015-01-26	- Removed Trial Design Dataset navigation table from Section 2.3 - Improved SDRG Template usability - Minor revisions to instructions in SDRG Completion Guidelines - SDRG Examples updated to match revised SDRG Template
v1.1	03-May-2013	SDRG Package v1.1 2013-05-13	Initial Version
Nonclinical Study Data Reviewer's Guide			
v1.0	03-Mar-2016	Nonclinical SDRG Package v1.0 2016-03-03	v1.0 for Federal Register Notice Docket No. FDA-2016-N-0701 -Public Review

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Pooling Issues – Differences with CSR (2)

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Different MedDRA Version

4.5 Discrepancies with analysis performed on single studies

The following tables list discrepancies with regards with outputs available in the single study clinical study reports and reasons.

ISS ADAM CSR Table Nr	Discrepancy and Reason
ADAE All AE Tables	Studies 001, 002 and 005 were using MedDRA versions available at the time of final analysis (version 14.0 and 16.1). For the purpose of this ISS, in order to update the coding to a more recent MedDRA version and to align all studies to the same version, some adverse event got a different preferred term (PT) and/or body system (System Organ Class SOC) compared to the one assigned at the time of db-lock/final analysis. Therefore some discrepancies in the number and incidence (%) of each AE (SOC and PT), might be observed in the ISS tables if compared to same tables in the single study clinical study reports. Although studies 006 and 008 were already using MedDRA version 18.0 at the time of the database lock and therefore at final analysis, during the up-version of previous studies not using version 18.0, AE coding for these two studies was also reviewed. In this review an independent coding specialist questioned some of the coding applied to study 006 and 008. In particular it appeared that in some cases the primary SOC pathway was not chosen. Therefore in some cases the SOC and PT for studies 006 and 008 got a different term compared to what was used at the time of final database lock. Additional details can be found in section 5.2.4



Pooling Issues – Differences with CSR (3)

Different MedDRA Version

Bridge Document provided in appendix

8.3 Appendix III: Adverse Events MedDRA version up-versioning bridge document

The following table provided details about changes occurred in the Adverse Events MedDRA coding to version 18.0. The column “Item Changed” reports the name of the CDISC SDTM AE variable for which a change occurred after applying MedDRA version 18.0, while “Original Coding” and “After up-versioning to MedDRA Version 18.0” show the applied change on the term (variable) referenced by the “Item Changed” column.

Subject Id	Investigator Term	Item Changed	Original Coding	After up-versioning to MedDRA Version 18.0	Original MedDRA version used
001-12-004	WORSENING OF PAIN	AELLT	Arthralgia aggravated	Knee pain	14
001-30-006	WORSENING OF INDEX KNEE PAIN POST INJECTION	AELLT	Arthralgia aggravated	Knee pain	14
30-007	POST INJECTION MILD WORSENING OF INDEX KNEE PAIN	AELLT	Arthralgia aggravated	Knee pain	14
001-30-002	WORSENING OF INDEX KNEE	AELLT	Arthralgia aggravated	Knee pain	14

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PINNACLE²¹ Validation Issues

Data-issues of locked studies

- Documented in the Reviewer Guide
- « **Hard-coding** » agreed with sponsor when correction was obvious i.e. start>end but clearly wrong year or confirmation obtained from source document without unlocking data (!! « A Note to File » is needed in the programming documentation and mentioned in the RG)

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- **(for sponsor) Adopt CDISC ASAP, starting with CDASH 'Lost in Traceability' has a cost!!!**
- **(for sponsor) Vendor Surveillance, make sure they do it right and consistently**
- **Plan for the unexpected**
- **Reviewer Preferences**
- **A lot of documentation effort (cSDRG and ADRG)**

References

- «Lost» in Traceability, from SDTM to ADaM finally Analysis Results Metadata» A. Tinazzi, CDISC Europe Interchange 2016
- «Looking for SDTM migration specialist » A. Tinazzi, PhUSE 2014
- «Interpreting CDISC ADaM IG through Users Interpretation» A. Tinazzi, PhUSE 2013
- «The do's and don'ts of Data Submission» A. Tinazzi, BIAS 2013
- «Traceability: Plan Ahead for Future Needs» – S. Minjoe, T. Petrowitsch, PhUSE 2014
- «Traceability and Data Flow PhUSE-CSS WG»
http://www.phusewiki.org/wiki/index.php?title=Traceability_and_Data_Flow
- «Summary of Traceability References PhUSE-CSS Wiki Page»
http://www.phusewiki.org/wiki/index.php?title=Summary_of_Traceability_References



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Cytel, Shaping the Future of Drug Development

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Cytel

Angelo Tinazzi, Director

Standards, Systems, CDISC Consulting, Statistical Programming

CDISC E3C Member

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Angelo Tinazzi is a Director in the Statistical Programming Department at Cytel. Angelo brings more than 20 years of experience in the field of Clinical Research in the area of data-management and statistical programming with different roles in Academic Organizations, CROs and Pharmaceutical Industries, in Italy, Switzerland and UK.

His skills include strong statistical programming (SAS), deep knowledge of data standards (CDISC SDTM and ADaM), data submission requirements (i.e. FDA), project management and line-management. He has strong expertise in Oncology although he has been exposed to several other Therapeutic Areas such as Cardiovascular and Multiple Sclerosis.

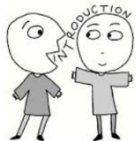
Prior to joining Cytel, Angelo worked at Merck Serono, SENDO Foundation, Phamarcia & Upjohn, Simboligica SAS Quality Partner, the UK Medical Research Council and the Institute for Pharmacological Research “Mario Negri”.

Angelo is a member of the European CDISC Committee (E3C) since 2015 and also an active member of the CDISC ADaM Team. Since 2013 is member of the BIAS scientific committee (the Italian Association of Biometricians working in the industry). He is also a regular presenter at conferences such as PhUSE and CDISC Europe Interchange on different topics ranging from CDISC to SAS and therapeutic area related presentations.

Angelo is Italian, working in Switzerland and living in France.

An FDA Submission Experience Using the CDISC Standards

The purpose of this presentation is to share an FDA submission experience using the CDISC standards. After introducing the key current requirements when submitting data sets to the FDA, either SDTM or ADaM, some key learning will be shared. This includes, for example, interaction with the FDA and the additional requests we received as well as the feedback after performing the test submission.



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How?

<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards>

- FDA Study Data Technical Conformance Guide
- FDA Standards Catalog
 - Exchange Format
 - i.e. SAS XPT, XML, PDF, ASCII
 - Regulatory Applications
 - Electronic Common Technical Document (eCTD)
 - Data Exchange Format
 - SDTM, ADAM (Clinical Study Datasets)
 - Define.xml (Study Data Definition)
 - Terminology Standards
 - CDISC Controlled Terminology
 - MedDRA, WHO-DD
- CDISC Metadata Submission Guidelines



The Data Package (2)



AE



adsl

- Clinical Study Datasets



XXXX-00
1-define



define2-
0-0

- Study Data Definition



aCRF



SDRG



ADRG

- Supportive Documents to Study Data Definition



opencdis
c-report-
definexm



opencdis
c-report-
data

- Data Validation Reports

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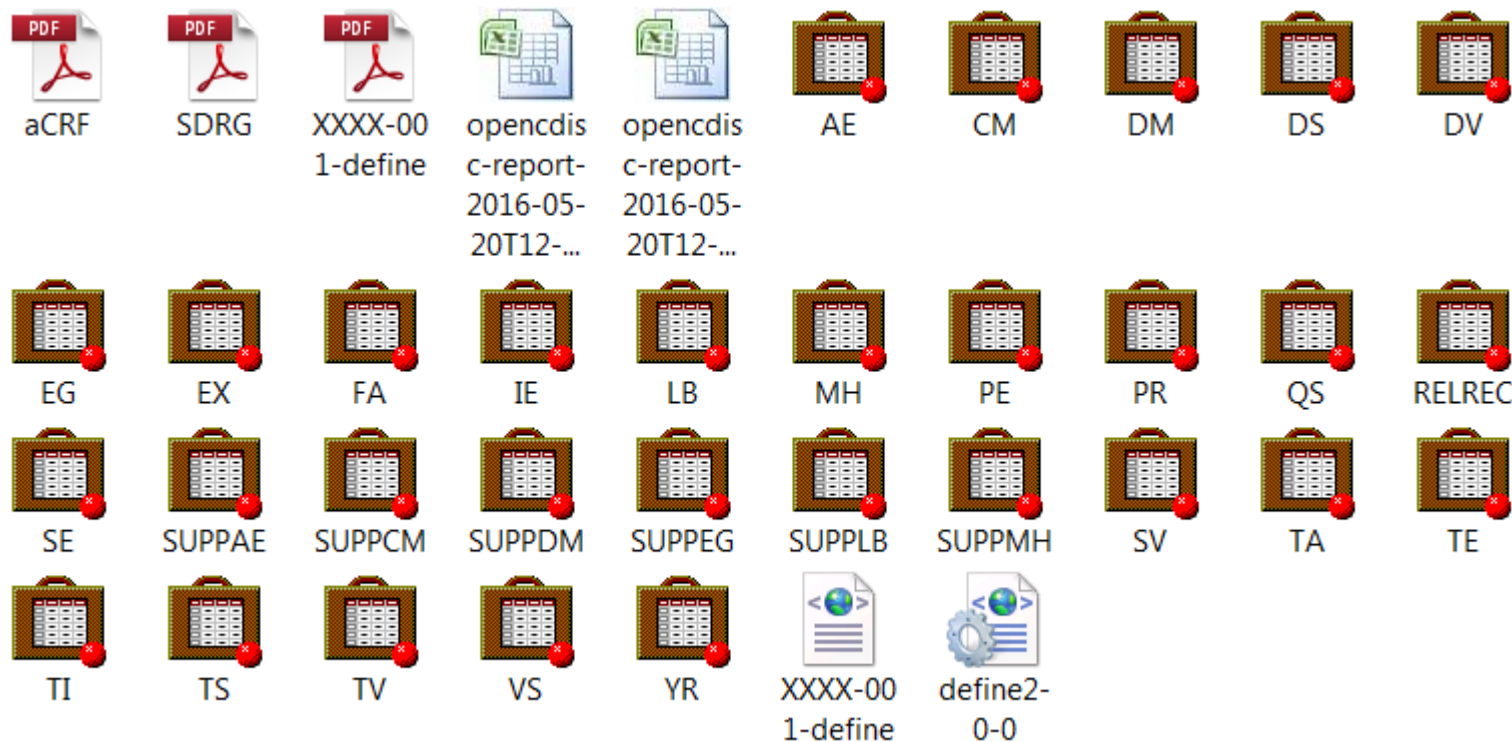
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The Data Package (3)

../m5/datasets/**001**/tabulations/sdtm



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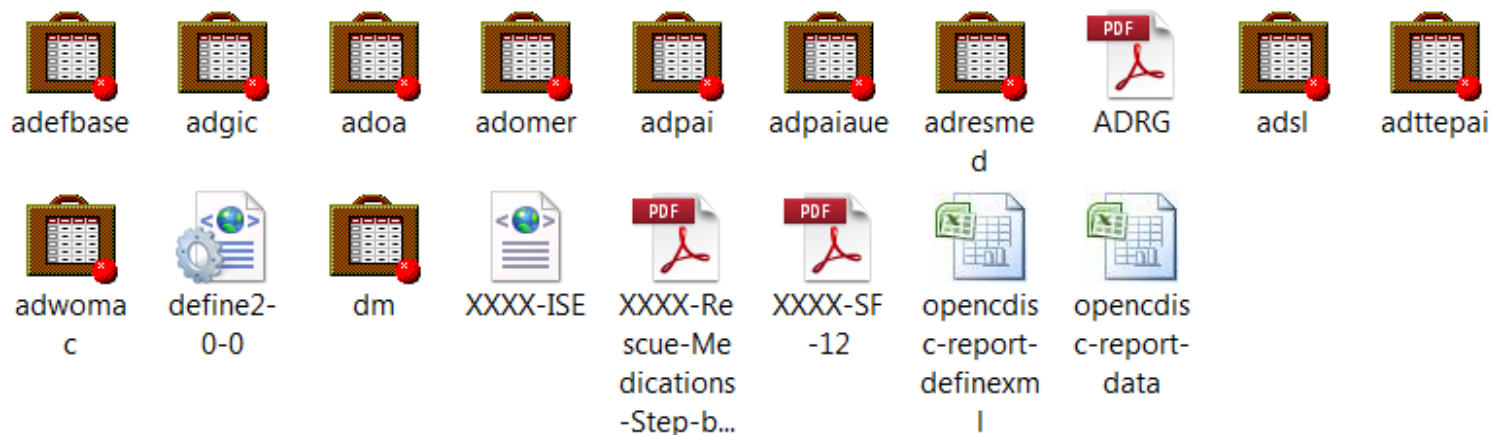
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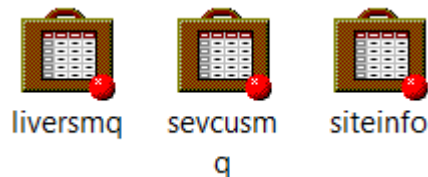


The Data Package (4)

../m5/datasets/**ISE**/analysis/adam/datasets



../m5/datasets/**ISS**/analysis/misc



Lookup datasets used in the creation of some ADAM datasets

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The Data Package (5)

Submitting Programs FDA Requirements

4.1.2.10 Software Programs

Sponsors should provide the software programs used to create all ADaM datasets along with the tables and figures associated with primary and secondary efficacy analyses in order to help reviewers to better understand how the datasets, tables and figures were created. The specific software utilized should be specified in the ADRG. The main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms. Therefore, it is not necessary to submit the programs in a format or content that allows the FDA to directly run the program under its given environment. Any submitted programs (scripts) generated by an analysis tool should be provided as ASCII text files or PDF files, e.g., adsl.sas should be submitted as either adsl.txt or adsl.pdf.

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The Data Package (6)

../m5/datasets/ISE/analysis/adam/programs

 ADEFBASE.sas	UltraEdit Document (.txt)
 ADGIC.sas	UltraEdit Document (.txt)
 ADOA.sas	UltraEdit Document (.txt)
 ADOMER.sas	UltraEdit Document (.txt)
 ADPAI.sas	UltraEdit Document (.txt)
 ADPAIAUE.sas	UltraEdit Document (.txt)
 ADRESMED.sas	UltraEdit Document (.txt)
 ADSL.sas	UltraEdit Document (.txt)
 ADTTEPAI.sas	UltraEdit Document (.txt)
 ADWOMAC.sas	UltraEdit Document (.txt)

ADaM Programs

Tables Programs

 T-GIC.sas	UltraEdit Document (.txt)
 T-GIC-CAT.sas	UltraEdit Document (.txt)
 T-OMERACT.sas	UltraEdit Document (.txt)
 T-PAIN.sas	UltraEdit Document (.txt)
 T-PAINAUC.sas	UltraEdit Document (.txt)
 T-PAINDUR.sas	UltraEdit Document (.txt)
 T-PAINTTE.sas	UltraEdit Document (.txt)
 T-RESCMED.sas	UltraEdit Document (.txt)
 T-RESP.sas	UltraEdit Document (.txt)
 T-WOMAC.sas	UltraEdit Document (.txt)

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SDTM Mapping – Gap Analysis (1)

- Initiated prior to commencing migration activities
- How to perform gap analysis
 - Itemization and evaluation of files to support migration activities
 - Document inventory
 - Study documents
 - CDISC Standards
 - Company Standards / Company Implementation Guidance
 - Validate sample CRF fields versus source data
 - External data requirements e.g. central labs or local labs
 - Comparison of protocol amendments/versions against CRF versions
 - Clarifies the scope and challenges of migration activities
 - Identifies differences in data collection formats

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CDISC SDTM Mapping – Gap Analysis (2)

Documents and Data Inventory

Protocol	Phase	Ongoing/ Closed?	Study Subjects	Country	Raw Data	SDTM	Analysis Data	protocol	SAP	aCRF	Blank CRF	CSR
TRIAL 01	Ia	Closed	CF with Pa	Netherlands	present	To migrate	Non-ADaM	v2.0.1 / 2006	v1.1 / 2007	v1.7.4 / 2007	NA	v1.1 / 201301
TRIAL 02	Ib/Ila	Closed	CF with Pa	Hungary, Serbia	Waiting- will get from another vendor	To migrate	Non-ADaM	v1.1 / 2007	v2.0 / 2010	v1.1 / 2007	NA	v1.1 / 201404
TRIAL 03	Ib/Ila	Closed	CF with Pa	Belgium	present	To migrate	Non-ADaM	v1.4 / 2008	v1.2 / 2010	v2.2 / 2008	NA	v1.1 / 201304
TRIAL 04	III	Ongoing	CF with Pa	North America, Europe, Australia, New Zealand	present	v3.1.3	Available	v1.4 / 2009	v2.1 / 2011	v1.5 / 2010	Available	Not Applicable

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Interaction with FDA – Pre (2)

Pre-NDA Meeting

Does the FDA concur with the Sponsor's plan regarding the composition and format of the clinical data submission for the XXXXXXXX NDA?

Do not use «Open Question», always propose solutions and ask for confirmation (seek for an agreement)

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Interaction with FDA – Pre (1)

Type of Meetings

- Type A: *a meeting needed to help an otherwise stalled product development program proceed*
i.e. meetings for discussing clinical holds
- **Type B:** pre-IND, end-of-Ph-I, pre-NDA
- **Type C:** any non Type A / Type B meeting regarding the development and review of a product

Formal Meetings Between the FDA and Sponsors or Applicants

<https://www.fda.gov/downloads/drugs/guidances/ucm153222.pdf>

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Interaction with FDA – Pre (2)

Pre-NDA– Data Submission Strategy Additional Details/requirements

- Lab with Normal Ranges
- Use WHO drug dictionary
- Unique coding / nomenclature for Placebo across studies
- Common variables across datasets
- Case summaries and CRF for all SAEs, deaths and Discontinuation due to Adverse Events

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FDA Interaction with FDA – Pre (3)

Pre-NDA– Data Submission Strategy Additional Details/requirements (cont)

- Site Level Dataset (optional for now!)
- For Pivotal studies:
 - Number of subjects screened for each site by site
 - Number of subjects randomized for each site by site, if appropriate
 - Number of subjects treated who prematurely discontinued for each site by site

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Interaction with FDA – Pre (5)

Pre-NDA – Data Submission Strategy Additional feedback

2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the adverse event data set and provide a variable that gives the numeric MedDRA code for each lower level term on the case report form.
3. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
6. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.

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Interaction with FDA – Pre (6)

Pre-NDA– Data Submission Strategy Additional feedback

5. **Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.**

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SDTM Mapping (1)

- Relatively Easy to handle
- A lot of Questionnaires
 - Pain Assessment
 - WOMAC
 - GIC
 - SF-12
 - KOOS
- **Most of them are not covered by any CDISC standards**
- Easy treatment exposure - one single day injection

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SDTM Mapping (2)

Be Harmonized

– visit/visitnum

VISIT NUM	VISIT	001	002	005	006	008	009	VISIT (Original as in CRF if different)
1	Screening	√	√	√	√	√	√	Day-21 to -1/SCR in 001
1.1	Day-1		√					Day-14 To -1/Screening in 002
2	Day 1 Baseline	√	√	√	√	√	√	
2.1	Day 2^	√	√				√	
2.2	Day 3		√					
2.3	Day 4		√					
2.4	Day 5		√					
2.5	Week 1	√						Week 1 (Day 8) in 001
2.6	Day 14		√					
2.7	Week 2		√					
2.7	Week 2	√						Week 2 (Day 15) in 001
2.8	Week 3		√					
3	Week 4	√	√		√	√		Week 4 (Day 29) in 001
3.1	Week 5		√					
3.11	Day 42		√					
3.2	Week 6		√	√			√	
4	Week 8	√			√	√		Week 8 (Day 57)

- Consistent terminology
- Consistent QNAM in SUPPxx

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CDISC SDTM Mapping (4)

Study Population i.e. per protocol

- Not fully derivable
- Peer review process
- Integrated from xls files into SUPPDM (possible with 3.2) and DV



**SDTM IG 3.3 Draft Study Population not in SDTM,
only in ADaM!!!**

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SDTM Mapping (5)

- **Unscheduled VISITNUM and EPOCH derivation**
 - IG gives some suggestion to when unplanned visits to maintain chronology
 - PhUSE CSS provides some more detailed approaches for VISITNUM and EPOCH derivation
 - Be aware deriving VISITNUM for unscheduled visits can be very time-consuming

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Pooling Issues – Differences with CSR (4)

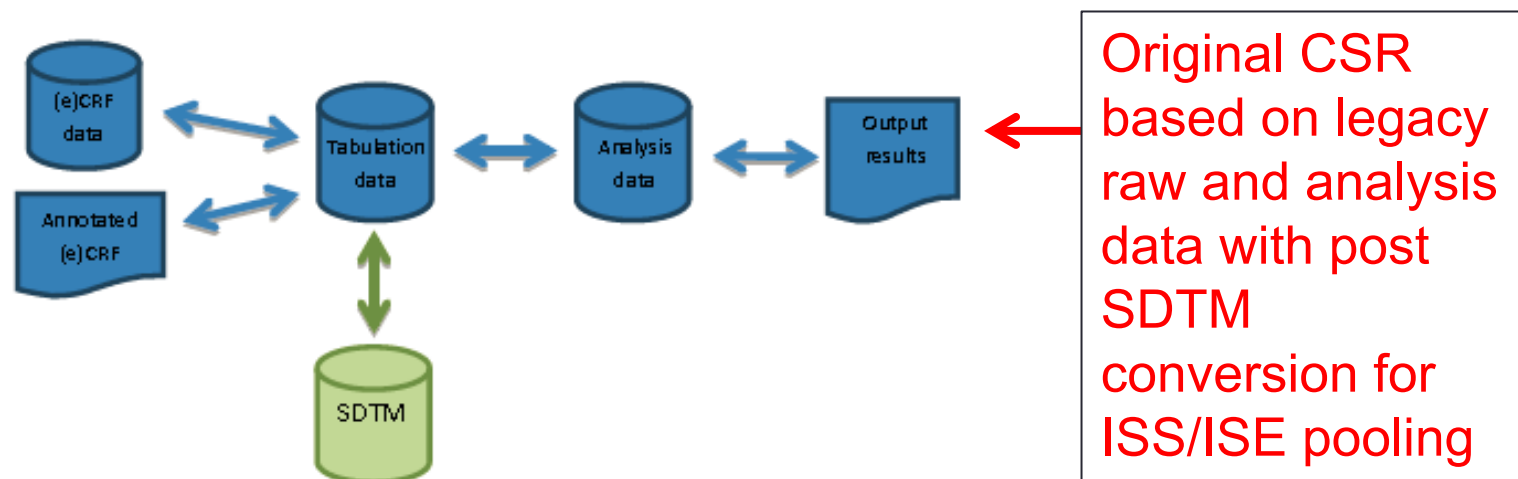
Different visits windowing in the ISE

ISE ADAM Study CSR Table Nr	Discrepancy and Reason
ADPAI 001 14.2.1.x and 14.2.2.x (all pain endpoint summaries)	The visit / week windowing in 001 final analysis was different i.e. week 1 was from day 1 to day 8 whereas in ISE (see SAP section 10.1.1) we applied the windowing from day 1 to day 7 as we did for the analysis of study 006 and 008.

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CDISC SDTM Mapping – CDISC Traceability

- 3 studies migrated prospectively
 - perfect CDISC traceability SDTM → ADaM → Analysis Outputs → CSR
- 3 studies migrated post CSR → traceability issue



Traceability Issues mentioned in FDA Study Data Technical Conformance Guidance

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PINNACLE²¹ **Validation Issues (1)**

- Performed with Pinnacle 21
- Several 'false' positives → RG
 - Validation checks for BDS for non-BDS ADaM
 - Extensible Controlled Terminology

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PINNACLE²¹ Validation Issues (2)

eCTD Limitation to 1000 characters length

Domain	Record	Count	Variables	Values	Pinnacle 21 ID	Publisher ID	Message	Category	Severity
DEFINE			Value, Attribute	- When only year was available, OADIAGY was computed as year of study drug administration (ADSL.TRTSDT) – year of diagnosis - When only month and year was available, the day was imputed to 1 and OADIAGY was computed as (study drug administration (ADSL.TRTSDT) – date of Osteoarthritis index knee diagnosis (OADIAGDT)+1)/365.25 - Otherwise if the diagnosis date was not partial the	DD0086		Invalid length of attributes in Define.xml	Structure	Error

Additional Documents provided define.xml

ADaM-IG 1.0

- + Analysis Data reviewer's Guide
- + Rescue Medications Consumption Derivation
- + SF-12 Composite Score Derivation Algorithm
- + Analysis Datasets
 - Baseline Efficacy Endpoint AD (ADFFBASE)

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