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Experiences in Leading a Company-Wide First CDISC Filing from a Programming Perspective

Sho-Rong Lee, Genentech, a Member of the Roche Group, South San Francisco, CA

ABSTRACT

The FDA first began accepting CDISC submissions about a decade ago. Some companies have CDISC filing experience, others are in the active preparation phase, and there are others currently evaluating their capacity to launch the processes. Many factors need to be considered prior to launching a CDISC filing: support from management and filing team, adoption of SDTM data mapping and ADaM analysis data derivations, CDISC awareness training in various functions, eSubmission CRT metadata documents and structure, annotated CRF, and Controlled Terminology, just to name a few. This paper describes an approach to initiating a company-wide first CDISC submission, the design and construction of CDISC tools and processes, and the discussion of challenges, successes, and lessons-learned. The goal is to present insights gleaned from the recent CDISC submission experience of Genentech, a Member of the Roche Group, thereby benefiting the industry.

INTRODUCTION

Submitting a filing to the FDA (Food and Drug Administration) using Clinical Data Interchange Standards Consortium (CDISC) data standards is strongly encouraged in the pharmaceutical industry, however, each submission is unique. The New Drug Application (NDA) submission under discussion involved an oncology trial of an indication with new endpoints. Currently, there is no standard of care. Therefore, upon approval of this first in class medicine, the company will bring an entirely new medication to the market for the first time.

We will first look at the characteristics of this filing that led us to consider a submission using CDISC data standards with a focus especially on SDTM and ADaM data adoption and eSubmission preparation. In addition, we will discuss the processes we designed and the tools we built. Finally, we will look into the lessons-learned and discuss the challenges and successes.

REASONS FOR A CDISC FILING

To initiate a company-wide first CDISC filing is a daunting but exciting task! With an unlimited numbers of unknowns lying ahead, why did we decide to submit a CDISC filing? Two years prior to the submission, the question of how best to present clinical data to seek FDA approval was seriously pondered.

This filing was comprised of numerous clinical studies including several pharmacokinetic studies. The timelines for all the studies were closely interdependent and involved time constraints.

An additional factor pushing us toward a CDISC filing was the need for data consistency. It was believed that adopting the industry data standards would expedite FDA's review, because the consistent look and feel of the data across studies greatly facilitates data retrieval and analysis.

CDISC data standards were not new to Genentech. Prior effort, such as a CDISC pilot study, had been underway and the needed CDISC knowledge and experience was already developing. Consequently, the decision was made to go forward with a CDISC filing.

ALLOCATION OF CDISC PROGRAMMING RESOURCES

In order to secure resources for CDISC programming, an early assessment was made of prospective resource needs, taking into account the number of studies and their different phases as well as their timelines. The document was then presented to management for evaluation. All groups supported the importance of cross-functional personnel. These key staff members would be able to bridge some or all areas including statistical programming, clinical programming, electronic submission, biostatistics, and regulatory affairs. Apart from the internal resources, the need for external expert consultants as team members was also recognized.

A filing team was also established with representatives from regulatory affairs, clinical science, pharmacology, biostatistics, programming, drug safety, manufacturing, commercial, medical writing, and publishing. It was tasked with governing the scope and timelines of the submission.

Based on study timelines, it was determined that separate programming groups take on the responsibility of mapping SDTM data from the clinical database as well as the construction of the ADaM analysis data. In addition, each programming group would prepare for its respective eSubmission tasks. Draft timeline documents were then devised to gain efficiency.

Furthermore, there were numerous other tasks necessary for CDISC compliance. These included, but were not limited to, CDISC awareness trainings for staff of all functions, data flow design for both clinical studies and ISS/ISE (Integrated Summaries of Safety and Efficacy), CRTs (Case Report Tabulations) metadata document formats for both SDTM and ADaM data, Controlled Terminology construction, conformance checks on both SDTM and ADaM data, eSubmission processes and tools such as a reviewer's guide document and annotated CRF, and a test submission.

A special characteristic of this filing was that it consisted of several pharmacokinetic studies, making it necessary to discuss and sketch pharmacokinetics data flow upfront. All of these capabilities had to be in place and implemented in a pre-defined time frame.

EMBRACING THE SDTM AND ADAM DATA STANDARDS

A timeline for mapping SDTM was drafted for all clinical studies encompassed in this submission and by a designated programming group. The process involved first setting up a template mapping file so that mapping consistency could be achieved in all studies. This uniformity was greatly beneficial later when the time available to map the outsourced studies' SDTM data was circumscribed. Conformance checks for SDTM mapping were also performed under the collaboration with CRO consultants of CDISC submission expertise.

Upon receiving SDTM data, the statistical programming group derived ADaM analysis datasets. Project-level macros and template programs were developed and documented specifying common datasets, variables, ordering of variables, naming conventions, and the rules specific to the project. This greatly facilitated consistency across studies, thereby increasing efficiency. These tools also functioned to help train newcomers and allowed the QC process to go smoothly.

Before the ADaM programming effort was initiated, team members of programming groups received an on-boarding training on SDTM and ADaM data requirements. This was followed by additional trainings conducted for both programming groups and biostatisticians. In addition, late joining staff, such as CRO contract programmers, was able to take advantage of the documentation.

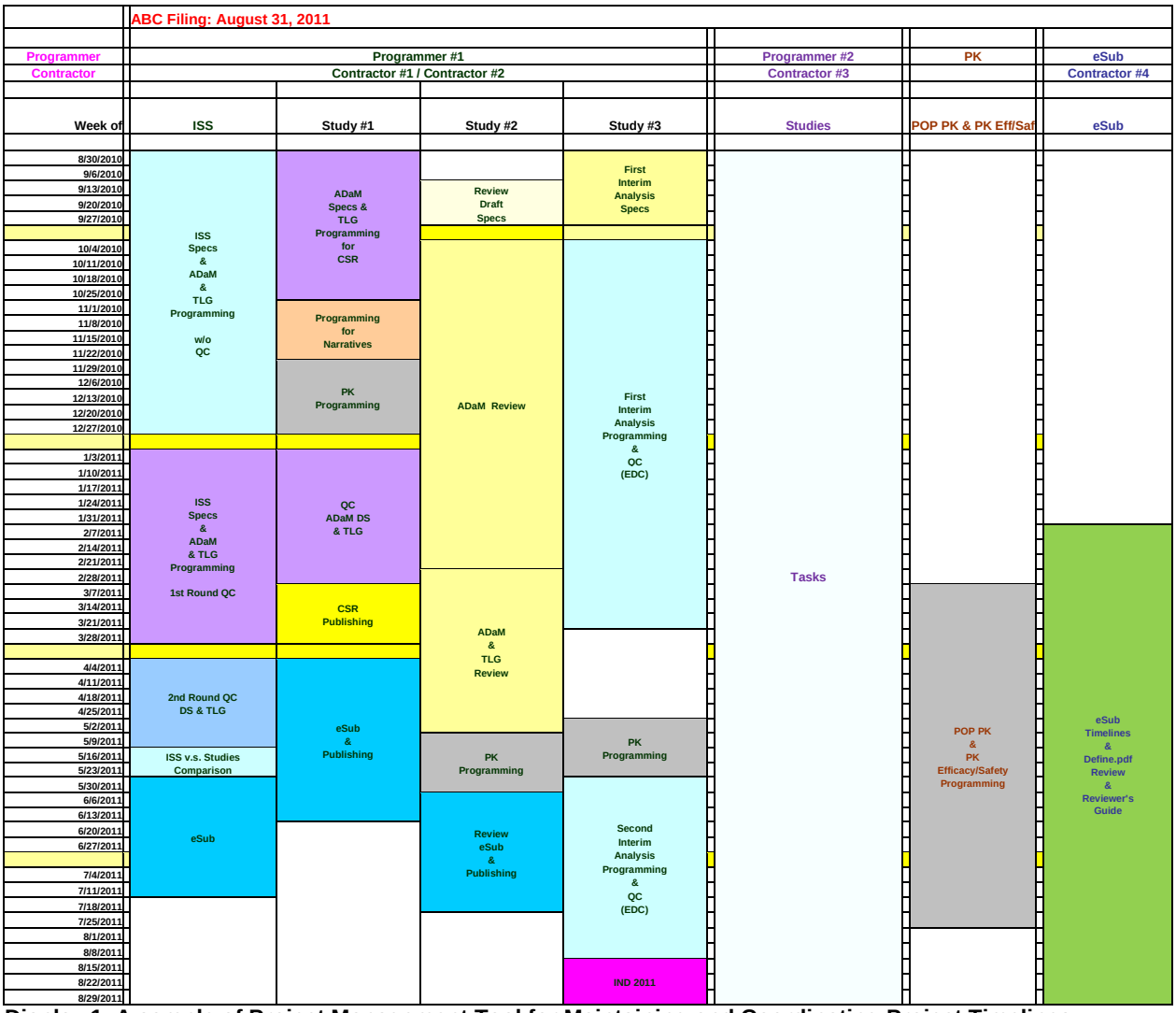
Regular group meetings were held to share information and timelines among team members as well as among groups in an efficient and timely manner. Communication was vital in this filing since the time for data construction was pre-specified but the information was subject to constant shifts as further details were obtained.

Documentation was another essential element that helped center and align team members, especially new teammates, getting everyone oriented to the project requirements. Because proper documentation was drafted early on to maintain the CDISC requirements that applied to all studies, consistency was maintained across all study mapping processes.

Additional documentation for SDTM and ADaM procedures were prepared and made available to all team members by posting it in a central location. This helped team members effectively locate the most up to date information and timelines. Information pertaining to the whole project timelines triggered down from the filing team was then efficiently and easily accessible by all team members.

Planning was crucial in such a filing, let alone with the new CDISC data format to create. The programming groups first allied with the biostatisticians to support a CDISC filing. A data submission plan was drafted by the biostatisticians early on to help guide the process and secure the resources needed. The plan comprised of each of the studies and their data submission components, also served to guide the scheduling of eSubmission activities.

Project Management (PM) tools were essential for maintaining and coordinating timelines as well as displaying responsible staff and for keeping track of all programming activities. Different approaches were attempted, but Microsoft Excel seemed to be the best and simplest tool among all. In the preparation of the submission, the activities were purposely staggered and the Excel file clearly identified the timing of the workload per programmer. The following is an example.



Display 1. A sample of Project Management Tool for Maintaining and Coordinating Project Timelines

In addition, close communication within the filing team and attendance at team meetings were required to get the programming timelines on track as well as to make quick decisions. In summary, early planning and constant communication helped the CDISC filing progress immensely.

The team was extremely cohesive and team dynamics were great. Flexibility in adapting to changes and enthusiasm for making the first CDISC filing a reality were essential. Without effective team work, the filing could not have succeeded.

PREPARATION OF ESUBMISSION

The team sought advance direction on eSubmission CRT metadata requirements in the initial stage of programming activities. After numerous discussions and consultations, the decision was made to prepare define.xml for SDTM data and define.pdf for ADaM data. This was believed advisable because the define.xml for ADaM data was not yet mature in the industry as well as in the company. The team later determined to also submit define.pdf and define.html for SDTM metadata for reviewer's printing and browsing purposes.

Roles and responsibilities were defined early on for the delimitation of programming groups responsible for SDTM mapping and ADaM analysis data derivation. This early determination helped the team to enable programming activities quickly. Annotated CRF and define documents followed. eSubmission group and experienced consultants accomplished this task.

A test submission was also requested by the team and was submitted to the FDA Office of Business Informatics. Since this was the company's first CDISC filing, it was prudent to test the CDISC data format prior to the actual submission. The team put together a package based on one clinical study and the conformance checks feedback was satisfactory.

The eSubmission lead programmer role was created for this filing because the new CDISC data submission was underway. This team member took charge of the eSubmission related timelines, reviewed the clinical metadata documentation, and ensured that deliverables were on track. This lead role is strongly recommended for future CDISC submissions.

The eSubmission tools that converted in-house analysis metadata information into CDISC compliance CRT define documentation were built immediately before the eSubmission preparation phase. A document specifying eSubmission tools workflow and requirements was created prior to the first clinical study data conversion. This document assured a consistent approach in converting CRT metadata information into define documents across studies. It also aided new team members in performing the conversion with little in-person guidance.

Controlled terminology was prepared along with the CRT metadata information conversion and was set apart as a section within the define document with proper links affixed back to the metadata section. In case of additional explanation required in the CRT metadata document, an additional data specification document was also appended to the define document.

Due to the new CDISC data format, the electronic submission folder structure also required careful consideration. The eSubmission group adopted the FDA guidance and utilized experience from the test submission to build the best filing structure in eCTD (electronic Common Technical Document) for CDISC data. Legacy data format was also incorporated.

To help reviewers better understand the CRT metadata information, a reviewer's guide document was created for each clinical study, if deemed necessary, as part of the filing package. In particular, the team had prepared the reviewer's guide documents for the pivotal trial and ISS. A brief description of this CDISC filing was mentioned in eCTD Module 1.

One component in this eSubmission worth noting was to compile site investigator's information so as to satisfy FDA Division of Scientific Investigations (DSI) routine requirements. Despite it not being required during the eSubmission preparation phase, the team decided to furnish it prior to submission. This turned out to be a desirable decision in that DSI sent in the request to the sponsor soon after submission.

Another integral part of the submission was to supply programs governed by the pre-NDA meeting agreement. In this filing, the construction of required programs did not deviate from other submissions. However, be mindful to coordinate with the CRO well in advance to reserve sufficient resources for each task, such as the submission-ready program development.

One wise decision the team made was to have an experienced CDISC vendor to provide consultation to the team. Regular meetings of programming groups with the consultants were conducted to discuss current issues. This worked to prevent delays in decision making. The vendor's input provided valuable guidance to the team and is strongly recommended for future CDISC filings.

LESSONS-LEARNED

The team conducted lessons-learned sessions to better understand the challenges and successes of this company-wide first CDISC filing. The experience gained was invaluable and the team provides the following suggestions organized in four categories for future CDISC submissions.

- *Planning and Training*

  - Planning makes a difference. Take advantage of Project Management tools. Software, as simple as Excel, can be a good candidate. Be thorough and careful in drafting timelines before launching a first-time CDISC programming effort - because there is no prior CDISC filing schedule to rely upon. Development of detailed timelines minimizes the need to constantly be aligning staff with project needs.

  - On-boarding training is required for a successful CDISC filing. Consider preparing a slide deck module early on for team members' CDISC training as an awareness course as well as a refresher.

  - Take smart risks. Obtain health agency consent on the agreement before programming activities begins by allying with Biostatistics. This conserved resource and saved team time especially during the eSubmission preparation phase.

- If there are outsourced studies involved in the submission, coordinate with CRO ahead of time in terms of CDISC data conversion to ensure the data structure is consistent with in-house studies. This will avoid the difficult situation of improperly formatted data arriving late in the process when resources are scarce. Review outsourced study's CDISC mapping specifications early.

❖ *Communication and Documentation*

- Good communication facilitates quick decision making within groups as well as cross functions to include all stakeholders. Define expectations and communication style upfront to minimize the redundancy of back and forth communications.

- Organize regular group meeting to expedite information dissemination, to manage timelines, and to ensure programming consistency.

- Be flexible and expect roadblocks. Even though using CDISC data standards in a submission for the first time might seem frightening, the unexpected can still be minimized or controlled with proper planning and constant communication.

- Let all functions know of CDISC requirements early on. Broad advertising of CDISC requirements will result in better communication throughout the preparation of submission.

- It is recommended to test out the resource needs upfront in reviewing data specification documents and CRT metadata information for more accurate resource estimation.

- A central location for documentation will allow all team members to readily obtain the most up to date information. It also shortens the time needed for existing team members to train new team members. Therefore, always document the processes and workflow and post the documents as well as health agency and CDISC guidance in a central location. It will benefit the team members by reducing time spent on providing training and guidance to newcomers, and it will ensure consistency of data mapping and data derivations. A little investment in proper documentation can go a long way!

❖ *Roles, Assignments and Teamwork*

- Designating liaisons for the programming groups to serve as the single contact person for specific functions, improves and speeds up communication. For example, our team created eSubmission, pharmacokinetics, and SDTM liaisons from the statistical programming group to the electronic submission group, pharmacokinetics function, and clinical programming group, respectively.

- Assigning a lead role to each task increases efficiency in completing the task. For example, because our team created an eSubmission lead role, an ADaM data lead role, an ISS lead, and a technical lead role, information triage and quick decision making were achieved.

- If permissible, avoid adding staff late in the submission process because the learning curve does take time. Well in advance planning to secure resources upfront helped the team tremendously.

- If there are non-standard components in the filing, make sure to design the work flow upfront, to define the scope and analysis, to develop a filing checklist, and to allocate resources appropriately prior to the initiation of programming. Assigning roles and responsibilities to best facilitate the work flow as the programming phase begins will reduce confusion among team members, and will facilitate keeping track of timelines as well as securing resources appropriately.

- Reserve consultation early to assist filing team members in learning to make informed decisions especially in this company-wide first CDISC submission. Therefore, the participation of consultants with CDISC expertise is beneficial and recommended.

- Acknowledge team member's achievement while preparing for the submission as well as respect one another to motivate team members. This greatly boosts morale.
- Regular casual lunch gatherings help team members stay connected!

❖ *Decision-Making and Processes*

- If an Independent Review Facility (IRF) is included in the filing, coordinate with the IRF CRO data manager to determine the data structure prior to the beginning of IRF review. This could reduce additional complications from CDISC data conversion.
- Avoid re-visiting decisions. Do not be afraid to take time in the beginning to set up a strategy for good decision-making even though it might seem like time wasted.
- Frontloading work helps, when possible. For example, eSubmission metatdata conversion tools and Controlled Terminology structure can be set up way in advance.
- Construct just-in-time processes and tools to ensure seamless delivery. In addition, robust tools should be built with benefit of future submissions in mind.
- For complicated data flows, such as pharmacokinetics and ISS, upfront examination of risk assessments should be sketched in advance. This will result in more accurate resource allocation and timelines.
- Perform both SDTM and ADaM conformance checks early in order to have all deliverables ready on time in preparation for eSubmission and to ensure that data is conformed and there is consistency across studies.
- Conduct follow-up knowledge sharing so that all the pioneering work that is done for this filing will benefit the company's future CDISC filings.
- Anticipate significant savings as a result of your CDISC filing! The estimate of our effort indicates a considerable saving in ADaM data programming as well as in eSubmission effort.

CONCLUSION

The combination of an enthusiastic and talented team guided by well in advance planning and good communication utilizing proper PM tools resulted in a successful filing. The time saved, thanks to CDISC data standards, was considerable and consisted mainly of reductions in programming time as well as shortened FDA review time, as a result of consistent look and feel data for all studies in submission. We demonstrated that we could put together a CDISC submission and in so doing paved the way for the company's future CDISC submissions.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Name: Sho-Rong Lee
Enterprise: Genentech, A Member of the Roche Group
Address: 1 DNA Way
City, State ZIP: South San Francisco, CA 94080
Work Phone: (650) 225-6149
E-mail: lee.shorong@gene.com