Tough Start? Don't Panic! Your Submission Can Still Be Successful

Regulatory eSubmission Lessons Learned for a Late Stage Acquisition

PP03

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INTRODUCTION

Acquisitions have increased in the biopharmaceutical world and, as a result, so have the need for legacy data conversions, which is always a challenge. We recently had a successful eSubmission with a very complicated regulatory submission strategy including many legacy studies. This poster will discuss the following:

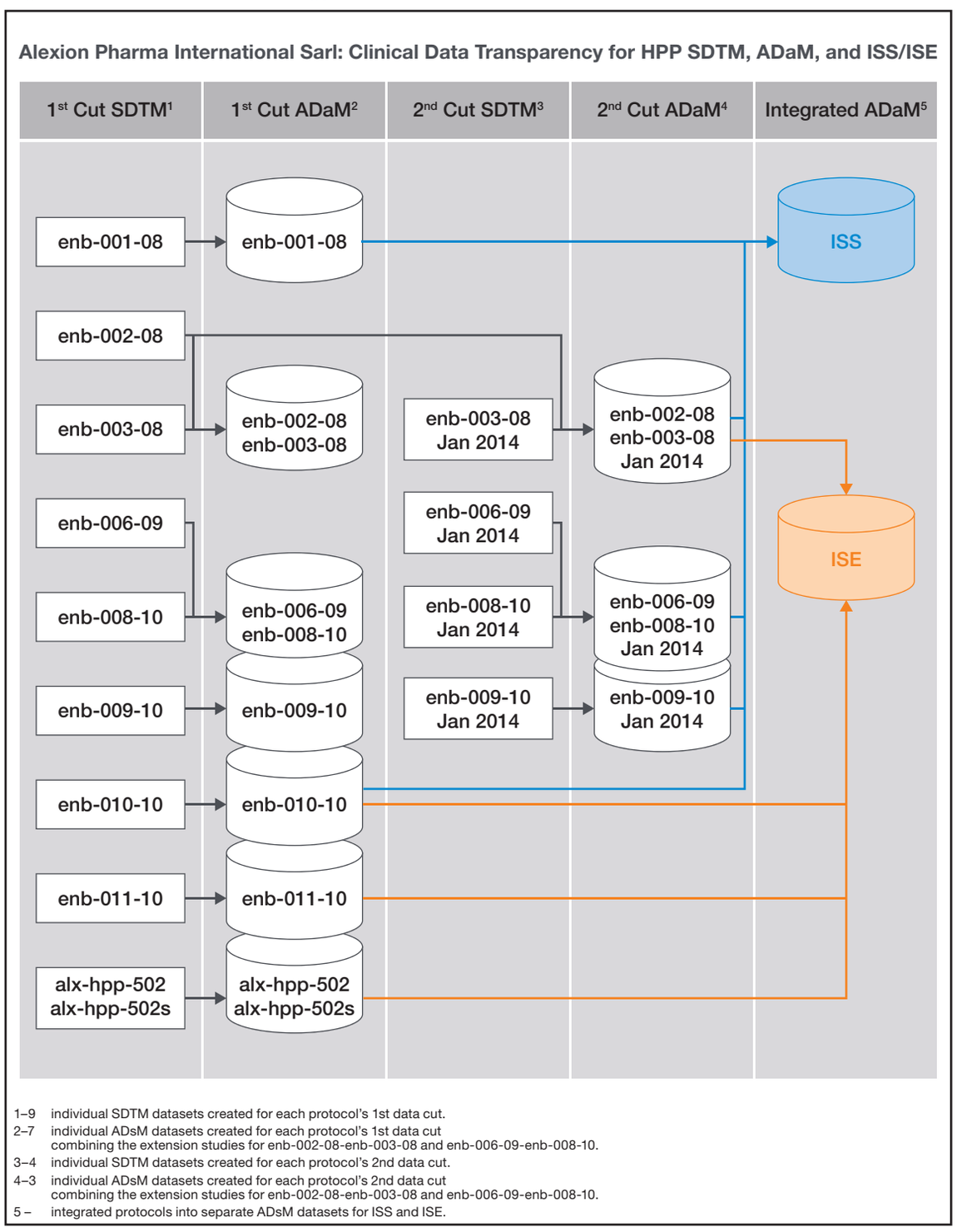
- How we quickly assembled supplemental teams to distribute risk and workload
- Prioritized rigorous efforts on SDTMs to minimize rework and prevent multiple rounds of changes downstream
- Created an innovative way of managing SUPPQUAL data during many interim data transfers that helped save time and resources
- Communicated with FDA reviewers efficiently and effectively about our complicated data submission strategy ensuring fewer questions

BACKGROUND AND CHALLENGES

- Key CRO was unable to meet its commitment in the middle of the submission, then withdrew from the contract and left the team very vulnerable
- Nine individual legacy clinical studies plus integrated summaries of safety and efficacy (ISS/ISE)
- Multiple data cuts and 3 EDC systems; many external non-SAS datasets
- Complicated regulatory submission strategy

SCOPE OF WORK

Figure 1 – Submission Strategy



1–9 individual SDTM datasets created for each protocol's 1st data cut.
2–7 individual ADsM datasets created for each protocol's 1st data cut combining the extension studies for enb-002-08-enb-003-08 and enb-006-09-enb-008-10.
3–4 individual SDTM datasets created for each protocol's 2nd data cut.
4–3 individual ADsM datasets created for each protocol's 2nd data cut combining the extension studies for enb-002-08-enb-003-08 and enb-006-09-enb-008-10.
5 – integrated protocols into separate ADsM datasets for ISS and ISE.

WHY AND HOW DID WE SUCCEED

- Diversified vendor network: initial strategy was to streamline the outsourced multiple functional areas by working with a single vendor. After the original CRO announced they couldn't meet their commitment, we quickly assembled supplemental teams of highly skilled and very professional individuals selected from multiple organizations. Most of them came pre-vetted as we had successfully worked with them previously
- Adopted original vendor's process/metadata into our own system: our original vendor used their own metadata system to create .pdf specifications for SDTM and ADaM as well as .sas7bdat metadata. We converted the .sas7bdat metadata into excel so that we could have editable SDTM/ADaM specifications instead of starting from scratch
- Efficiently managed many non-SAS external data in one central location for each protocol (as shown in **Figure 2**)

Figure 2 – Content of included SAS file for all non-SAS data for one study

```
%let abext      = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\ENB-002-08_AB_20131210.txt;     /* Antibody External */
%let pkextw     = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\ENB-002-08_PK_20130613.txt; /* Pharmacokinetic External From Wil Research */
%let ppiexte    = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\ENB-002-08_PPIENB_20130606.txt; /* PPI Enobia */
%let dvext      = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\ENB-002-08 Protocol Deviations_18Jun13.xlsx; /* Protocol Deviations */
%let lbrange    = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\lab-normal\002_LabTest Ranges 16Jul2013.xlsx; /* Lab test ranges */
%let lbconv     = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\lab-normal\002 003_LabTest Name Mapping and Conversion_03Oct13.xlsx; /* Lab mapping and unit conversion */
%let labref     = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\Lab_Tests.xls; /* Lab Tests */
%let labunits   = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\Lab_Units.xlsx; /* Lab Units */
%let exlot      = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\002 EX_LOT numbers_11Jul13.xlsx; /* Lot Number */
%let site       = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\002 Site Locations.xlsx; /* Site Information */
%let alpl       = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\ENB-002-08 ALPL Gene Mutation Analyses 08APR11.xlsx; /* ALPL Gene Mutation */
%let pkextc     = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\ENB-002-08_PKCB_20130605.txt; /* Pharmacokinetic External From CBRG */
%let BSIDEXT    = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\002 BSID_29May13_final data_text formats.xlsx; /* BSID External Data */
%let iarisr0203     = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\002_08__IAR_ISR_05JAN2015_SM_TO.xls; /* Injection/Infusion Associated and Site Reaction for ADAE */
%let bmiagerev      = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\bmiagerev.xls; /* BMI */
%let wtleninfnew    = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\wtleninfnew.xls; /* Weight/Length */
%let wtagegt36      = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\wtagegt36.xls; /* Weight/age */
%let wtageinf       = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\wtageinf.xls;
%let lenageinf1gt36 = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\lenageinf-1gt36.xls;
%let lenageinf1     = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\lenageinf-1.xls;
%let headcircboys   = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\headcirc_boys.xlsx; /*Head circumference - boys*/
%let headcircgirls  = D:\SAS\ASFOTASE\HPP\ENB-002-08\DATA\SOURCE\headcirc_girls.xlsx; /*Head circumference - girls*/
```

- Prioritized rigorous efforts on SDTM
  1. Due to the 3 different EDC systems, the source data looked very different for the same data in different studies. We standardized the individual SDTMs from different databases, different studies, including controlled terms, to prepare for the integrated analysis
  2. We also realized any change in SDTM will potentially impact ADaM/TLF programming. We put in rigorous efforts/resource in finalizing SDTM as early as possible
  3. We ran OpenCDISC as early as the draft SDTM passed validation, and in frequent intervals after each database update. Although there were a lot of findings in the OpenCDISC report because of data issues, we focused on rectifying any data structure findings before ADaM got started. This way, we avoided making changes all the way from SDTM/ADaM/TLF after database lock
  4. We implemented an innovative way of managing SUPPQUAL data by developing a new process and macro. SUPPQUAL variables were mapped and programmed as if they were additional variables in the parent domain (as shown in **Figure 3**). These would become a "QNAM" row in the SUPPQUAL. All SUPPQUAL variables are programmed even if the source data were not present (e.g. not all comment fields populated). The macro would automatically structure the parent and SUPPQUAL domain using metadata created from the specifications, and removed any null records from the SUPP domain. If there were no data to populate SUPPQUAL then it would not be produced. Using this process and macro, we did not need to re-check the source data at each data transfer. This saved us so much time/resource, especially for multiple database locks occurring within a week

Figure 3 – Subset of example specifications that would be converted to metadata to produce SDTM domains

Domain	Variable Name	Variable Label	Submit	Supp	IDVAR	QEVAL	QORIG	Definition
DV	DVTERM	Protocol Deviation Term	Yes	No				=EXTERNAL.DVEXT. DESCRIPTION; IF EXTERNAL. DVEXT.DESCRIPTION exceeds 200 characters then only display the first 200 characters in SDTM. DV.DVTERM. All characters after 200 will be placed in SUPPDV
DV	DVTRMCN1	Protocol Deviation Term Continued	Yes	Yes	DVSEQ		eDT	=IF EXTERNAL.DVEXT. DESCRIPTION exceeds 200 characters then include all text after 200 characters

- Took into consideration the connection from SDTM to ADaM: since SDTMs will need to be mapped into ADaM for analysis, when there are multiple options for SDTM mapping, we always chose the most efficient way to map the SDTM to facilitate ADaM and analysis. **Call for CDISC and industry attention to build the road map from SDTM to ADaM**
- Efficiently and effectively communicated with FDA review division
  1. Visual flowchart (as shown in figure one) describing our complicated data submission strategy, especially due to different database cut for individual CSR and ISS/ISE
  2. A teleconference was held with the FDA review division about the submission data a couple of months before the planned submission date. We were asked to combine our SDTMs in the core-extension studies (002/003, 006/008). We explained to the biostat reviewers that what we did in our submission package is strictly following CDISC SDTM standard; hence the review division agreed with our original plan and saved the company a great deal of time by not re-constructing our SDTM/ADaM and all the related submission documentation
  3. We provided clear and accurate documentation (i.e. Define.xml, Define.pdf, SDRG, ADRG) to the review division, which ensured fewer questions from the reviewers
     a. Our submission documentation was based on our SDTM/ADaM specifications, which have been through very thorough review/validation by statistician and development/validation programmers. We have made it a priority to have specifications correct at the programming stage, if there was change in the SAS programming code, we required the specifications to be changed first
     b. Our submission package (define, SDRG and ADRG) also went through thorough review/QC process by lead statisticians and lead programmers

CONCLUSIONS

- The more detailed plan (i.e. submission strategy, CRO selection, timeline) you have, the easier the project will go, the better result you will have in the end
- SDTM is NOT easy, nor is it trivial
- Specifications are NOT just for programmers; specifications will turn into define/SDRG/ADRG. So programs and specifications need to be consistent and synchronized
- Documentation is VERY important. Documentation = communication with FDA reviewers
- FDA reviewers are not unreasonable. Don't be afraid to ask questions and speak up

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