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Models, Metadata, and Messaging: Exploring Standards Governance in the CDISC Era

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ABSTRACT

The number of sponsors establishing internal standards governance continues to grow as CDISC (**C**linical **D**ata **I**nterchange **S**tandards **C**onsortium) standards evolve from regulatory guidance to requirement, prompting an emerging uncertainty about how to achieve standards governance that is tailored for each sponsor's situation. How does an organization find the proper balance between efficiency & innovation, facilitation & bureaucracy, and compliance & leniency? What are the standards management issues that prevent sponsors from determining scope, instituting processes, or leveraging the standards metadata?

Having been immersed in standards on both sides of the pharmaceutical industry - sponsor companies and contract research organizations - I will represent 6 case studies in standards governance in order to explore the challenges and potential solutions for sponsors as they implement and subsequently manage these new standards as part of their clinical data processes. My objective is to provide sponsors with insight that can be taken back to the office as an aid as they labor with the oversight of their standards.

THE CDISC LANDSCAPE

Over the last 15 years, the development of CDISC standards has grown from being collaborative "guidance" that offers benefits in the regulatory review of submissions, towards being binding requirements that are necessary for submissions to regulatory authorities. Along the way, sponsors have begun to realize that the trial efficiency and data consistency associated with these same standards can also offer the benefits of decreased regulatory review times and shorter time-to-market.

REGULATORY PROGRESSION

Within the last 3 years, regulatory authorities around the globe have demonstrated their intent to require the use of CDISC standards in regulatory submissions.

- **European Union**
  European Medicines Agency (EMA) - a decentralized agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. Currently the European Medicines Agency Management Board on 12 June 2014 agreed the policy on publication of clinical trial data (Publication and access to clinical-trial data, EMA/240810/2013), together with more user-friendly amendments, and is currently in the process of being finalized.

  This publication states, in Section 4.2 **Data standards**, that "*For the time being, this can be according to CDISC (Clinical Data Interchange Standards 244 Consortium) or other appropriate standard. In future, CDISC shall be the required standard, in line with future guidance from the Agency*[1]."

- **Japan**
  Pharmaceuticals Medical Devices Agency (PMDA) - the Japanese regulatory agency that works together with Japan's Ministry of Health, Labor and Welfare. They conduct scientific reviews of marketing authorization application of pharmaceuticals and medical devices and monitoring of their post-marketing safety. They expect that the use of such accumulated data will reduce the workload of regulatory submission for sponsors, improve PMDA's evidence-based reviews and consultations, and lead to development of new guidelines, which will eventually result in the rise of the success rate of drug development.

Their current guidance issued on 20 June 2014, Basic Principles on Electronic Submission of Study Data for New Drug Applications, states, in Section 3. **Electronic data and its method of submission**, sub-section 2) **Format of electronic data required for submission**, that "*Individual study data should be prepared using the Study Data Tabulation Model (SDTM) and be submitted along with the definition file for variables (e.g. Define.XML). For analysis datasets, the dataset based on the Analysis Data Model (ADaM) should be submitted along with its definition file (e.g. Define.XML) and the program for creating the ADaM dataset*[2]." The timeframe for implementation of this regulation is such that it "will be a requirement for those products that are submitted for application from fiscal year 2016, starting from a date that will be notified later."

- **USA**

  Food and Drug Administration (FDA) - the regulatory agency within the US Department of Health and Human Services that is responsible for protecting the public health by assuring that drugs, vaccines and other biological products and medical devices intended for human use are safe and effective, while also advancing the public health by helping to speed product innovations. They have been working in tandem with the CDISC organization for nearly 15 years to develop clinical data standards that allow for flexibility in scientific content and are easily interpreted, understood, and navigated by regulatory reviewers, thus facilitating a decrease in regulatory review time.

  The most recent draft guidances issued in February 2014 that will specify the requirements for electronic submissions consist of:

  - Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act[3]
  - Providing Regulatory Submissions in Electronic Format — Standardized Study Data[4]
  - Study Data Technical Conformance Guide[5]

  These publications indicate the most forceful regulatory language to date about the use of standards in regulatory submissions to the FDA.

  > "*Currently, the Agency can process, review, and archive electronic submissions of study data that use the standards, formats, and terminologies specified in the Data Standards Catalog posted to the FDA's Study Data Standards Resources Web page and incorporated by reference into this document. The Data Standards Catalog provides a listing of supported and/or required standards, their uses, the date FDA will begin (or has begun) to support a particular standard, and the date support ends (or will end), the date the requirement to use a particular standard will begin (or has begun) and the date such requirement ends (or will end), as well as other pertinent information. The Agency may refuse to file an electronic submission unless its study data conforms to the required standards, formats, and terminologies specified in the Data Standards Catalog*[4]."

  The Data Standards Catalog explicitly "*contains a listing of the data standards supported by FDA*[6]" for electronic submissions. Currently the only standards listed for clinical & non-clinical study datasets are CDISC. The Study Data Technical Conformance Guide describes the use of SDTM and ADaM and "*provides specifications, recommendations, and general considerations on how to submit standardized study data using FDA-supported data standards located in the Data Standards Catalog*[5]." When these documents are finalized (anticipated by the end of 2014), they will together serve as the requirements for electronic data submissions. The timeframe for implementation of this regulation is that it will be "*required no earlier than 24 months after a final guidance is issued*[3]."

EMERGENCE OF THERAPEUTIC AREA (TA) STANDARDS

CDISC has also been part of an ambitious initiative for the expedited development of TA standards. The Coalition For Accelerating Standards and Therapies (CFAST) was formed in 2012 as a partnership between CDISC and the Critical Path Institute (C-Path) to accelerate clinical research and medical product development by creating and maintaining data standards, tools and methods for conducting research in therapeutic areas that are important to public health. As of May 2014 CFAST's most recent pipeline is very close to the publication of new therapeutic area standards projects in Diabetes, CV Endpoints, and QT Studies, with additional areas in Hepatitis C, Schizophrenia, and Influenza among those anticipated within the next 9 months.

CDISC SHARE

As the industry moves further in the direction of being standards-based and metadata-driven, the CDISC SHARE initiative has recently delivered a metadata repository (MDR) from which CDISC will manage and distribute the standards metadata that it maintains ownership of, including standards that are being (and will be) developed.

- iSHARE - the interactive tool used by the CDISC standards development community for developing, governing, and publishing the standards. It is the source for content that is available for export in eSHARE.

- eSHARE - the eSHARE website serves subscribers that implement the CDISC standards, containing exports in multiple formats (e.g. ODM, Define-XML, CSV) as well as multiple versions of the standards. The eSHARE exports reflect the standards content being governed in iSHARE.

Although currently the standards metadata from SHARE is available only as downloadable exports (e.g.: XML, XLS, etc.), the intent in the future is to develop more direct interfaces between SHARE and the sponsors' own MDR that would ensure a more seamless and automated process for distributing each update of the standards metadata out to the industry.

PROCESS: BURDEN VS EFFICIENCY

While clinical processes are necessary to approve requests, maintain standards, and utilize standards, they can also be considered burdensome and frustrating for the clinical resources that work within them. Paying attention to this frustration when developing and implementing these standards governance processes can help mitigate potential obstacles down the road. In particular, focusing on timely turnaround for new requests and quick, reproducible application of standards in trial execution will breed a significant measure of trust by the clinical organization regarding the use of standards.

A clinical trial can simply be boiled down to the practice of taking a clinical hypothesis from theory to result. However, it is a complex undertaking that requires a mixture of standardization and innovation to effectively and efficiently produce those results. The standardization yields efficiency (and thus cost reduction), while the innovation yields effective and precise results (and thus regulatory approvals). Balancing these 2 components in a sponsor's clinical processes is critical if they are to deliver successful submissions that are regulatory-compliant and also obtain faster time-to-market for their products.

The following 2 case studies help to illustrate positive and negative outcomes from different standards governance approaches to process:

Background:	**Case Study 1**
• Tier 1 company	
• Total of 16 FTE in standards governance (mixture of full-time and part-time)	
• In the midst of integrating 2 very different legacy corporate cultures	
Standards Governance:	
• New standards development processes were not correctly sequenced among existing trial execution processes	
• Development of standards was singularly tied to FPI date	
• Use of unstable draft protocol as origin of standards requests	
• Partially developed standards were released for use (and considered "at risk")	

Background:	**Case Study 2**
• Tier 1 company	
• Total of 10 FTE in standards governance (mixture of full-time and part-time)	
• Needed to standardize in order to gain efficiencies from outsourcing partners	
Standards Governance:	
• Standard, accessible electronic request structure that effectively logged and tracked the requests and the decisions-making	
• Governance processes conducted within MDR as workflows that provided system-based structure, controlled activities, and tracking for the user	
• Protocol must be finalized before standards development efforts begin	
• Standards development independent of the study timelines that generated the request (escalation process existed)	
• Transparent prioritization of requests based on company-wide designation of "top-priority" compounds	

LEVERAGING METADATA

With the rise of CDISC standards and the CDISC SHARE metadata repository, the opportunities for implementing standards-based, metadata-driven processing are increasing too. Standards metadata, be it from SDTM, ADaM, or sponsor-specific sources, can serve as the consistent consumable for processes that are part of the clinical data lifecycle, with the goal being more efficient mechanisms to produce regulatory compliant deliverables. The often overlooked factor in leveraging metadata in this fashion is that the benefits are highly dependent on this metadata being centrally and effectively managed before distribution across the lifecycle.

Most sponsors are now generating metadata as part of their clinical trial processes, often with the goal of facilitating consistency and (in a few cases) automation. The primary metadata problem currently seen across the industry is the use of what is sometimes referred to as a "First Generation MDR", where the metadata within a single sponsor is stored in separate locations and in a variety of metadata structures, all within ungoverned spreadsheets. Sponsors have found it difficult to leverage this metadata for multiple processes, to rely on the correctness of the metadata, and to sync it with the standards metadata delivered by CDISC.

A "Next Generation MDR" that centrally manages and governs the metadata within an interactive tool and a stable metadata model delivers metadata that can be reliably consumed by clinical processes and systems. The centralized governance facilitated by this level of MDR yields adherence to standards across the organization, and thus consistent data meaning and easier integration of data for analysis and submission purposes. If the MDR also incorporates governance workflows within the tool itself, it can also bring about shorter, more transparent standards development timeframes that beget increasing trust in the standards governance effort across the clinical groups.

The following 2 case studies help to illustrate positive and negative outcomes from different standards governance approaches to metadata management:

Background:	**Case Study 3**
• Tier 1 company	
• Total of 8 FTE in standards governance (mixture of full-time and part-time)	
• Hurried, beleaguered initiative to generate metadata for use in a forthcoming MDR	
Standards Governance:	
• Informal collection of cross-functional experts improperly tasked with approving standards requests (no credible leader)	
• Inordinate percentage of request approval time spent debating eCRF format in standards governance	
• Singular assemblage of metadata in massive spreadsheet that spanned collection, analysis, and submission data	
• Compilation of metadata was difficult to acquire across multiple groups with conflicting priorities and agendas	

Background:	**Case Study 4**
• Tier 2 company	
• Total of 4 FTE in standards governance (all part-time)	
• Adopted CDASH and SDTM to standardize to effectively address regulatory questions	
• Wanted to generate metadata for use in a new MDR	
Standards Governance:	
• Broad cross-functional input into implementation of CDASH & SDTM, despite little standards governance	
• Driver for the initiative was to ensure maximum utilization of the investment in MDR	
• Leverage standard SDTM mappings within MDR to execute transformations	

from collection to SDTM
• Leverage standard macros within MDR to execute analysis programs

THE MERGER OF COMPLIANCE AND MESSAGING

The standards themselves are vital, reusable pieces that decrease run-times for clinical trials. As customization of these pieces increases, the study execution time increases, the consumption of resources increases, and the consistency of the data from study to study is decreased. Astute messaging around reasonable compliance targets inspires trust in standards governance, especially when a sponsor's standards governance is early on the learning curve. It can yield a favorable mindset of "pulling down" the standards rather than having the standards be "pushed down" onto study teams from above.

There is no substitute for an effective high-level directive delivered by a respected member of senior management that clearly states the requirement to use the standards across the organization. This directive can then be used by the standards governance as an authorization to "spend" effort and resources to ensure compliance to the standards and delivery of consistent data for purposes of analysis and submission.

Not every sponsor is fortunate to have that high-level directive. Many clinical organizations are faced with producing regulatory-compliant submissions with our senior leadership guidance, facing shrinking timelines, an array of data structures, and a diverse set of data meanings. Standards governance groups within these organizations face uphill battles everyday with sectors of the organization that have different views on standardization and compliance. They attempt to utilize a mixture of process control and skillful messaging to encourage clinical teams to raise the percentage of standards they use in their everyday work routine, thereby freeing up more time to spend on the truly innovative aspects of their job.

The following 2 case studies help to illustrate positive and negative outcomes from different standards governance approaches to compliance and messaging:

Background:	**Case Study 5**
• Tier 1 company	
• Total of 3 FTE in standards governance (all part-time)	
• Multiple business units, autonomous in both trial execution and budget	
Standards Governance:	
• Few small pockets of standards governance in CRF Design attempting to introduce consistency and CDISC concepts	
• No high-level messaging on benefits or usage of standards	
• Difficult for Drug Safety group to efficiently manage safety data from multiple clinical sources	
• Currently at risk if regulatory authorities ask for SDTM or ADaM in submissions	

Background:	**Case Study 6**
• Tier 1 company	
• Total of 12 FTE in standards governance (mixture of full-time and part-time)	
• Needed to standardize in order to gain efficiencies from outsourced partners	
Standards Governance:	
• Highly visible VP issued messaging on requiring the usage of standards	
• Initial standards governance was for standard collection modules only	
• Expansion of standards governance downstream via the use of analysis specs up-front when collection modules are approved	
• Compliance of collection modules achieved through a pro-active, library-based process for eCRF and database build	

CONCLUSION

There is no magic path of standards governance that every sponsor should follow. The various factors for each sponsor that affect standards oversight (such as size, tools, processes, and CDISC expertise) produce unique situations that require unique solutions. But after a comprehensive evaluation of these factors, an appropriate foundation of standards governance can exist through the skillful use of process, metadata, and messaging. Conversely, standards without standards governance are akin to having no standards at all, because their use by clinical operations becomes irregular, non-compliant, and eventually non-existent.

REFERENCES

[1] Publication and access to clinical-trial data, EMA/240810/2013

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[3] Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) (February 2014)

[4] Providing Regulatory Submissions in Electronic Format — Standardized Study Data, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) (February 2014)

[5] STUDY DATA TECHNICAL CONFORMANCE GUIDE, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) (February 2014)

[6] FDA Data Standards Catalog (v3.0 20140117), available as a download from the Study Data Standards Resources webpage at http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

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