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Developing, Implementing and Governing End-to-End Standards at Gilead

Dhananjay Chhatre, Gilead Sciences, Foster City, USA

ABSTRACT

Given the FDA (and upcoming PMDA) regulatory requirements for submitting standardized study data in submissions, Gilead Sciences has worked towards defining Global standards for SDTM, ADaM, SAP text, and TFL shells, following the successful implementation of our Clinical Data Management Global Library and Case Report Form (CRF) pages. This paper will focus more on current progress and future plans for standards governance, including necessary resources, internal structure, and utilities while briefly discussing Gilead's current status for end-to-end data standards development, and subsequent implementation. Standards-ancillary initiatives that build upon standards and improve efficiencies will also be discussed. Lastly, lessons learned and best practices will be described, for the benefit of industry and future projects seeking to implement and govern end-to-end standards.

INTRODUCTION

The FDA's binding guidance document publications required Sponsors to submit standardized study data for future regulatory submissions. [1] [2] [3] The intent of these standards is to enable the Agency to more efficiently review submissions by leveraging technologies and automation, aligning with CDER's 21st Century Review Process. [4] Standardized data allows regulatory reviewers to more fully understand and characterize the efficacy and safety of each medical product. The FDA Data Standards Catalog defines FDA-supported standards, as well as specific implementation timetables, which in turn inform Gilead's standards development processes. [5]

While many companies at that time had already been following and adhering to CDISC standards, others had created a company-specific standard that they used for regulatory submissions. [6] In order to comply with increased strictness of current and new validation rules, companies began to update internal processes and develop more CDISC-aligned standards. [7] Gilead has been in the process of developing global SDTM and ADaM standards since 2012, and we have recently finalized version 1 of our global SDTM and ADaM standards.

DEVELOPING END-TO-END STANDARDS

The initial development of end-to-end standards began with data management who developed global CRF pages out of necessity given the nature to silo by therapeutic areas (TAs) in the company. Once these standards had been developed and implemented across all TAs, downstream standards could be developed as well. While it was important to address regulatory requirements, the development and implementation of standards would allow for the development and use of utilities and automated processes which could increase quality, and reduce time to deliverables as well as overall person hours.

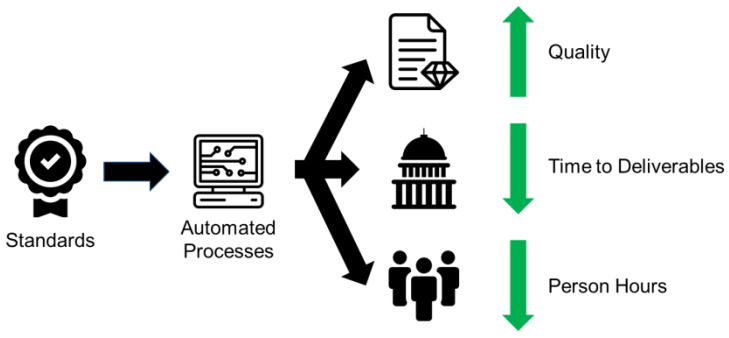

Figure 1: Standards can increase quality, efficiency, and consistency

FORMALIZED STANDARDS WORKING GROUPS

Although many updates were made to specific processes, leadership or membership, the notion of an SDTM Working Group and ADaM Working Group remained constant for developing cross-TA standards. What was quickly realized was the need for dedicated resources to do the heavy lifting of standards development, from researching variable mappings in the implementation guide, CDISC meeting minutes, or publically-available industry presentations, to developing draft mappings of variables with associated metadata, to managing discussions and escalating issues as

needed. While it was important to gain feedback, buy-in and comments from Statistical Programmers (SPs) across TAs that would be tasked with implementing these standards for their respective studies, these SPs simply did not have the bandwidth to research these topics or truly test them. As such, working groups were formalized in order to facilitate communication between them, as well as to provide an escalation pathway for topics that impacted multiple data states.

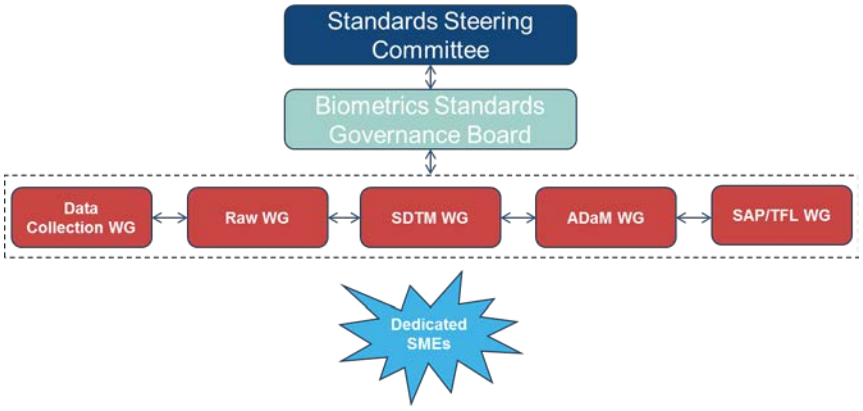

Figure 2: Formalized Standards Organizational Structure

To support the development effort, we expanded the standards team to include full time, dedicated subject matter experts, supporting SDTM, ADaM, project management, and testing of the standards themselves. As a result, it was critical that standards team members communicated with the working groups, standards steering committee members, and those that would ultimately implement these standards for their studies. A change management strategy was employed to drive process transformation both top-down and bottom-up, to initiate as much change in the status quo as was possible, including regular updates to leadership teams and during functional all-hands meetings, identification of change champions across TAs, co-creation and co–testing of content with end users, as well as a mechanism to capture questions and feedback anonymously.

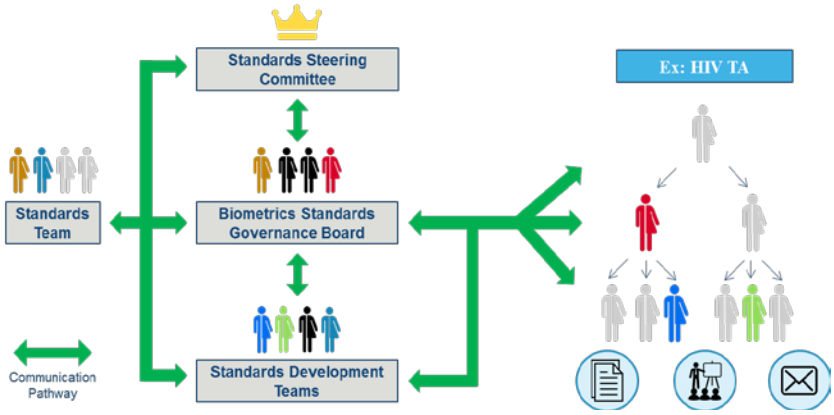

Figure 3: Increased Engagement via Bi-Directional Communication

IMPLEMENTING END-TO-END STANDARDS

Driving the implementation of developed standards could not be forced even if directed by TA or program leads. The time cost of changing mapping instructions and associated metadata mid-study was too high. As a result, the communication to study SPs was geared towards using the standards as a starting point for new studies and implementing only if possible for any ongoing studies. The new requirements for adhering to SDTMIG v3.2 and including define.xml v2.0 files in regulatory submissions after March 15, 2018 was a great opportunity to update our mapping specifications structure and develop new utilities to read those specifications files in order to generate datasets and define.xml files for regulatory submissions. In this way, we could ensure that new studies with a study start date (i.e. earliest informed consent date for all enrolled subjects) after March 15, 2018 had to follow the new standard and leverage the new utilities.

UTILITIES

Although Gilead had standard utilities to create datasets and a define.xml v1.0 file before, the March 15, 2018 requirements date was an opportune moment to create new utilities. [5] The standards team coordinated with users across TAs to develop requirements and use cases to pass on to our macros team. The entire development, testing and delivery timeline lasted roughly 18 months to generate both dataset and define utilities. Thanks to pre-planning, we were able to assist our Phase I teams in implementing these utilities before their studies started in time for submissions. To date, we have also worked with our late phase teams as they too have studies starting after March 2018. A key element of these new utilities includes quality control (QC) checks and reports to ensure that the study spec content and associated merge programs are aligned with utility expectations and developed company standards. This would identify upfront any issues the SP would face, as opposed to addressing them at time of delivery when timelines are already tight and staff members are stressed.

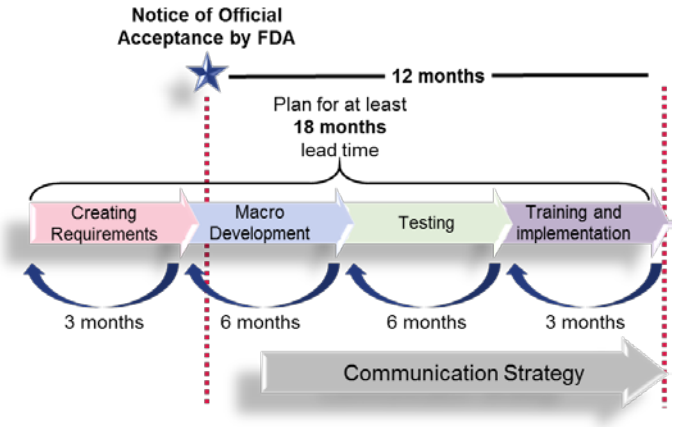

Figure 4: Planning Utilities Development to Address Future Requirement Effective Dates (illustrative)

PROCESS DOCUMENTATION

In order to align formal processes with what individual SPs were now being asked to do, the standards team began to update existing process documents (e.g. SOPs, WRKs, & MANs) as well as create new documentation. This would help ensure that future potential regulatory audits would not identify discrepancies between official procedures and what staff members were actually doing. Additionally, this helped enforce the best practices for future studies to implement the new data standards and corresponding utilities.

TRAINING

Since the new mapping specifications and utilities were different enough from historic tools and processes, the standards team created new trainings to describe the specs and the new process, which aligned with updated process documentation. In total, 11 new trainings were created, including not just SDTM, ADaM and define content, but also the use of Pinnacle21® and new programmatically consumable Data Transfer Specifications.

GOVERNING USE OF END-TO-END STANDARDS

Following standards development and subsequent implementation by various study teams, the Gilead standards team began to establish a formal governance structure as part of our operational efficiency. It was believed that in order for governance to be successful, we needed to create a mechanism to not only govern and oversee the activities and adherence to (or deviation from) standards, but begin to move towards enforcement of those standards. Alternatively, identified deviations observed across studies or even TAs could lead to new change requests to the standards themselves, serving as its own feedback loop.

PROCESS FLOW

We began to prepare for a future world where we could run real-time metadata comparisons of a study to a standard (or another study). To that end, we developed a standards governance model, at least for SDTM and ADaM, leveraging comparison functionality and custom QC checks.

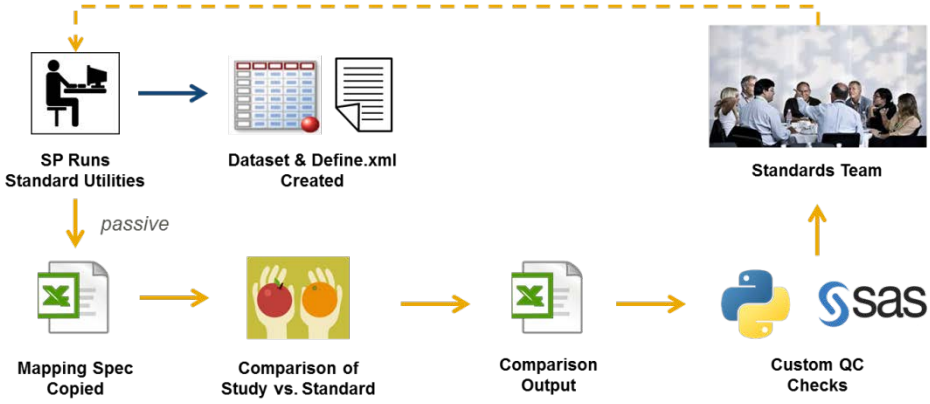

Figure 5: Focus on Effective Governance to Support Operational Efficiency

AUTOMATED CHECKS & ANALYSES

Our first step was to take a minimum viable product approach and conduct a proof of concept on this idea. The team developed a list of 34 checks (study to standard) addressing both SDTM and ADaM that would be important from a governance perspective, to serve as the initial assessment of standards adherence. Following automated comparisons of the study to the standard, we would run through this list of checks and produce an output that could be aggregated over time, allowing us to observe trends and proactively address potential changes to standards. This would also assist in working with and supporting SPs in real-time to identify root cause of changes made and assisting to align with standards as appropriate.

BIOMETRICS ESUBMISSIONS TEAM

A critical aspect of governance requires staying abreast of regulatory changes/updates and applying them in-house. While Gilead has a dedicated standards team, the bulk of work has been to adhere to FDA requirements. With other agencies (e.g. PMDA) seeking standardized data submissions, with varying degrees of rigidity and expectations, we are looking towards building out a Biometrics eSubmissions Team as an extension of our standards team. Any regulatory impact would need to be implemented internally through changes to training, procedural documents, utilities or the standards themselves, all within scope of the standards team. Considering the submission as the "end" of end-to-end data standards, this team's extension would be responsible for the real-time governance review aspect of study deliverables, as it relates to standards adherence. The new eSubmissions Team would also interact extensively with our internal Regulatory Operations and Regulatory Affairs teams, coordinating support for any regulatory meetings or responding to queries related to data standards. The new eSubmissions Team would also be responsible for creating a standard approach and process for developing submission deliverables; this includes review and QC that could be automated and made more efficient than current manual processes.

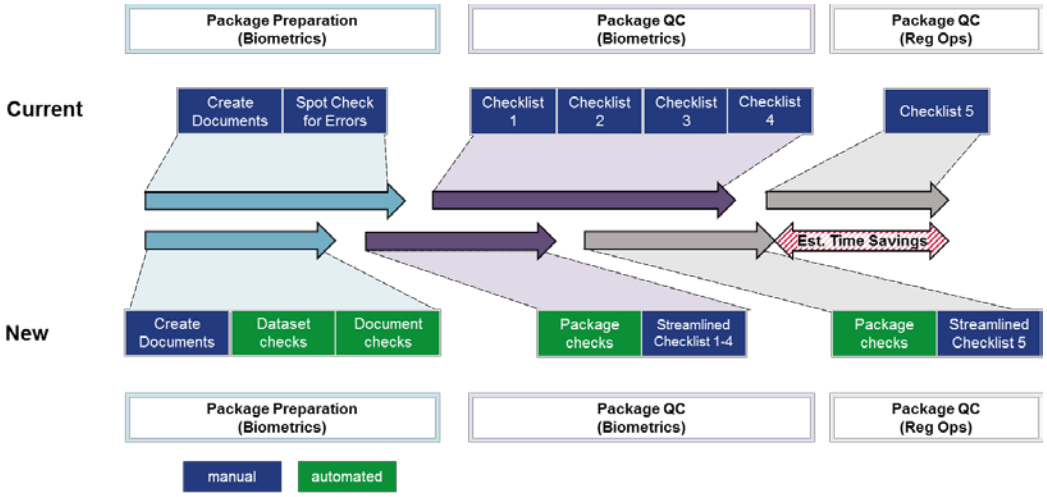

Figure 6: Proposed Changes to Development of Regulatory Submission Data Packages

CONCLUSION

While it has been a long and stressful road, the development and implementation of standards at Gilead has allowed for the advent of utilities to automate much of the rote work currently performed manually by SPs, data standards team members, and Regulatory Operations staff. We were able to not only document lessons learned but act on them to further improve efficiency gains. We have begun the first steps of governance, and we envision much more to be learned in 2019, related to standards ROI and key performance indicators to validate (or not) the benefits of a dedicated in-house standards team and eSubmissions Team.

REFERENCES

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7. **FDA.** *Validator Rules.*

ACKNOWLEDGMENTS

I would like to acknowledge and thank the great standards team at Gilead for their continued dedication and hard work in getting the standards published and governed, as well as the many volunteers who contribute to standards development concurrently with study work.

CONTACT INFORMATION

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

Dhananjay (DJ) Chhatre
Gilead Sciences
333 Lakeside Drive
Foster City, CA 94404
Work Phone: 650-389-8873
Email: Dhananjay.Chhatre@gilead.com
Web: www.gilead.com