Paper SA09

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

Aldrich Salva, Genentech, South San Francisco, USA
Elma Zannatul Ferdousy, Genentech, South San Francisco, USA
Iris Zhao, Genentech, South San Francisco, USA

ABSTRACT

This paper explores the insights derived from the unique challenges of two concurrent supplemental Biologics License Application (sBLA) submissions for a drug-device combination product in the midst of improvements due to an identified issue.This submission involved two distinct Phase III studies with multiple datacuts, necessitated by shifting filing timelines due to device remediation efforts. It also included the integration of pooled safety data from three additional studies to support the Integrated Summary of Safety (ISS).These elements led to the creation of numerous data packages, presenting challenges to the team in consistency, data quality, and conformance. Key takeaways for the team in overcoming these challenges included seamless collaboration among various teams, rigorous implementation of data conformance tools, and thorough documentation across the various data packages. Despite the complexities, the eSubmission was successfully completed on time.

INTRODUCTION

The activities described are aimed at obtaining FDA approval for two new indications of a previously approved drug-device combination product. This goal required submitting two individual Supplemental Biologics License Applications (sBLAs), each based on separate phase III trials for the new indications. Initially, the plans for study and submission timelines were relatively straightforward until an issue with the device portion of the product was identified, leading to a voluntary market recall and a pause in new interventions in the ongoing clinical trials.

This pause had downstream effects on the sBLAs, as the issue necessitated device improvements and extensive testing, which took considerable time. After remediation, a Prior Approval Supplement (PAS) was required to both reintroduce the product to the market and proceed with seeking approval for the additional indications. Consequently, the filing timelines shifted, causing the planned primary CSR data and snapshots to be over a year old at the time of submission. The team had to secure additional snapshots with new analyses for both studies approximately a year later. Thus, each sBLA would include data from an initial CSR snapshot and an updated analysis snapshot taken a year later. This added complexity to the submission process, which will be detailed in this paper.

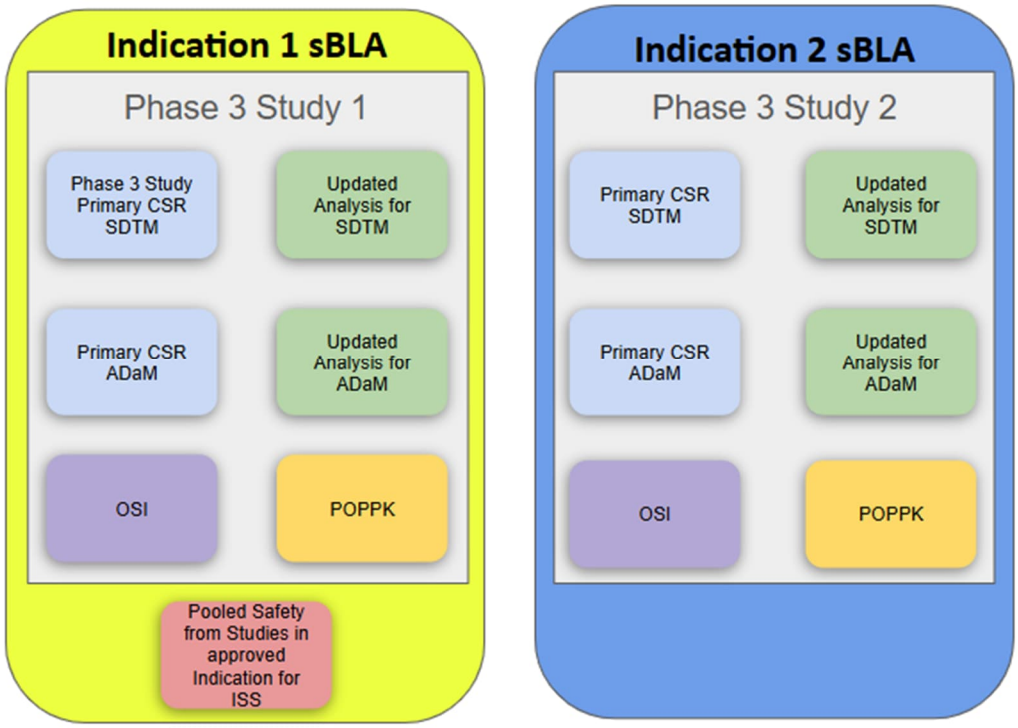
THE SUBMISSION PACKAGES

For the sBLA submissions, key elements of a CDISC data package were required for both studies. These elements are as follows:

- 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 and ADaM Reviewer's Guide)
- Office of Scientific Investigations (OSI) Package (including site-level dataset, Data definition File, Reviewer's Guide, and site-level listings)

Complexities arise when multiplying these elements by the number of packages being created to reflect the multiple snapshots per study. To add to this, included in one of the sBLA's is the Integrated Summary of Safety which required pooling of three other studies from the originally approved indication to demonstrate long term safety of the product.



CHALLENGES

The submission of dual sBLAs presented multiple challenges that required strategic problem-solving and collaboration across teams. These challenges primarily revolved around data consistency, handling external spreadsheet trackers, ensuring compliance with regulatory requirements, and managing the complexities associated with multiple data cutoffs.

HANDLING OF EXTERNAL SPREADSHEET TRACKERS

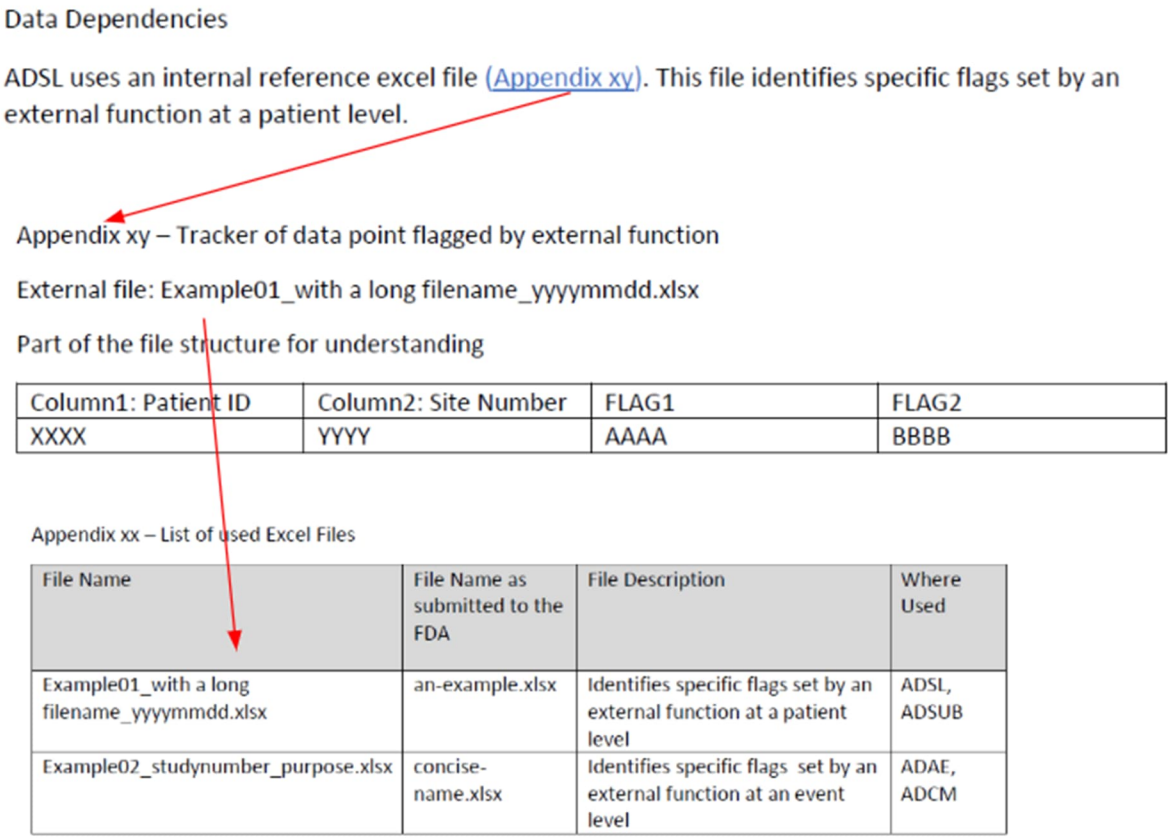
A significant challenge encountered during the submission process was the handling of external spreadsheet trackers. Many essential data points were not directly collected through CRF or non-CRF systems but were provided by other functional teams or required cross-functional collaboration for review. As a result, standard SDTM or ADaM datasets could not be used, leading to extensive reliance on Excel-based trackers across both studies. Specifically, the first study required managing seven spreadsheets for the primary CSR and five for the updated analysis, while the second study required six spreadsheets for the primary CSR and three for the updated analysis.

The use of spreadsheets was unavoidable due to the nature of certain data processing tasks. For example, during one AE basket review, data was extracted from the AE dataset using MedDRA baskets and then sent to the safety team

for adjudication. The safety team reviewed the data and returned a spreadsheet with a confirmed flag, which was subsequently merged back into the ADAE dataset.

Given the volume of spreadsheets, the eSub team recommended converting them into SAS datasets before submission to prevent accidental modifications and ensure data integrity during transfer. However, formatting challenges arose during this conversion, as certain variable names were too long to fit within SAS naming conventions. Consequently, a compromise was reached where the original Excel files were submitted alongside detailed documentation in the ADRG Appendix.

To maintain clarity and transparency, spreadsheet details were documented extensively in multiple locations. A brief description was provided in the ADRG appendix, listing each spreadsheet (e.g., Appendix 8.1, 8.2) and summarizing its purpose and associated variables. The following are examples of how this was structured in the ADRG



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

Additionally, a comprehensive summary of all spreadsheets used in the study was included later in the ADRG, specifying file names, descriptions, and points of use.

One critical adjustment made was referencing spreadsheets by their appendix number rather than their actual filenames in dataset descriptions. This ensured that the spreadsheets were officially part of the ADRG and prevented confusion about their classification as external files. Such an approach streamlined the review process and provided a structured framework for handling these essential but unconventional data sources.

CONSISTENCY ACROSS FILES

Maintaining consistency across different versions was crucial to ensuring the integrity of the submission. It is straightforward that SDTM and ADaM should use the same versions since they rely on the same data and are developed simultaneously. A practical approach was referencing SDTM for SDTM IG version, controlled terminology (CT) version, and setting the same in the ADaM package, assuming the SDTM versions were correctly implemented. Additionally, the MedDRA versions needed to remain consistent across datasets.

One specific challenge in the two sBLA filings was managing two cutoffs per study, which led to instances where versions were inconsistently applied. During review, discrepancies were observed in the P21 package, where some versions in the updated analysis packages were earlier than those in the primary packages. After consultation with regulatory experts, it was determined that either the versions should remain consistent across both cutoffs since they originated from the same study, or, if a difference was necessary, the later package should always use the later version.

Ensuring consistency extended beyond datasets to documentation as well. For instance, discrepancies in the number of discontinued patients were noted between the OSI BIMO Reviewer's Guide, the SDTM Reviewer's Guide, and the ADaM Reviewer's Guide. To resolve these discrepancies, the team reviewed all sources and aligned the numbers accordingly.

USE OF P21 ENGINE

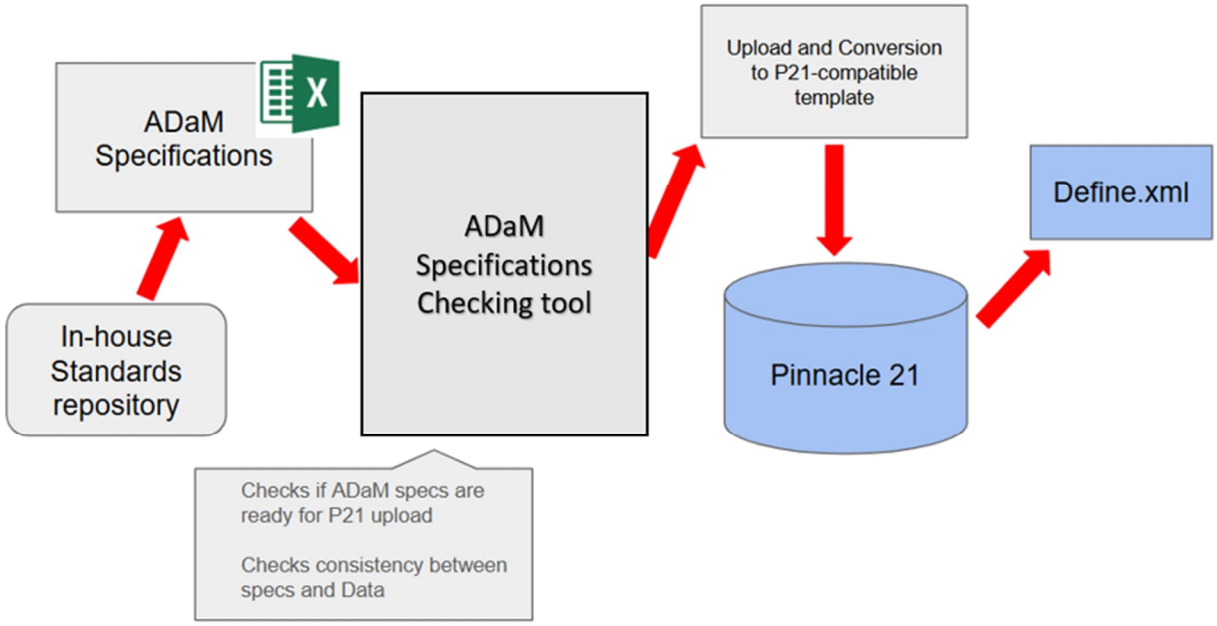
A correct P21 engine should be used to ensure compliance and optimize submission quality. Initially, we used the P21 2204.1 engine by default, which resulted in lower conformance scores. After further discussion, we determined that switching to the FDA 2204.1 engine, as the submission was exclusively for the FDA, improved the scores immediately.

P21 2204.1 includes checks for both FDA and PMDA, which may result in additional issues being flagged. While useful during study processing, submission teams should transition to Health Authority (HA)-specific engines such as FDA 2204.1 or PMDA 2211.0 for final submissions to align with regulatory expectations. Ensuring the correct P21 engine version in advance helps streamline the submission process and avoid unnecessary validation issues.

TOOLS for Monitoring Quality of Data

Various tools have been utilized to ensure data quality, including Pinnacle 21 (P21) and several in-house tools such as an ADaM Specification checker and SDTM data quality checks tools. P21 has served as the final data validation tool before submission to regulatory bodies. Given that latter two are proprietary in-house tools, a brief overview of their functionalities is provided here.

Our in-house AdaM specification checks tool is an R package primarily accessed via a Shiny app. It identifies inconsistencies within ADaM Data Specifications and ensures alignment with ADaM Datasets. By identifying inconsistencies within the ADaM specs, the team could proactively resolve issues, reducing the risk of errors in the final submission. The tool also helped align ADaM Datasets, ensuring consistency across different study snapshots and improving data integrity. Additionally, this tool facilitates a seamless upload of AdaM spec files into Pinnacle 21 during the eSUB process by validating the structure of the Data Specification Workbook, including essential sheets and columns, as well as checking for non-industry codes and ensuring compliance with variable name and label length standards. This proactive approach helped maintain high data quality, reducing submission delays and potential regulatory concerns.



The SDTMchecks tool is a set of R functions designed to identify common data issues in SDTM datasets. It enables users to efficiently run data checks through a user-friendly, customizable browser-based application that generates a report highlighting critical data concerns. Since late 2022, the SDTMchecks R package has been publicly available as an open-source tool within Pharmaverse and on CRAN. For the study team, SDTMchecks was instrumental in identifying common issues in SDTM data and detecting problems in raw datasets. By leveraging this tool, the team was able to proactively address data inconsistencies before submission. Prior to taking the snapshot, we collaborated closely with the Data Quality Lead (DQL) to implement necessary steps for resolving raw data issues. Additionally, when issues were linked to programming errors, we made targeted updates to our SDTM programming, ensuring data accuracy and compliance with regulatory standards. This proactive approach helped maintain high data quality and streamlined the submission process.

Pinnacle 21 (P21) is a widely used software tool for validating clinical trial data against regulatory submission standards such as CDISC SDTM, ADaM, and Define.xml. It ensures data compliance with regulatory requirements set by health authorities like the FDA (U.S.) and PMDA (Japan) before submission. Though we used our in-house AdaM Specifications checking tool and SDTMchecks apps throughout the study, we started rerunning p21 before taking the final snapshots. By using Pinnacle 21 (P21) early in the process, the study team gained significant advantages in ensuring data quality, regulatory compliance, and submission readiness. Early validation allowed the team to detect and resolve errors proactively, preventing last-minute fixes that could have delayed submissions. Aligning datasets with FDA, and CDISC standards from the start helped minimize non-conformance risks and maintain data integrity. The automation of validation checks reduced manual review efforts, streamlining the team's workflow and improving efficiency. Additionally, early use of P21 facilitated seamless collaboration among programmers, statisticians, and regulatory teams, ensuring that submission packages were well-prepared to meet health authority expectations. This proactive approach enabled the study team to prevent submission delays, make informed decisions, and navigate the regulatory submission process more effectively.

KEY TAKEAWAYS

Given the complexity and challenges of this filing, the team derived the following key takeaways from this experience that can be applied to future filing activities.

WHAT WORKED WELL

Proactive and timely engagement with the eSubmissions lead was essential in optimizing the submission process, especially due to the significant reliance on external spreadsheets. This collaboration allowed the team to implement necessary measures in advance, mitigating potential delays. Consistent utilization of quality assurance tools such as Pinnacle 21 (P21), AdaM Specifications checking tool, and SDTMChecks facilitated ongoing data validation, ensuring adherence to regulatory requirements and swift issue resolution. Emphasizing consistency across all data and documentation packages remained a top priority, which included synchronizing specifications, documentation, aligning controlled terminologies, and maintaining coherence between ADaM and SDTM datasets.

PLAN EARLY

Early planning is crucial for ensuring a successful and timely eSubmission. By starting the planning process early, teams can gain a thorough understanding of complex regulatory guidelines set by the health authorities. At times, project teams are too busy and focused on preparing for unblinding and the key analysis that filing requirements take a backseat until after the key readout. However, by continuously considering filing and eSubmission requirements throughout the study's conduct, teams can ensure that necessary conformance activities and required documentation are completed in a timely manner. Given that the filings described in this paper are two separate sBLA’s being completed by one small team, it had benefited from this mindset.

..BUT BE FLEXIBLE

Things may not always go according to the plan. Even the most meticulously prepared plans and timelines may require revision due to factors that are sometimes beyond the team's control. . In the case of these filings, the device recall required the team to pivot from their plans and adapt to the situation. Specifically with the addition of the updated analyses, the team had decided that the best course of action would be to submit separate data packages for each snapshot. Initially, there were differing opinions about this course of action. However, the team demonstrated their flexibility by presenting the pros and cons of the various proposals. This ability to objectively assess and discuss different viewpoints is a testament to their adaptability. With this said, thoughtful re-purposing of documentation, code, and resources helped the team tackle these multiple data packages.

CONCLUSION

Preparing a quality eSubmission package is challenging even in ideal conditions. However, the inherent complexities of a drug-device combination product introduced additional challenges, necessitating greater effort from the team to complete the deliverables. The challenges and best practices mentioned above represent a small list of specific insights that the team wishes to share as valuable lessons learned from this submission. Think of it like sailing a ship: you can chart the perfect course, but it's your ability to adjust the sails and use every tool at your disposal that keeps you out of trouble when the storms hit. The same goes for preparing an eSubmission package—planning is crucial, but flexibility and adaptability are what truly steer you through the challenges to success.

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CONTACT INFORMATION

Contact the author at:
Author Name: Aldrich Salva
Company: Genentech
Address: 1 DNA Way, South San Francisco, CA 94080-4990, United States
Work Phone: +1 650-892-3292
Email: salva.aldrich@gene.com
Website: https://www.gene.com

Author Name: Iris Zhao
Company: Genentech
Address: 1 DNA Way, South San Francisco, CA 94080-4990, United States
Work Phone: +1 650-822-3190
Email: zhao.chen@gene.com
Website: https://www.gene.com

Author Name: Elma Zannatul Ferdousy
Company: Genentech
Address: 1 DNA Way, South San Francisco, CA 94080-4990, United States
Work Phone: +1 650-241-5975
Email: ferdousy.elma@gene.com
Website: https://www.gene.com