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OCS UPDATE: OCS CLINICAL SERVICES & THE TRACEABILITY ASSESSMENT

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FDA 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.

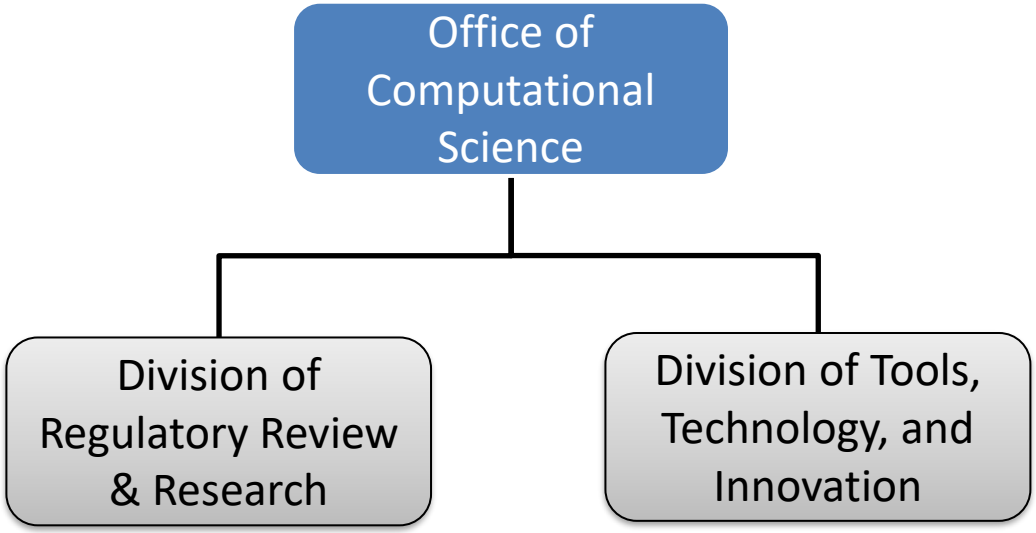
Agenda

- Background
- OCS Clinical Services Overview
- Traceability Overview and Example

CDER Organization Chart

- OCS is under the Office of Translational Sciences in CDER
- OCS supports multiple Offices across the Center
- Interacts with other Offices within Center for various initiatives

OCS Mission and Vision

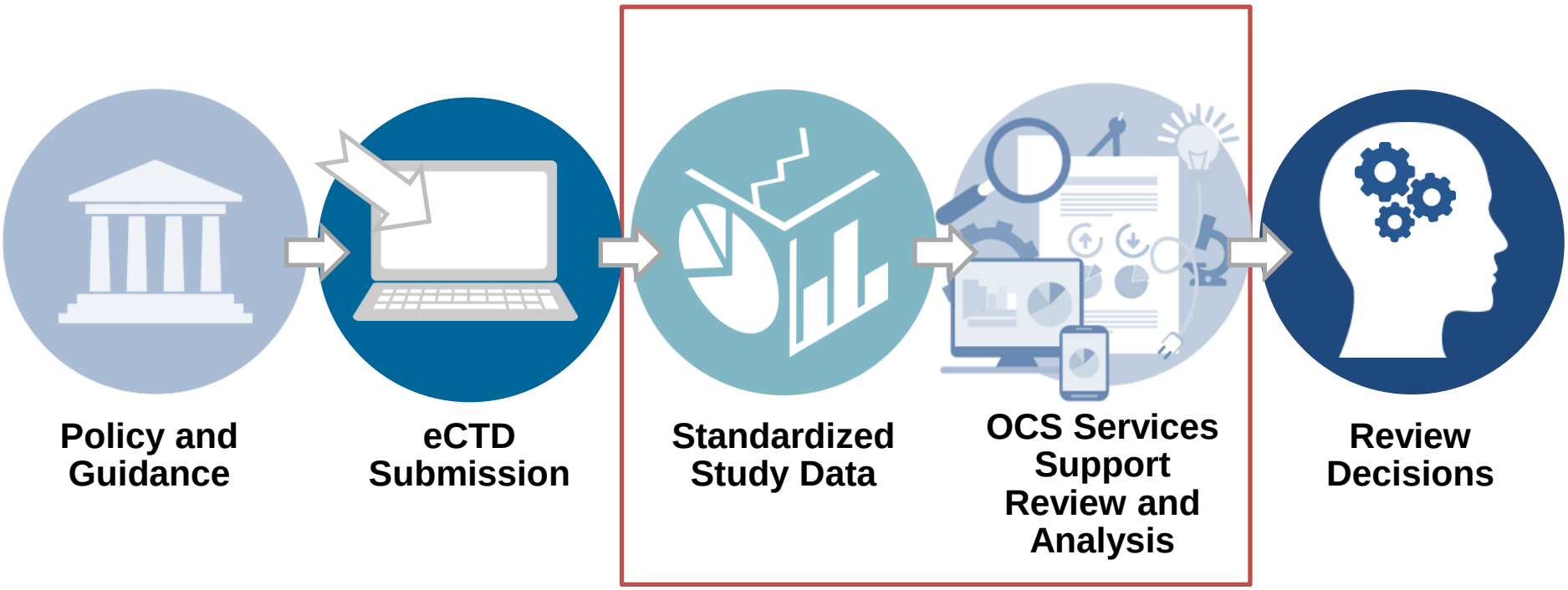


- Provide CDER reviewers solutions that improve the scientific review process by integrating data, tools, and training
- Drives modernization of CDER's scientific review process through the implementation of tools, services, and training to enable reviewers to apply their expertise to information

OCS Impacts to Regulatory Review

- Provide services for CDER reviewer use that validate data and provide data exploration and exploratory analyses
- Develop and support tools for CDER reviewer use that support data visualization and safety signal detection
- Develop and maintain OCS Data Central which loads validated data to different tools for use by CDER reviewers and OCS services

From Data to Review

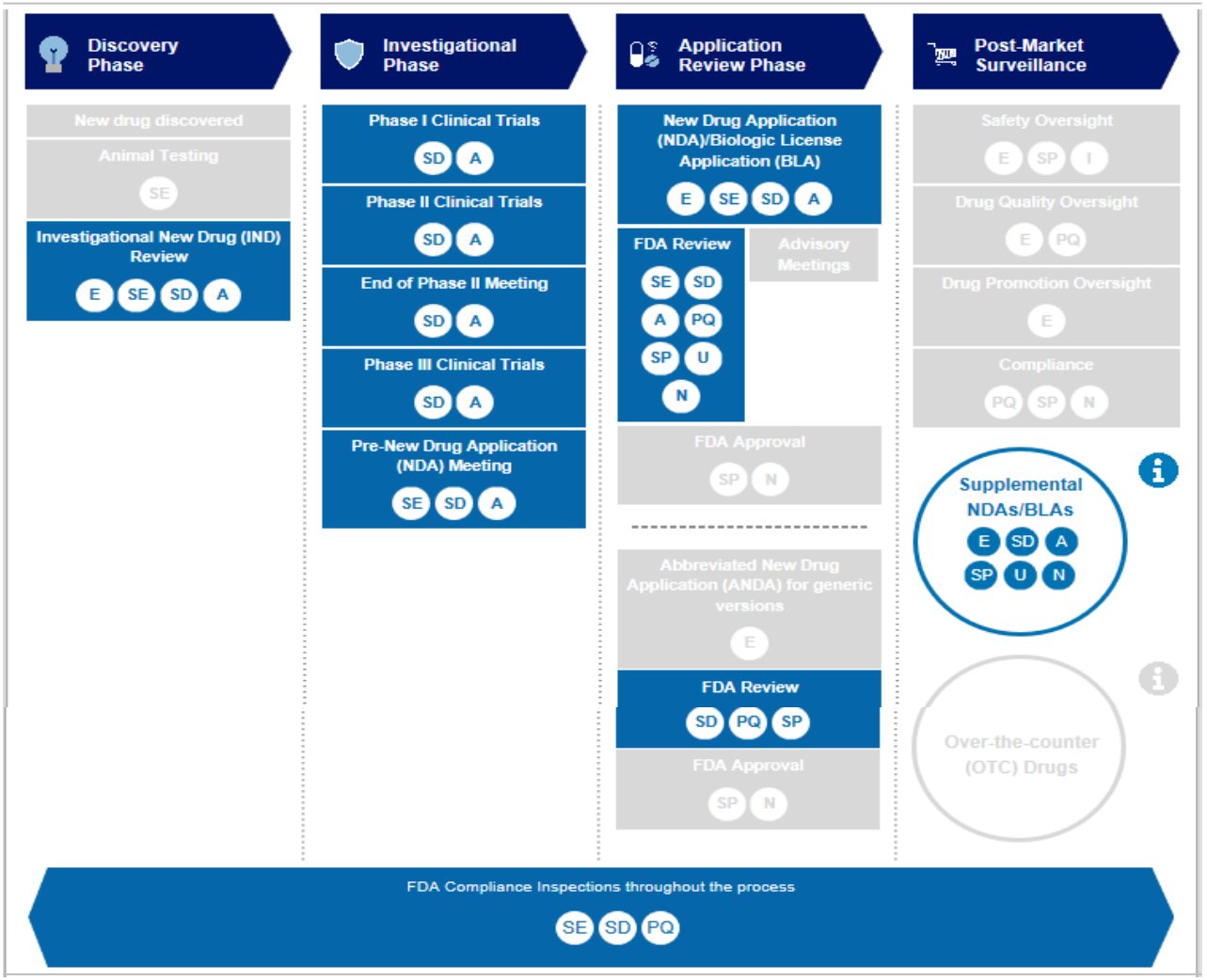


Data Standards Resources

- Data standards help FDA receive and review submissions more efficiently and effectively

Interactive display to select from:

- All [All]
- PQ/CMC [PQ]
- eCTD [E]
- SPL [SP]
- SEND [SE]
- ICSR [I]
- SDTM [SD]
- UNII [U]
- ADaM [A]
- NDC/MPID [N]



https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm531293.htm

OCS CLINICAL SERVICES OVERVIEW

OCS Clinical Services

- Provides OND medical officers and clinical data specialists key data quality and exploratory safety analysis information early in review process
- **Goal**: Provide service early in review process so reviewers better understand the data to conduct an effective evaluation of the drug submission

OCS Clinical Services Offerings

Assessments	Purpose
SDTM to ADaM Traceability Assessment	• Traces SDTM to ADaM data to identify differences that may exist between key datasets • Datasets include: Demographics, Adverse Events, Laboratory, and Vital Signs
ISS Traceability Assessment	• Traces the individual study ADaM data to the ISS ADaM data • Identify differences that may exist between key datasets and validates MedDRA up-coding.
ISS Overview	• Summarizes key information in the ISS data package • Includes datasets, variables, data flow, and important documentation
Exploratory Safety Analysis Bundles	• Provides analyses for: adverse events, liver labs, and disposition/demographics • Identifies and explains discrepancies between generated outputs and output in the Clinical Study Report (CSR).

SDTM TO ADAM TRACEABILITY OVERVIEW

SDTM to ADaM Traceability Overview

- Study Data Tabulation Model (SDTM) to Analysis Data Model (ADaM) Traceability Assessment traces SDTM data to the ADaM data
- Though records should match 1:1, identifies differences that may exist between key datasets and to assess their level of impact

- Datasets compared include four topic areas:
  - Demographics (SDTM.DM and ADaM.ADSL)
  - Adverse Events (SDTM.AE and ADaM.ADAE)
  - Laboratory (SDTM.LB and ADaM.ADLB)
  - Vital Signs (SDTM.VS and ADaM.ADVS)

Two Key Areas of Assessment

- Assessment focuses on two key areas:
  - **Record Count Reconciliation:** Summarizes which records exist in one dataset but not the other and understanding why
  - **Variable Comparison:** Compares key variables present in both datasets to identify differences in values and assess impact
- SAS programs used to perform the record count reconciliation and subsequent variable comparisons
  - SAS programs are customizable to adjust for variations in variable names and formats

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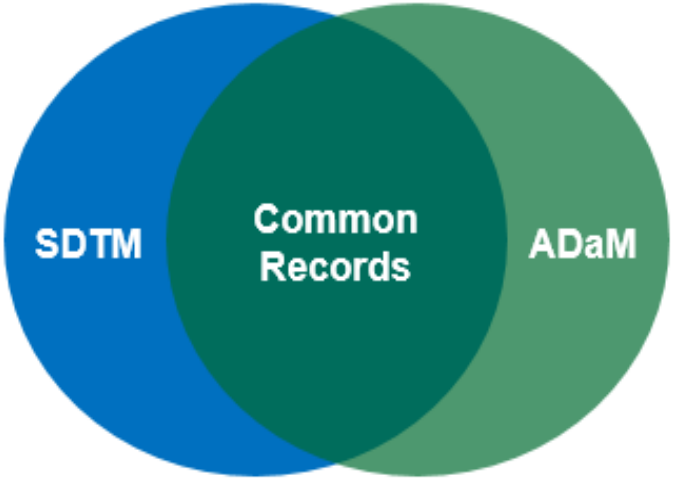
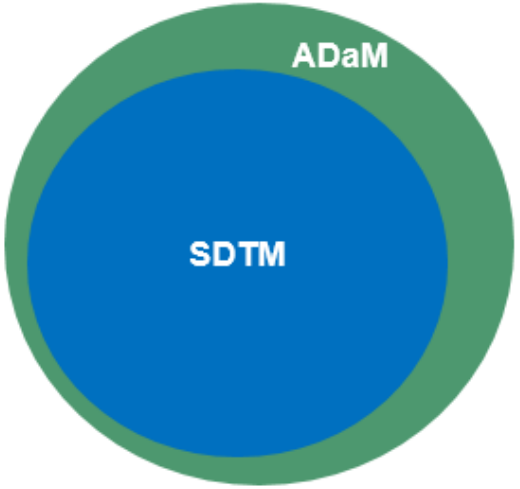
Record Count Reconciliation

- **Objective**: Categorize records not submitted in both datasets and assess impact
- May see records submitted in one dataset but not other, for example:



Distinct records in both datasets



Derived records in one dataset

Variable Comparison

- Records mapped using Unique Subject Identifier (USUBJID) for Demographics, and both USUBJID and Sequence Number (xxSEQ) for Adverse Events, Laboratory, and Vital Signs
- Highlights the importance of submitting **Sequence Number** variable in both SDTM and ADaM datasets
- IRs result when re-sequencing or mismatches occur in sequence numbers across datasets

SDTM TO ADAM TRACEABILITY EXAMPLE

Adverse Events Record Count Differences

- Examples of observed findings related to record count differences between the AE and ADAE and their level of impact are listed in the table below:

Key
No Impact
Low Impact
High Impact

Finding	Impact
Events that occurred after the ADAE-defined TEAE cutoff date captured in the AE domain are not preserved in the ADAE dataset	**Low impact**: The treatment emergent flag in the SUPPAE domain or in the ADAE dataset can be leveraged to assess treatment emergent adverse events (TEAEs)
Events that occurred prior to the screening period are captured in the AE domain and are not preserved in the ADAE dataset	**Low impact**: It is expected that events captured prior to the screening period are captured in the Medical History (MH) domain
Unexplained removal of adverse events in the SDTM or ADaM datasets without a clear explanation provided in the documentation	**High impact**: The unexplained removal of events denoting treated subjects call into question the data practices of the applicant

Adverse Events: Variables Checked

- Below is a table containing the variables checked between the AE domain and the ADAE dataset:

Category	AE Variable Name	AE Variable Label	ADAE Variable Name	ADAE Variable Label
MedDRA Coding	AEDECOD	Dictionary-Derived Term	AEDECOD	Dictionary-Derived Term
	AEBODSYS	Body System or Organ Class	AEBODSYS	Body System or Organ Class
Severity/ Toxicity	AESEV	Severity/Intensity	ASEV	Analysis Severity/Intensity
	AETOXGR	Standard Toxicity Grade	ATOXGR	Analysis Standard Toxicity Grade
Seriousness and Seriousness Qualifiers	AESER	Serious Event	ASER	Analysis Serious Event
	AESHOSP	Requires or Prolongs Hospitalization	AESHOSP	Requires or Prolongs Hospitalization
	AESDTH	Results in Death	AESDTH	Results in Death
	AESLIFE	Is Life Threatening	AESLIFE	Is Life Threatening
	AESMIE	Other Medically Important Serious Event	AESMIE	Other Medically Important Serious Event
	AESCONG	Congenital Anomaly or Birth Defect	AESCONG	Congenital Anomaly or Birth Defect
	AESDISAB	Persistent or Significant Disability/Incapacity	AESDISAB	Persistent or Significant Disability/Incapacity
	AESCAN	Involved Cancer	AESCAN	Involved Cancer
	AESOD	Occurred with Overdose	AESOD	Occurred with Overdose

Adverse Events: Variables Checked

- Below is a table continuing the list of variables checked between the AE and the ADAE datasets:

Category	AE Variable Name	AE Variable Label	ADAE Variable Name	ADAE Variable Label
Date/ Time	AESTDTC	Start Date/Time of Adverse Event	ASTDT/ ASTDTM	Analysis Start Date/ Analysis Start Date & Time
	AEENDTC	End Date/Time of Adverse Event	AENDT/ AENDTM	Analysis End Date/ Analysis End Date & Time
Other	AEACN	Action Taken with Study Treatment	AEACN	Action Taken with Study Treatment
	AEOUT	Outcome of Adverse Event	AOUT	Analysis Outcome of Adverse Event
	AEREL	Causality	AREL	Analysis Causality

- A treatment emergent flag check is also completed if a treatment emergent flag variable is submitted in the Supplemental Adverse Events (SUPPAE) domain:

Category	SUPPAE Variable Name	SUPPAE Variable Label	ADAE Variable Name	ADAE Variable Label
TEAE Flag	AETRTEM	Treatment Emergent Flag	TRTEMFL	Treatment Emergent Flag

Adverse Events: Variable Differences

- Examples of observed findings related to value differences across key variables between the AE domain and the ADAE dataset and their level of impact are listed in the table below:

Key
No Impact
Low Impact
High Impact

Finding	Impact
Date and/or time values differ between datasets	Missing or partial dates in SDTM.AE are imputed in ADaM.ADAE as defined in the documentation such as the ADRG or the SAP. Partial dates in the SDTM.AE domain may be missing either day, day and month, or day, month, and year (i.e., missing), which is imputed as a full date in the ADaM ADAE dataset. **Mismatching dates may impact duration analysis and assessing exposure and relation to study drug**
	Mismatching nonpartial date values that <u>do not</u> align with the source identified in the Define.xml file or other documentation. **Mismatching dates may impact duration analysis and assessing exposure and relation to study drug**
Difference in Treatment Emergent Flag	Discrepancies are due to differences in the flag derivation between SDTM and ADaM (or ADaM and ISS ADaM) as defined in the SDTM and ADaM Define.xml file, SDRG and ADRG, or SAP documentation
	Mismatching records that <u>do not</u> align with the derivation provided in the documentation call into question the data practices of the applicant

Difference in Treatment Emergent Flags

- Below is an illustrative example of differences in treatment emergent flag due to differences in flag derivation between SDTM and ADaM:

DM			AE			SUPPAE	ADAE		
USUBJID	RFXSTDTC	RFXENDTC	AEDECOD	AESTDTC	AEENDTC	AETRTEM	ASTDTM	AENDTM	TRTEMFL
Subject A	2020-01-02 T12:00:00	2020-01-02 T12:00:00	Fatigue	2020-01-02 T10:00:00	2020-01-08 T:10:00:00	Y	2020-01-02 T10:00:00	2020-01-08 T:10:00:00	
Subject B	2020-01-02 T12:00:00	2020-03-02 T12:00:00	Nausea	2020-01	2020-02-05 T:10:00:00	N	2020-01-02 T12:00:00	2020-02-05 T:10:00:00	Y

- **Subject A**: Derivation of SUPPAE.AETRTEM only takes the date component of AESTDTC into account, ignoring the time component. Since derivation of ADAE.TRTEMFL takes both date and time into account, the treatment emergent flag is null in ADAE
- **Subject B**: Partial date in AESTDTC results in AETRTEM set equal to 'N'. After imputing start and end date in the ADAE dataset, the AE now falls within the treatment emergent window in ADAE and is set equal to 'Y'

Conclusion

- OCS provides data quality and analysis support early in review process to allow reviewer to focus on science in review rather than data submitted
- OCS Clinical Services provides data quality and exploratory safety analysis bundles helping reviewers increase efficiency and effectiveness of review
- Traceability is key to understanding differences between SDTM and ADaM and allows reviewers to confidently use submitted data packages throughout review
- Traceability Assessment aims to help the reviewer understand the impact of differences observed in the datasets for their application

Thank You!

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Division of Regulatory Review and Research

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