

Genzyme's GetSMART Program: Implementing Standards End-to-End

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Genzyme, a Sanofi company, is dedicated to making a major positive impact on the lives of people with serious diseases. Since 1981, the company has grown from a small start-up to a diversified enterprise with many established products and services serving patients in more than 100 countries. A center of excellence in rare disease, Genzyme has a record of innovation and a unique and pioneering approach to developing breakthrough treatments by applying the most advanced technologies in the life sciences. Genzyme is also leading the way in building a sustainable future through the appropriate application of standards and enabling technology to clinical development and beyond.

Genzyme has an entrepreneurial culture which thrives on empowering individual teams to be innovative and results oriented. A major aspect of Genzyme's historical growth has been achieved through mergers and acquisitions. Such factors have significantly contributed to making Genzyme successful. However, those same factors have created opportunities for improved operational efficiencies, increased data quality and more efficient and cost effective practices for complying with regulatory guidance and requests regarding Genzyme's clinical information. The following outlines Genzyme's vision, business justification, work performed to date and future direction for implementing clinical data standards while preserving Genzyme's unique capabilities, talent and culture.

The "GetSMART" Vision

At the end of 2008 Genzyme initiated GetSMART, a Strategic, Measurable, Achievable, Realistic, and Time-based program, to implement global clinical information standards. The GetSMART vision is to consistently define, use, and reuse clinical information across the development lifecycle through the use of standards in order to facilitate the exchange of information (data and content), streamline our business processes and prepare to comply with existing regulations, current regulatory requests and likely future mandates.



Key goals of GetSMART include:

- Facilitate the exchange of information internally within Genzyme and externally with vendors, partners, providers, patients, investigators, regulators and other third parties.
 - Significantly reduce time spent by Genzyme personnel understanding, checking, reconciling and integrating data received by internal partners and external vendors.
- Streamline business processes associated with the definition, collection, integration, analysis, reporting and use of clinical information.
 - Use and reuse of content. Define once; use many times, in many ways.
 - Technology-enable Genzyme's business processes. Once information is defined and applied consistently, technologies can enable successful use, exchange and governance of information.
- Improve operational oversight.
 - Make interactions/decisions regarding Genzyme's clinical information easier/faster.
 - Apply flexible resourcing models; reduce resource spending; cycle times and iterations.
- Prepare to fulfill current regulatory guidelines and requests and likely future mandates.
 - Have a streamlined, non-bureaucratic and technology-enabled governance process
 - Have a systematic and well planned change management approach to be prepared for likely future mandates.

Achieving the GetSMART Vision

The GetSMART initiative is comprised of the following five (5) workstreams: Structured Content Management, Data Collection and Processing, Analysis and Reporting, Core Infrastructure and Standards Governance. The first three Workstreams mirror stages in the clinical data lifecycle. The fourth and fifth streams are fundamental in enabling and supporting standards implementation throughout the product lifecycle. Embedded in all workstreams, and therefore not called out as a separate workstream, is complying with existing regulations, on-going monitoring of external data standards activities and preparing to comply with anticipated standards-related regulations.

1. The Structured Content Management (SCM) Workstream:

Consistently define, use and reuse our clinical information (including both content and data) within and across clinical programs and in downstream processes. A key workstream activity is implementing topic-based structured content management which includes new business processes and technological capabilities.

Business Justification:

Without structuring the content and defining how and where the content is used, there is limited automated (re)use of protocol information. Genzyme believes the business value for topic-based structured content comes from reusing information across the clinical data lifecycle and business processes; therefore, across multiple types of documents and systems. We expect to realize the following benefits from implementing topic-based structured content:

- **Ensure Quality and Standards:** Improve the overall quality and consistency across documents by presenting the “right” information in the “right” location. It enforces standard text and

vocabulary that's harmonized with data standards, SOPs and "built-in" best practices thereby ensuring "Quality by Design".

- **Enhance Transparency:** By understanding where and when the content has been used, one can assess the downstream impact of content changes on other business processes and documents.
- **Reduce Re-writing and Review Time:** Reuse of approved quality content (e.g., text, data and figures) allows authors and reviewers to focus on new content.
- **Improved Search Capabilities:** Robust metadata on topics enables effective search by subject matter extending far beyond traditional "keyword searches".
- **Enable Service Providers and Collaboration with Business Partners:** Assign parallel writing tasks at the topic level to external partners. Business partners get the right information to support their work up front, reducing the number of questions and time spent searching for documents.

2. The Data Collection and Processing Workstream:

Automate the use and reuse of Case Report Form (CRF) standards in upstream and downstream processes. Workstream projects include defining and implementing CRF standards and associated edit checks based on industry standards (CDISC CDASH) as well as Genzyme-specific Therapeutic Area standards, where industry standards do not yet exist. Definition of a Genzyme-specific central lab standard (CDISC LAB) is included in this workstream. This workstream also has accountability for producing a Genzyme electronic library of standard case report form information harmonized with Genzyme-defined standards in addition to data transfer specifications for central lab data.

Business Justification:

There is significant opportunity to streamline CRF and database development, to enable data processing efficiencies and facilitate data exchange through the use of clinical data standards. Standards help improve the communication and coordination of activities between Genzyme and our vendors/partners (ex. CROs, Central Labs, EDC vendors).

3. The Analysis and Reporting Workstream:

Define and implement Genzyme's Analysis, Reporting and Submission Data Standards (CDISC SDTM, ADaM and define.xml). Workstream project activities include implementing tools and processes to automate the production of datasets and Tables Listings and Figures (TLFs) via the use of metadata.

Business Justification:

Analysis, reporting and submission data standards help ensure that deliverables produced internally or externally can be efficiently and accurately generated, combined, analyzed, and submitted. Submitting compliant datasets helps streamline FDA Reviewer's assessment of Genzyme submissions.

4. The Core Infrastructure and Architecture Workstream:

Facilitate the exchange of information and enable the automation and streamlining of business processes related to clinical information. Workstream activities include defining and implementing a semantically-aware service oriented architecture based on the HL7/CDISC BRIDG Information Model and simplifying technology and data integration. A critical workstream project is the implementation of a metadata repository. Genzyme evaluated and recently selected a commercial metadata management tool and is currently working with the vendor to further refine its design before moving into implementation later this year. Implementing Structured Content Management capabilities (mentioned above) and data validation tools are additional examples of core infrastructure activities.

Business Justification:

A central architectural vision provides IT governance direction for assessing the technology and infrastructure project portfolio. Leveraging industry standard tools allows Genzyme to focus resources on streamlining the unique data collection and processing activities that support Genzyme's core competency: the development of products on the cutting edge of translational medicine. For example, Genzyme will improve the quality of our data and efficiency of our data verification processes by implementing data validation tools based on industry standards to data across the lifecycle (from collection to submission). Validation tools streamline checking of data and information provided from internal and external partners to ensure the information adheres to the Genzyme-defined standards. A metadata repository (MDR) provides essential foundational capabilities for achieving Genzyme's vision of a metadata-driven clinical data lifecycle; it is a key component to obtaining return on investment from Genzyme's standards implementation. A MDR facilitates the definition, use, maintenance and governance of Genzyme's clinical information standards. It facilitates the sharing of information about the data as it moves through its lifecycle, thereby enabling consistency, accountability and true control of data. The MDR provides an automated way to manage and govern millions of data elements across therapeutic areas, products, studies and functions. Also, the metadata repository along with a common, standards based information model (BRIDG) provides a core piece of the semantic Infrastructure for other Genzyme applications.

5. The Standards Governance Workstream:

Define the Standards Governance Organizational Framework and supporting processes. Workstream activities include defining governance processes, roles and responsibilities and technical framework that control the availability, usability, integrity and security of Genzyme's clinical data and metadata.

Business Justification:

Standards governance processes and supporting technology help ensure that standards are appropriately maintained and consistently implemented across clinical programs. The standards governance framework and processes also help ensure that Genzyme's standards implementation maintains an appropriate level of flexibility when implementing standards.

The Importance of BRIDG

Genzyme and external applications mapped to the BRIDG are able to share Information because they share a common information model as well as a consistent and predictable set of data definitions. There are also standard attributes for each class and attributes are harmonized across various use cases. Initially only being used for HL7 RCRIM/FDA/CDISC message specification, it is becoming a global public standard and is currently going through the ISO JIC (Joint Initiatives Council) process to become an ISO standard. Starting with BRIDG on projects like *RegistryNXT!* helped speed development as we weren't starting with a blank slate. It also created a sturdy foundation upon which to implement applications. There are still some challenges with the BRIDG model (for example, it does not include Therapeutic Area standards today); however, in Genzyme's experience, the benefits outweigh the limitations.

Progress to Date

Since kicking off standards workstream activities in Q1 2009 Genzyme has reached many major milestones. To date we have achieved the following in each of the workstreams:

- **The Structured Content Management (SCM) Workstream:**
 - Defined and implemented a Global Protocol Template and authoring guidance.
 - Mapped the Genzyme Protocol Template to the BRIDG Protocol Representation sub-domain model and clinical trial registration transparency needs.
 - Initiated a topic-based structured protocol authoring proof-of-concept pilot and defined:
 - An initial content architecture leveraging the BRIDG Protocol Representation sub-domain model and extensions to the model to support topic-based structured content.
 - Design patterns which maintain the key business relationships between topics.
 - An initial version of a Structured Protocol Template.
- **The Data Collection and Processing Workstream:**
 - Defined and globally implemented the following Genzyme-defined standards based on CDISC:
 - Standard Safety Case Report Forms (CRFs) based on the CDISC CDASH model (v1.0)
 - Central lab standards based on the CDISC Lab model (v1.0)
 - Began work on the development of therapeutic area CRFs, starting with Lysosomal Storage Disorders
- **The Analysis and Reporting Workstream:**
 - Defined and globally implemented the following Genzyme-defined standards based on CDISC:
 - SDTM implementation guide based on the CDISC SDTM IG (v3.1.1 and v3.1.2)
 - Developed an initial toolset for utilizing standards metadata in selected downstream processes.
 - Kicked off a project to define and implement Genzyme-specific ADaM standards based on CDISC ADaM model v2.1 and ADaM IG v1.0. The project includes development of a Genzyme-specific implementation guide and a strategy for deriving Genzyme ADaM datasets based on both CDISC ADaM standards and Genzyme's business need. Additionally, ADaM related processes will be formalized, standardized and added to existing SDTM processes in Genzyme's SCE environment.

- **The Standards Governance Workstream:**
 - Defined and implemented a global, cross-functional Standards Governance Organizational Framework and supporting processes that has become part of the way Genzyme's clinical development operations do business.
 - Implemented a collaboration portal pilot to support and automate the standards governance workflow and processes.
- **The Core Infrastructure and Architecture Workstream:**
 - Development of *RegistryNXT!*, a new standards-based patient registry platform, that contains both observational and clinical trial data for rare inherited metabolic disorders that result from defects in lysosomal function. The underlying technology architecture is based on the CDISC/HL7/NCI/FDA BRIDG information model such that each registry is able to function on a common metadata-driven framework, while allowing each registry to select components most appropriate to their scientific and lifecycle goals. *RegistryNXT!* enables the real-time reporting of disease registry data for physicians and care teams. The first release of *RegistryNXT!* went into production in April, 2011 for Gaucher disease.
 - Development of requirements, evaluation and selection of a vendor for a pilot implementation of a Metadata Repository, a core part of the semantic infrastructure to foster interoperability.

Realizing the Benefits of upstream CDISC Standardization

The maturity of our CDASH and SDTM standard implementation is already providing measureable downstream benefits for products that have utilized Genzyme defined standard CDASH CRFs and SDTM implementations.

- Incorporating SDTM into our case report forms minimizes the transformation required to produce SDTMs and allows for standard routines to perform the transformations. The streamlined processes have reduced the overall cost and time to perform these tasks.
- The time and cost to produce ADaM datasets based on standard data collection (CDASH) and SDTMs is reduced because analysis code can more easily be re-used across products. We hope to increase these efficiencies once we have developed Genzyme ADaM standards based on the CDISC ADaM model.
- As external resources and CROs have become more proficient in CDISC standards, the startup time and cost associated to learn and effectively implement standards has been reduced. As an example, consultant resources have been able to immediately lead product activities that included mapping of raw data because of their familiarity with the CDISC standard and the availability of documentation of Genzyme's SDTM implementation guidelines.

Extending Standards to Improve Connection with Patients and Providers

Because Genzyme's rare disease registry platform (*RegistryNXT!*) conforms to internationally-recognized health care standards, it makes possible the ability to collect uniform clinical and other data to evaluate outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical or policy purposes. It also provides the

future ability of facilitating collection, sharing and use of information in Electronic Health Records (EHRs). To the extent that EHRs capture data elements and outcomes with specific, consistent, and interoperable definitions — or to the extent that data can be found and transformed by other processes and technologies into standardized formats that match registry specifications, they avoid duplication of effort by participating clinicians and patients. On the other side, SDTM-based extracts can, in the future, be used for further analysis and reporting to meet Genzyme's commercial and regulatory requirements.

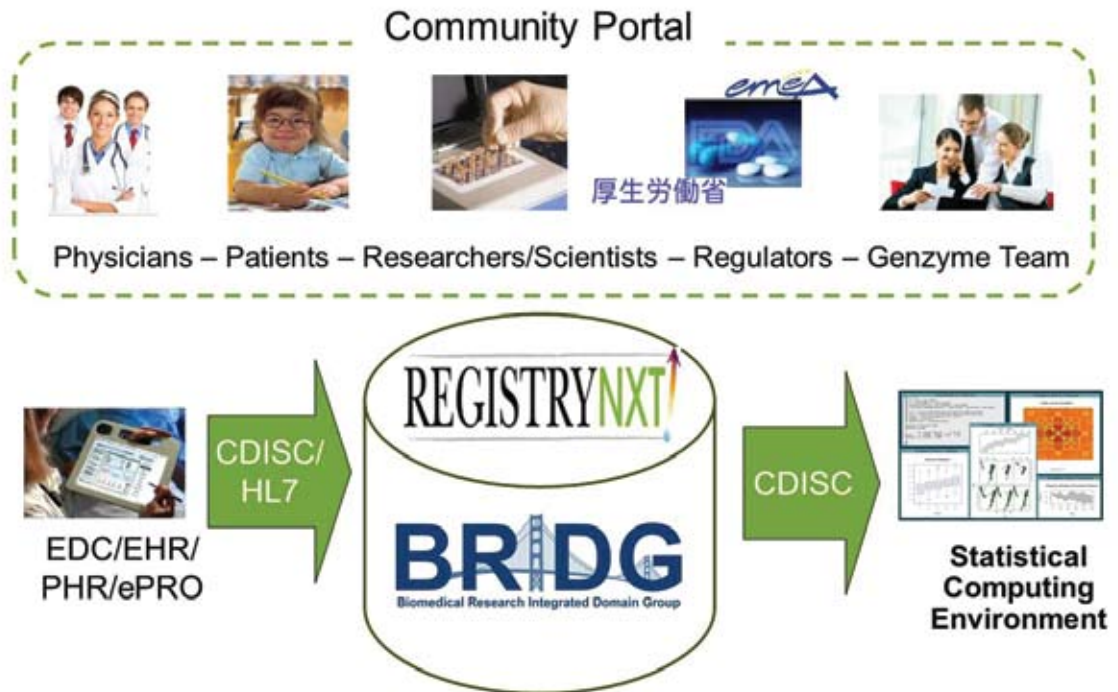


Figure 1: RegistryNXT! Extending Standards to Improve Connections with Patients and Providers

Maturing Genzyme's Standards Implementation

Genzyme is continuing to mature our standards implementation. On-going activities can be classified into 3 categories: Standards Development, Standards Governance and Technology-enabling our Standard Implementation.

- **Standards Development**

- Define new Genzyme-specific Therapeutic Area CRF standards
- Define Genzyme-specific ADaM implementation guidelines
- Maintain and evolve existing Genzyme defined standards

- **Standards Governance**

- Continue to gain experience governing newly defined standards; evolve our governance processes as people's knowledge of standards expands and participation in the governance organization increases.

- **Technology-enabling our Standards Implementation**

- **Metadata Repository:** Complete the pilot and implement release 1 of our Metadata Repository into production. Release 1 will include clinical and operational metadata for safety data from protocol development through the creation of SDTM datasets and the Define.xml. A governance workflow is being configured to manage the metadata elements which will be harmonized and mapped to Genzyme and external standards.
- **Structured Authoring Proof-of-Concept Pilot:** We have started our SCM activities with the protocol because it is the central document in a clinical trial used by cross functional stakeholders; the protocol is also the foundation for many other documents (e.g., ICF, IB, SAP, CSR) and information in other systems (e.g., CTMS, CDMS, CTT). This pilot will enable us to define protocol content in reusable topics and topics maps, increase Genzyme's knowledge of and familiarity with SCM applications, and recognize the business process changes needed to implement SCM (writing, publishing, reviewing, and approving topics and documents). We also plan to move towards a production implementation of selected SCM components using an iterative, risk-based approach for implementation.
- **Data Validation Tool Customization:** A vendor has been selected to automate Genzyme's data validation processes and define Genzyme-specific data validations to check CRF, Lab, SDTM and ADaM data against CDISC and Genzyme specifications to ensure compliant and quality data are produced, received and submitted. This project is scheduled to begin in Q3 2011 and will continue into 2012.
- **Continue to extend standards for supporting personalized medicine and translational research:** The promise of personalized medicine and the development of individualized, targeted disease prevention and care tailored to a specific patient can only be realized by coordinating and sharing diverse data from multiple disciplines, institutions, and sectors across the bench-to-bedside continuum. This requires and demands an information architecture and model that is end-to-end and based on standards. Data and information from diverse sources will need to be readily shared and analyzed across the entire health care and research ecosystem in order to be understood and treated from a multidimensional point of view. This comprehensive, interdisciplinary view should facilitate collaboration and cross-fertilization of ideas and allow practitioners, researchers, and industry to rapidly capitalize on the insights of others and accelerate the ability to diagnose, prevent, and develop treatments for multiple diseases in a targeted and personalized way. In the near to mid-term, this means continuing Genzyme's RegistryNXT! development, extending the platform to support other rare Lysosomal Storage Disorders (LSDs) including Fabry, Pompe and MPSI disease and to improve the quality of care for LSD patients worldwide through active publication of Registry findings and disease management approaches.

Summary

The past few years have been an exciting period for Genzyme and the GetSMART program! Genzyme-specific clinical information standards have been released globally and key, initial technology components supporting the use and governance of standards have been implemented. Genzyme is maturing its standards adoption by transitioning from implementing “best practices” into a period of governing and maintaining its standards. Benefits of GetSMART are starting to be realized as more clinical programs implement the standards but are expected to show even greater benefit in the coming years as programs advance through the clinical lifecycle and we can see the true end-to-end streamlining of business processes. Genzyme anticipates realizing significant operational benefits as we complete some of the programs to technology enable our processes.

Acknowledgments

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