



The Clinical Data
Science Conference

US 2025

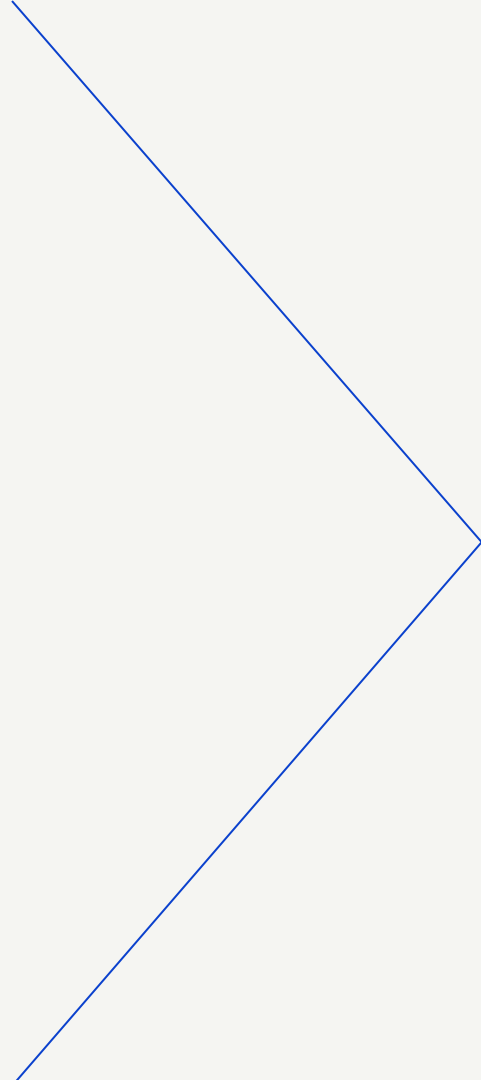
16-19 March

Renaissance Orlando at SeaWorld Florida

SA09 - Double Trouble: Essential Insights from successful Dual sBLA Submissions for a Drug-Device Combo

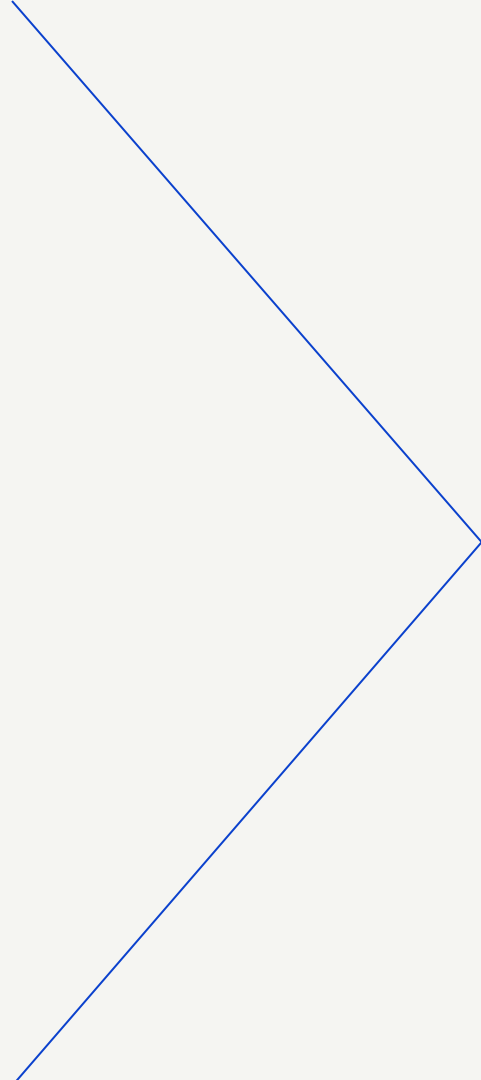
Aldrich Salva
Elma Zannatul Ferdousy
Iris Zhao

Agenda

A large blue arrow pointing from the word 'Agenda' on the left to a list of five items on the right. The arrow is composed of two diagonal lines meeting at a point on a vertical line that separates the title from the list.

1. Background
2. The Submission Packages
3. Challenges
4. Tools
5. Key Takeaways

Agenda

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1. **Background**
2. The Submission Packages
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Background

- FDA-Approved Drug-device combination product
- Concurrent sBLA submissions for two different indications involving two distinct phase III studies
- Voluntary recall of the product from the market
- Pause in new interventions in ongoing and planned clinical trials
- Planned Filings were delayed



*AI-generated image. Not the actual product.

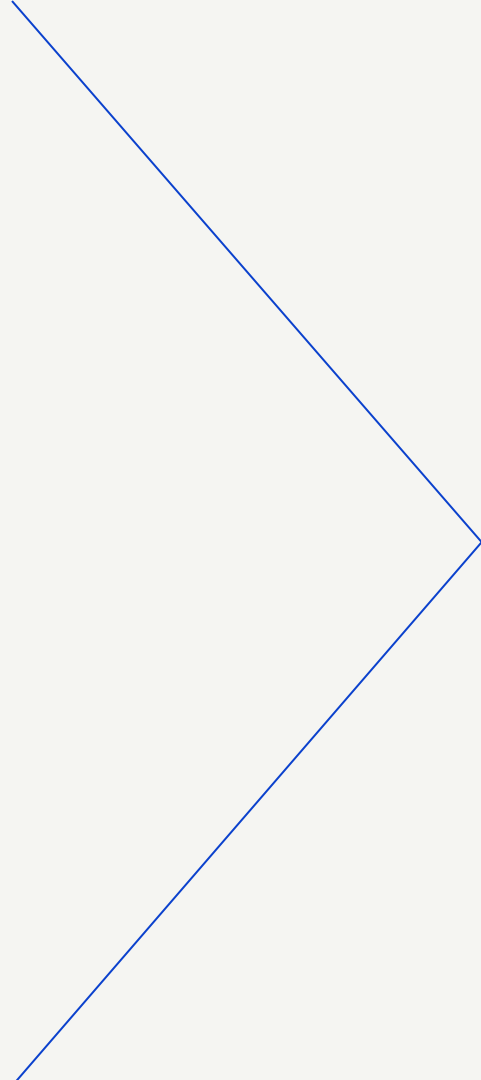
Background

- Device improvements and extensive testing
- Supplementary submission of data and documentation to support the safety and efficacy post-manufacturing changes
- Phase III Studies' primary CSR data and snapshots were over a year old at the time of filing
- New updated analyses and snapshots were to be included in the sBLA's



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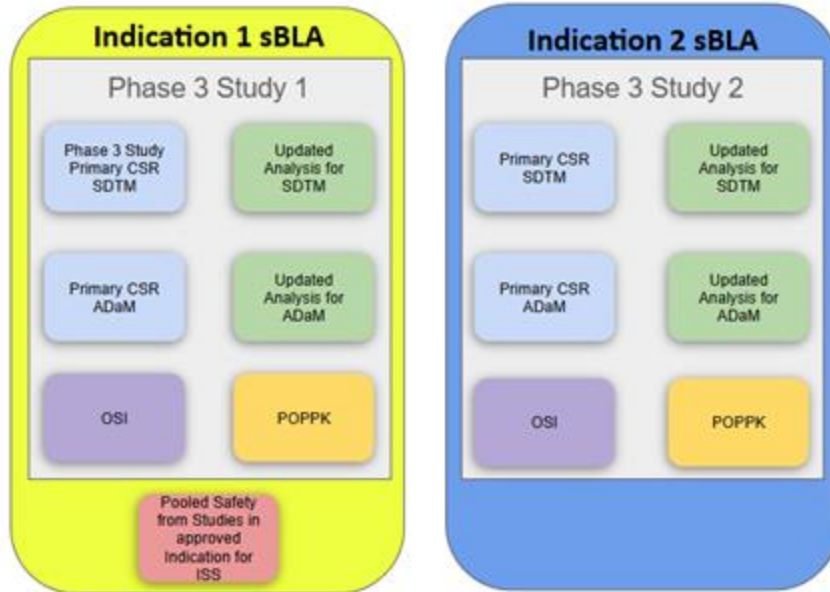
The Submission Packages



Key Elements of a CDISC Data Package:

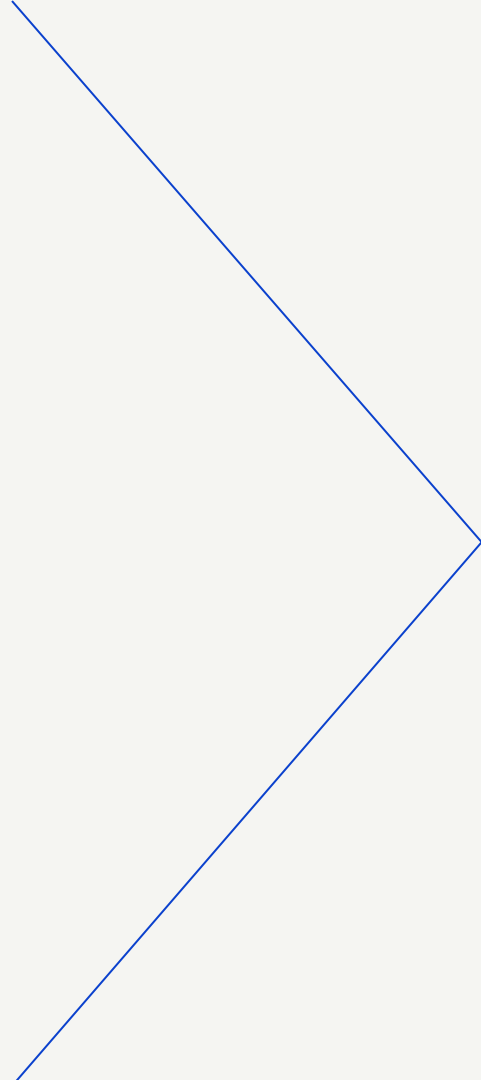
- Annotated Case Report Forms (**aCRF**)
- Tabulation Datasets (**SDTM** in XPT files) and Data Definition file (**define.xml**)
- Analysis Datasets (**ADaM** in XPT files) and Data Definition file (**define.xml**)
- **Software Programs** (readable code in TXT files and supporting Program Table of Contents)
- Documentation (SDTM Reviewer's Guide or **SDRG** and ADaM Reviewer's Guide or **ADRG**)
- **Office of Scientific Investigations (OSI) Package** (including site-level dataset, Data definition File, Reviewer's Guide, and site-level listings)

The Submission Packages



- Each sBLA included data packages for the 2 separate snapshots
- Primary CSR - SDTM, ADaM, OSI, and POPPK
- Updated Analysis - SDTM and ADaM
- Pooled Safety from a different indication to support Integrated Safety Summary (ISS)
- 13 data packages across 5 studies

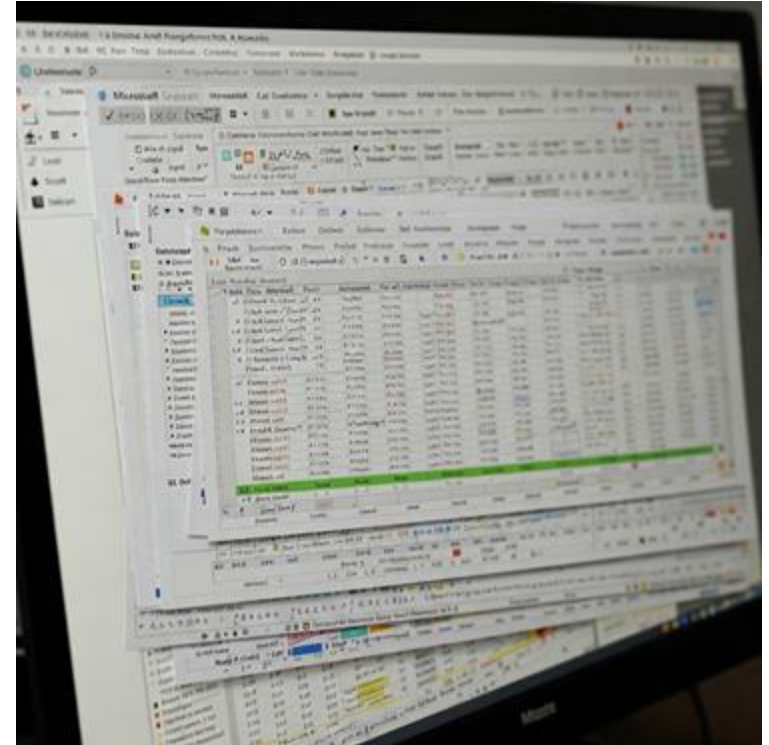
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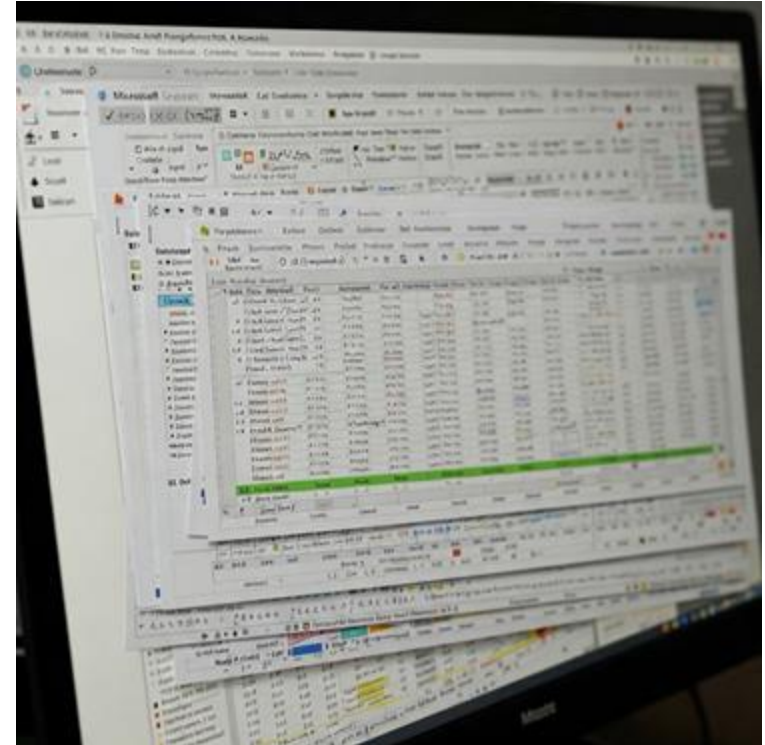
Handling of External Spreadsheets

- Some essential data points were not directly collected through CRF or non-CRF systems
- Input was provided by other functional teams or required cross-functional collaboration for review
- External spreadsheet trackers in xlsx or csv formats were used to supplement the analysis data
- Over 20 spreadsheets between the each of the 2 snapshots across the 2 Phase III studies



Handling of External Spreadsheets

- Best practice is to convert to SAS datasets as XPT files for submission but this could cause potential issues
- Variable name lengths exceeded, character formatting
- Already established analysis dataset programs would need to be updated



Handling of External Spreadsheets

Data Dependencies

ADSL uses an internal reference excel file ([Appendix xy](#)). This file identifies specific flags set by an external function at a patient level.

Appendix xy – Tracker of data point flagged by external function

External file: Example01_with a long filename_YYYYMMDD.xlsx

Part of the file structure for understanding

Column1: Patient ID	Column2: Site Number	FLAG1	FLAG2
XXXX	YYYY	AAAA	BBBB

Appendix xx – List of used Excel Files

File Name	File Name as submitted to the FDA	File Description	Where Used
Example01_with a long filename_YYYYMMDD.xlsx	an-example.xlsx	Identifies specific flags set by an external function at a patient level	ADSL, ADSUB
Example02_studynumber_purpose.xlsx	concise-name.xlsx	Identifies specific flags set by an external function at an event level	ADAE, ADCM

- Workaround: Retain in spreadsheet format for submission
- Submit detailed documentation in the ADRG
- This ensures traceability from spreadsheet to analysis dataset

Keep consistency in all the files and versions

- Between SDTM & ADaM
- Between different cutoff
- Between different packages (e.g. OSI v.s. ADaM.)
- Between TS and P21

Standard Used

SDTM-IG 3.2

Define-XML 2.0

Dictionaries Used

SDTM-CT 2022-12-16

MedDRA 25.1

WHODD GLOBALB3Mar22

LOINC 2.73

SNOMED 2019-09-01

UNII 2019-07-12

NDF-RT 2018-02-05

Primary
CSR

Standard Used

SDTM-IG 3.2

Define-XML 2.0

Dictionaries Used

SDTM-CT 2022-12-16

MedDRA 26.1

WHODD GLOBALB3Mar22

LOINC 2.77

SNOMED 2019-09-01

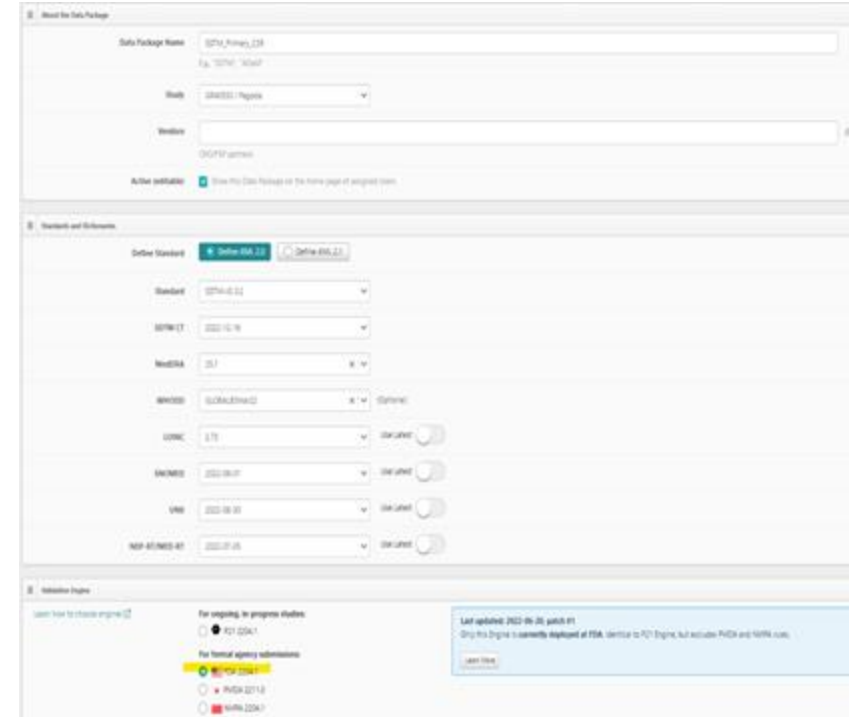
UNII 2019-07-12

NDF-RT 2018-02-05

Updated
Analysis

Use the correct P21 engine

- Initially all of our p21 reports have been rerun on p21 2204.1 engine as a default p21 engine and our scores were low.
- Since our submission was only for FDA, we rerun all of our p21 reports on FDA 2204.1 engine which has helped to increase the p21 score as per suggestion from eSub lead.
- Switching from p21 engine to FDA p21 engine. (as soon as we know about scope of submission)
- **Tip:** Use FDA 2204.1 engine if the submission is only for FDA for p21 run.



The screenshot shows a software interface with two main sections: 'About the Data Package' and 'Standards and Schemas'.

About the Data Package:

- Data Package Name:** A text input field containing 'P21_Package_220'.
- Study:** A dropdown menu showing 'GSK03377790'.
- Version:** A text input field containing 'GSK03377790'.
- Active publication:** A button labeled 'View this Data Package on the home page of progress.com'.

Standards and Schemas:

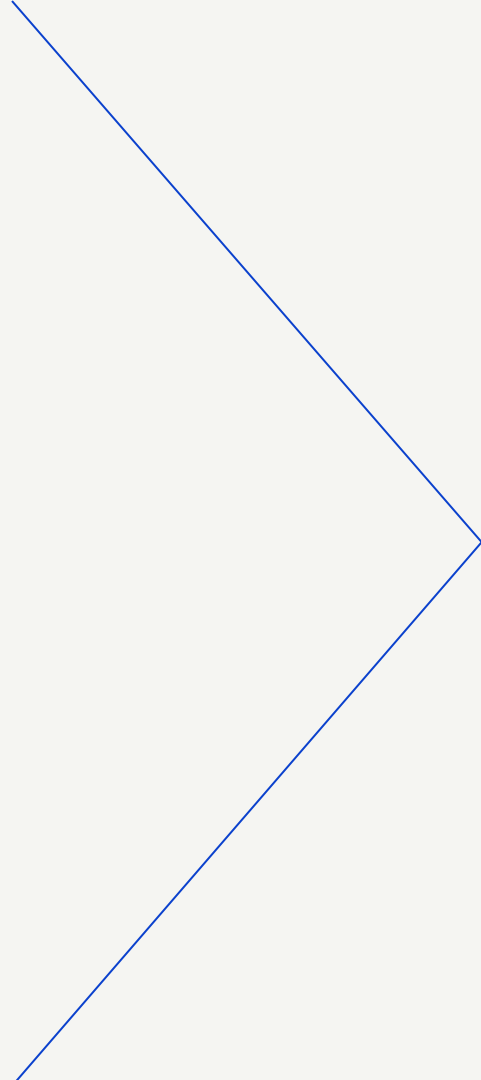
- Define Standard:** Two radio buttons, 'Define 2204.1' (selected) and 'Define 2204.2'.
- Standard:** A dropdown menu showing 'P21-02.02'.
- STN/CT:** A dropdown menu showing '2022-10-16'.
- Mod/ID:** A dropdown menu showing '202'.
- Mod/ID:** A dropdown menu showing 'GSK03377790'.
- CONN:** A dropdown menu showing '1.75'.
- CONN:** A toggle switch labeled 'Use latest'.
- CONN:** A dropdown menu showing '2022-10-17'.
- CONN:** A toggle switch labeled 'Use latest'.
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- CONN:** A toggle switch labeled 'Use latest'.
- CONN:** A dropdown menu showing '2022-10-17'.
- CONN:** A toggle switch labeled 'Use latest'.

Submission Engine:

- For ongoing, in progress studies:** A radio button labeled 'P21 2204.1'.
- For terminal agency submissions:** A radio button labeled 'FDA 2204.1' (selected).
- For FDA 2204.1:** A radio button labeled 'FDA 2204.1'.
- For FDA 2204.2:** A radio button labeled 'FDA 2204.2'.

Last updated: 2022-10-16 (by patch #1). A note states: 'Only this engine is currently deployed at FDA. Identical to P21 Engine, but excludes P21 and N21 rules.' A button labeled 'Learn More' is present.

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Package Quality

ADAM Package

ADRG: Good

Define: Good

Xpt files: Good

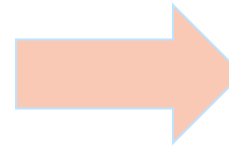


SDTM Package

SDRG: Good

Define: Improved the quality after suggestions from eSUB team.

Xpt files: Good



Tools used to monitor Quality of Data

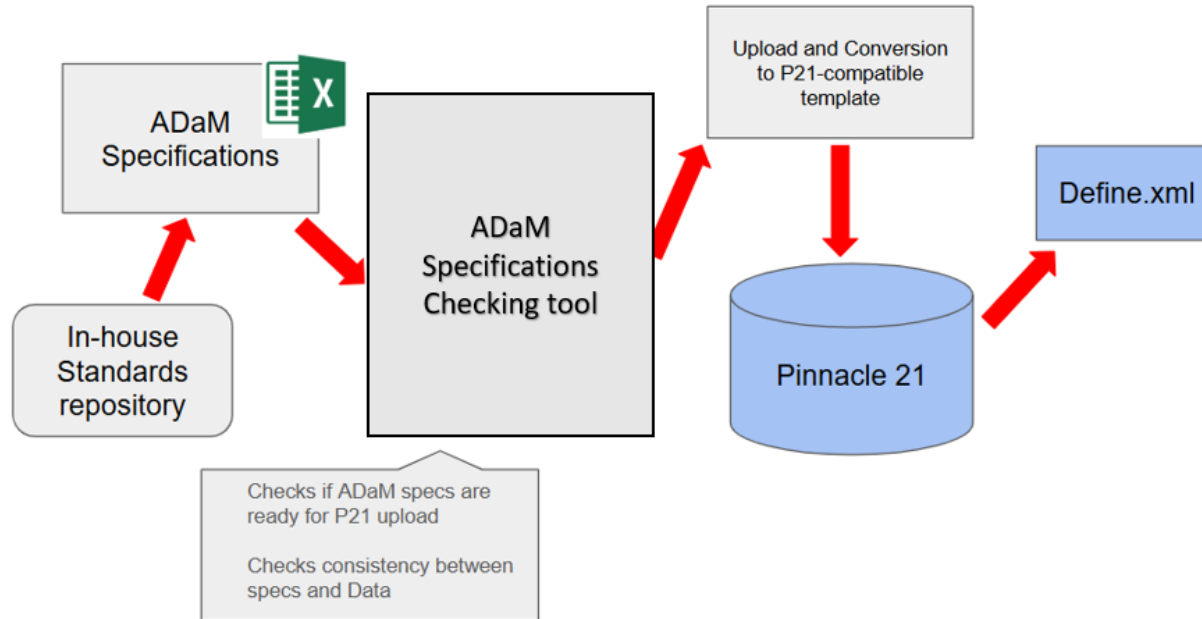
- ADaM Specifications Checking Tool
- SDTMchecks
- Pinnacle 21 Report



ADaM Specifications Checking Tool

- R package with a Shiny app designed to verify ADaM specifications.
- Ensures alignment between ADaM Data Specifications and Datasets, reducing inconsistencies.
- Validates Data Specification Workbook structure, checking essential sheets, columns, and variable naming compliance.
- Facilitates seamless upload of ADaM Spec files into Pinnacle 21, supporting the eSUB process.
- Enhances data integrity and reduces errors in regulatory submissions.
- Saves time on manual data checks, improving submission efficiency.

ADaM Specifications Check Workflow



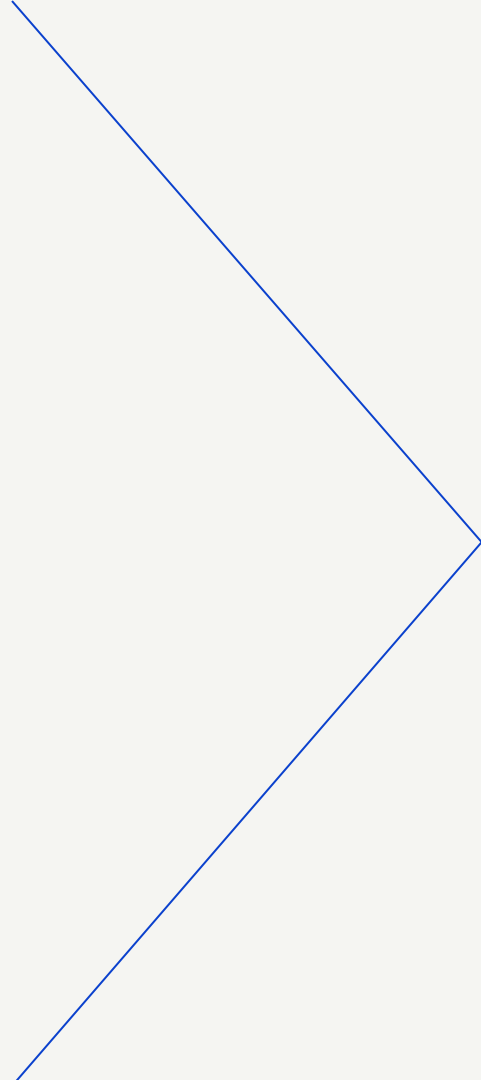
SDTMchecks

- SDTMchecks is an R package designed to identify common data issues in SDTM datasets.
- Provides a user-friendly, browser-based application that generates reports on critical data concerns.
- Publicly available since late 2022 as an open-source tool in Pharmaverse and CRAN.
- Helped the study team detect and resolve data inconsistencies before submission.
- Enhanced data accuracy and compliance by proactively addressing raw data and programming issues.

Pinnacle 21

- Pinnacle 21 (P21) is a key tool for validating clinical trial data against CDISC SDTM, ADaM, and Define.xml standards.
- Ensures regulatory compliance with FDA (U.S.) and PMDA (Japan) before submission.
- Early use of P21 helped detect and resolve errors proactively, preventing last-minute fixes.
- Automated validation checks reduced manual review efforts and improved workflow efficiency.
- Aligning datasets with FDA and CDISC standards minimized non-conformance risks.
- Facilitated collaboration among programmers, statisticians, and regulatory teams for a smooth submission process.

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Key Takeaways

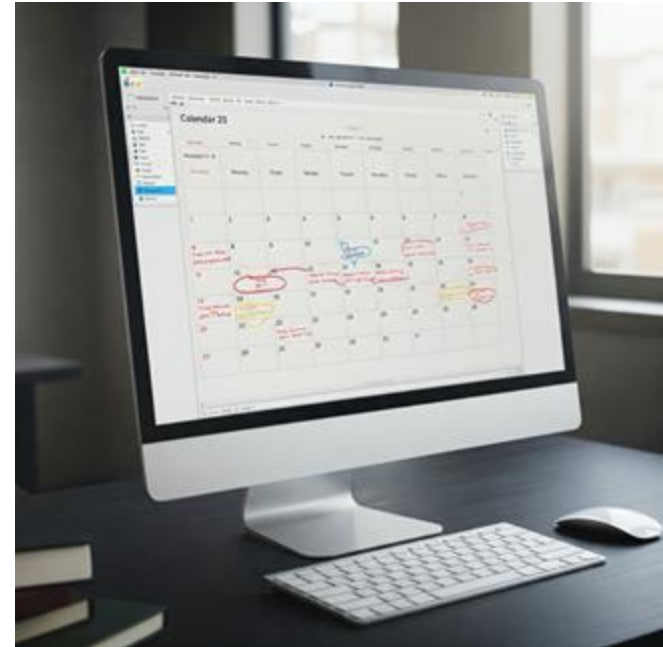
What worked well

- Engaging promptly with the eSubmissions lead optimized the submission process. This helped in making the best decisions for constructing the data packages
- Regular use of data quality and conformance tools ensured more streamline data package creation
- Maintaining consistency across all packages was vital, including synchronizing specifications, documentation, controlled terminologies, and coherence between ADaM and SDTM datasets.

Key Takeaways

Plan eSub Early!

- More time to to understand complex regulatory guidelines
- Filing requirements can be overlooked until after key readout
- Continuously consider filing eSubmission requirements throughout study conduct
- Ensure conformance activities and documentation are in place in a timely manner



Key Takeaways

..But be flexible!



- Plans and timelines may require revision sometimes due factors beyond control
- Be ready to adapt the team mindset and deliverables to the situation
- Apply this adaptability in transforming the packages to fulfill the new requirements
- Thoughtfully re-purpose or leverage previous work

Thank you!

Questions and Comments are welcome!

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