NNIT WHITE PAPER

Authorities' expectations for digital data submission in the pharma lifecycle

With a focus on CDISC data standards

Content

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Introduction

Drug development has undergone rapid globalization over the past decades1, which has beckoned for harmonized approaches across health authorities, internationally.

Furthermore, the efficient execution of clinical trials is reportedly constrained by the absence of global data standards and formats, which is contended to cost the pharmaceutical industry in excess of US$156 million annually[2].

Study data standards entail having a common, uniform framework for the exchange clinical and non-clinical study data between computer systems, which ensures a coherent system for handling study data[3]. Therefore, instituting these data standards not only amplify the effectiveness and efficiency with which health authorities manage submissions from clinical and non-clinical studies but also increases a reviewer's ability to fully assess the data on realms of efficacy and functional safety of a product[4].

Moreover, the utility of the data is expanded since the health authorities eventually leverage harmonized study data from various studies for their use in different researches and investigations3. Submission dossiers to health authorities are expected to adhere to submission requirements set by the health authorities.

The United States and Japanese health authorities, FDA and PMDA, respectively, have published guidance documents that require electronic submissions from clinical and nonclinical studies be submitted in line with CDISC data standards[23 24].

In the United States, the FDA released the final guidance in December 2014 that expects all studies commencing after 17th December 2016 onwards submit electronic study data to the FDA in CDISC format. On the other hand, Japan's PMDA started accepting electronic study data submissions in CDISC format, beginning October 2016 with a three and a half years transitional period[5].

Standards for Digital Study Data Submission

Digital Study Data Submission:
Advancements in global drug development have paved the way for more harmonized approaches among health authorities including the acceptance of digital or electronic study data submissions in a standardized format. CDISC data standards are extensively used as the preferred standard for submission of electronic data. The US FDA and Japan PMDA already expect that submission dossiers comply with CDISC data standards [23 24].

CDISC Data Standards:
CDISC is a global non-profit organisation that has developed platform-independent data standards to aid in the collection, exchange, submission, analysis and archival of electronic data. Hence, fostering efficient and swift review of data by health authorities. This translates into quicker approval and less waiting to get drugs to market.

Submission of standardized electronic study data to PMDA will be mandatory effective on 01st April 20205. In the EU, it is not yet mandatory to submit electronic study data to the EMA in a standardized format.

However, EMA has endorsed standardizing electronic study data in CDISC format. Nevertheless, due to data related issues such as data integration and interoperability, as well as the need to actively monitor data quality[4], it is foreseeable that EMA will in the imminent future, require that all electronic study data submitted to the agency conform with CDISC data standards.

Consequently, for regulatory compliance purposes, regulated companies involved in any electronic data submission to health authorities need to be aware of the best industry practice embodied in CDISC.

Background

All computerised systems used to execute any GxP related activities, particularly described in the FDA 21 CFR Part 11 and the EU Annex 11 are subject to regulatory inspection. Hence, the need to validate such computerised system is indispensable in demonstrating compliance with all applicable regulations. Moreover, validation also improve the quality and value of a computerised system by ascertaining its fit-for-purpose.

Already there are several customizable software available to CDISC implementer for checking and ensuring CDISC data standards compliance. These software systems are critical in the conversion or mapping of data into the respective CDISC data formats. Consequently, proper validation of these systems becomes essential since the success of CDISC compliant submissions significantly hinges on the fitness of the system in use.

HGP[22] is a business consultancy specializing in life sciences with well-seasoned and experienced CSV experts keen on regulatory compliance, who CDISC implementers can leverage to assess the quality, accuracy, reliability and performance of CDISC validation tools during the CSV process.

Objective

The main purpose of this white paper is to provide a general overview of the CDISC data standards and their implementation and validation. Moreover, the validation of the automated CDISC data validation tools is explored in accordance with GAMP 5 guidelines.

About CDISC Data Standards

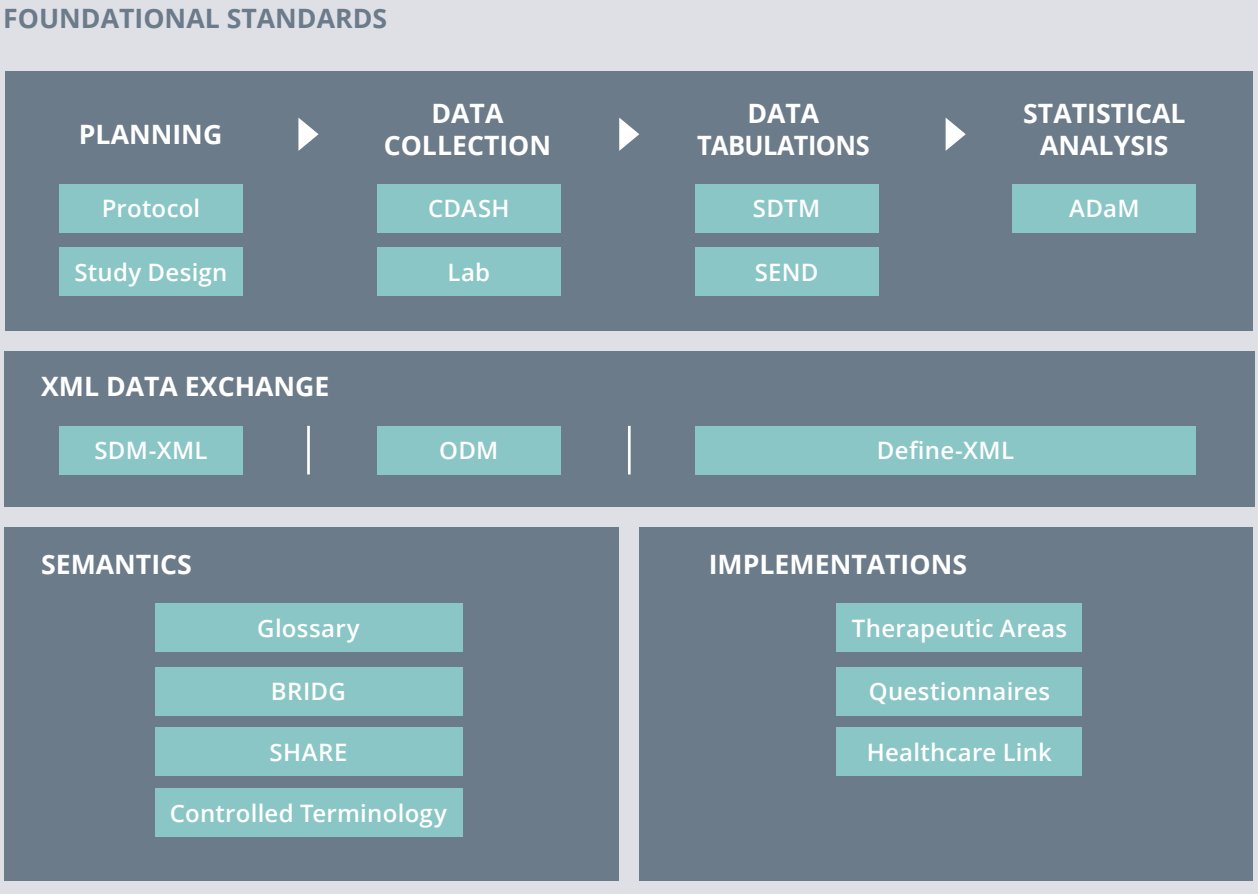
The aim of CDISC is to establish global, platform-independent data standards that enable information system interoperability to further medical research and similar healthcare areas[7].

Hence, promoting efficiency in the drug development process through improving the data flow within source, allowing data sharing and combining across different sources and stepping up data review process[7] while ensuring traceability for health authority submission[10].

Ultimately, CDISC standards aid in the acquisition, exchange, submission and archival of study data and metadata[7]. CDISC standards are available for free from the company's website and are vendor-neutral as well as platform-independent[7].

Figure 1 depicts CDISC foundational standards including all the models used to standardize data content throughout the entire clinical lifecycle, starting with planning followed by data collection then data tabulation and subsequently, statistical analysis[7].

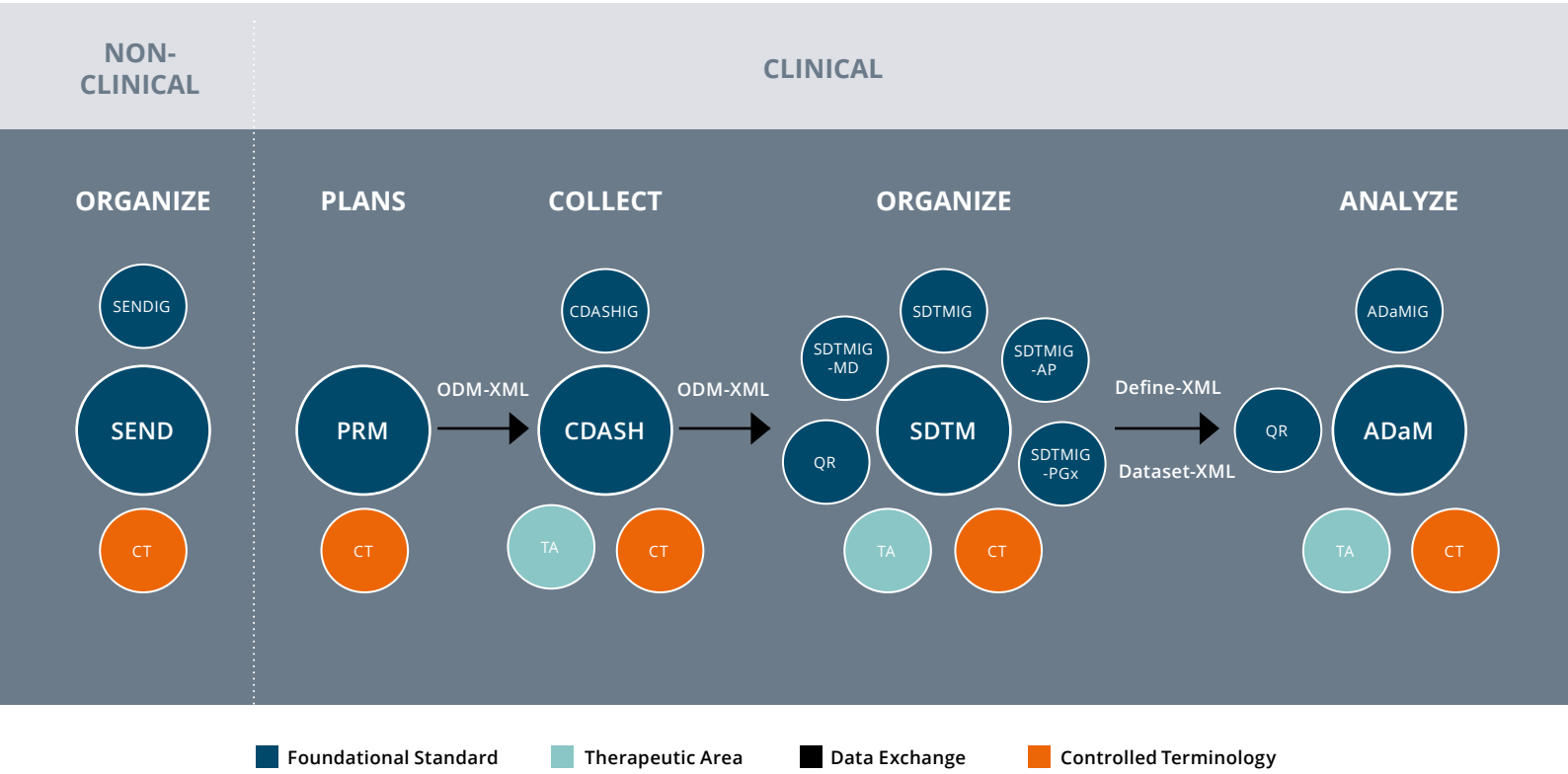
Figure 1 CDISC Foundational Standards[10]

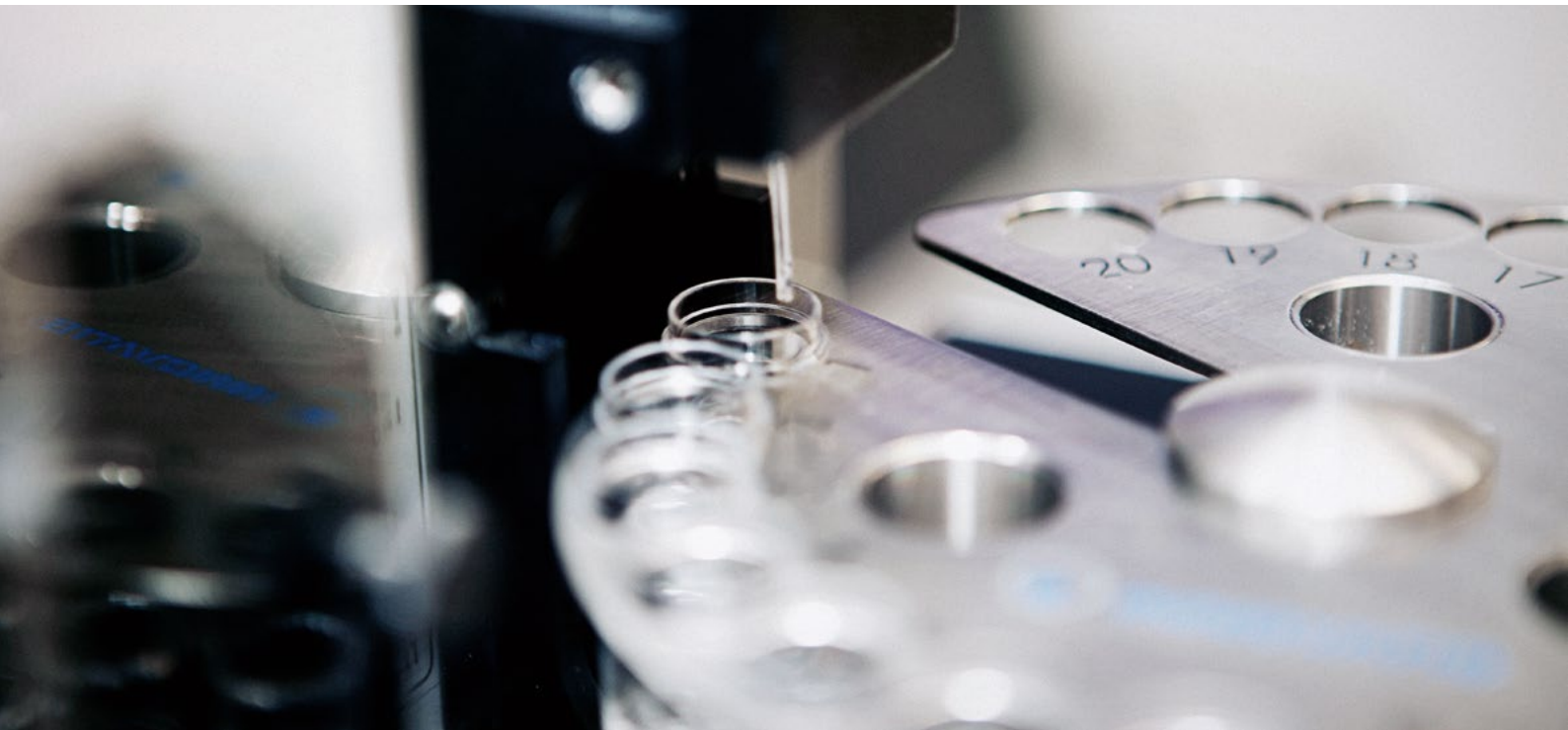


The CDISC foundational standards are the basis of the whole suite of standards that aid the clinical and non-clinical end to end research process[11].

Figure 2 provides another illustration of the CDISC Data Standards in the clinical Research processes[11]. The foundational standards gravitate towards the core principles for describing research data standards and represent the overall areas of interest that are common across all clinical research studies including demographics, medical history, concomitant medications, and adverse events among others[7].

Figure 2 CDISC data standards in the clinical research process[11]





The CDISC Standards required for submissions to health authorities with respect to the US FDA and JP PMDA are outlined in table 1.

Table 1 Required CDISC Data Standards for submissions to US FDA and JP PMDA

CDISC STANDARDS	US FDA	JP PMDA
SEND	✓	
SDTM	✓	✓
ADaM	✓	✓
Define-XML	✓	✓
Controlled Terminology	✓	✓
Therapeutic Area	✓	
ARM for Define-XML		✓

Of the above listed CDISC data standards, **SDTM** (Study Data Tabulation Model), **ADaM** (Analysis Data Model), **SEND** (Standard for Exchange of Non-clinical Data) and **Define-XML** (Extensible Markup Language) are the most commonly known, however, SDTM is the most widely used[8].

SDTM defines the standard structure in which study data tabulations are compiled while SEND specifies how to collect and represent nonclinical data in a consistent format.

ADaM defines the dataset and metadata standards that ensure that there is clear lineage from data collection to statistical analyses for clinical trial[17] and Define-XML furnishes the metadata for human and animal model datasets based on the SDTM and/or SEND standards and analysis datasets based on the ADaM[14].

SDTM has three basic structures referred to as General Observation Classes (events, interventions and findings), which are based on the type of collected data[15].

SEND is an implementation of the SDTM standard for non-clinical studies[16].

ADaM similar to SDTM, has three defined structures, namely the Subject Level Analysis Dataset (ADSL), the Basic Data Structure (BDS) and the Adverse Events Analysis Dataset (ADAE)[7]. ADaM structures are founded on SDTM data as input 7.

Define-XML is a machine-readable version of the regulatory submission.

CDISC Data Standards Implementation and Validation Tools

CDISC data standards implementation is a relatively complex and non-versatile process that can potentially present a range of challenges particularly technical and financial ones[9].

Errors during the creation and preparation of CDISC compliant data can eventually result in non-compliant submissions[9]. Therefore, several factors must be taken into consideration when developing a strategic plan for implementing CDISC data standards, for example, format and size of the collected data, data flow and available resources[9].

Furthermore, the key components of CDISC data standards, CDASH, SDTM and ADaM should also be factored in. Such an informed implementation strategy that accounts for these vital aspects, will not only promote cost effectiveness but also minimize the possibility of any unanticipated setbacks during the implementation process[9]. Overall, involvement of CDISC data standards experts might be necessary where in-house experts are lacking, especially in smaller biotech and pharmaceutical companies.

Since health authorities conduct compliance checks20 on the submitted data against the respective CDISC standards prior to the review process, CDISC data validation plays a crucial role in preparing submission-ready data. CDISC data validation entails checking whether data conforms to the applicable CDISC standards[21].

This is achieved in two kinds of validation checks that inspect the integrity and compliance of the data content and the file structures. The former requires a high level of human intervention in making sure that the collected data values are correctly transformed or transferred. But the latter lends itself well to the use of automated CDISC data validation tools.

Validation of CDISC Data Validation Tools

The most prominent CDISC data validation tools are Pinnacle 21 Enterprise and SAS Clinical Standards Toolkit which can be operated in either open or hosted environment[19]. These custom off-the-shelf products often can be used as delivered by the vendor with very limited configuration.

However, owing to the GxP relevant data handled or generated from these systems, they themselves are subject to validation to ensure fitness-for-intended-use and compliance with the related guidelines (GAMP 5, 21 CFR Part 11, EU Annex 11) governing CSV.

The following diagrams depicts the V-model approach for a GAMP 5 category 3 non-configured software and GAMP 5 category 4 configured software.

Figure 3 V-model approach for a GAMP 5 category 3 non-configured software

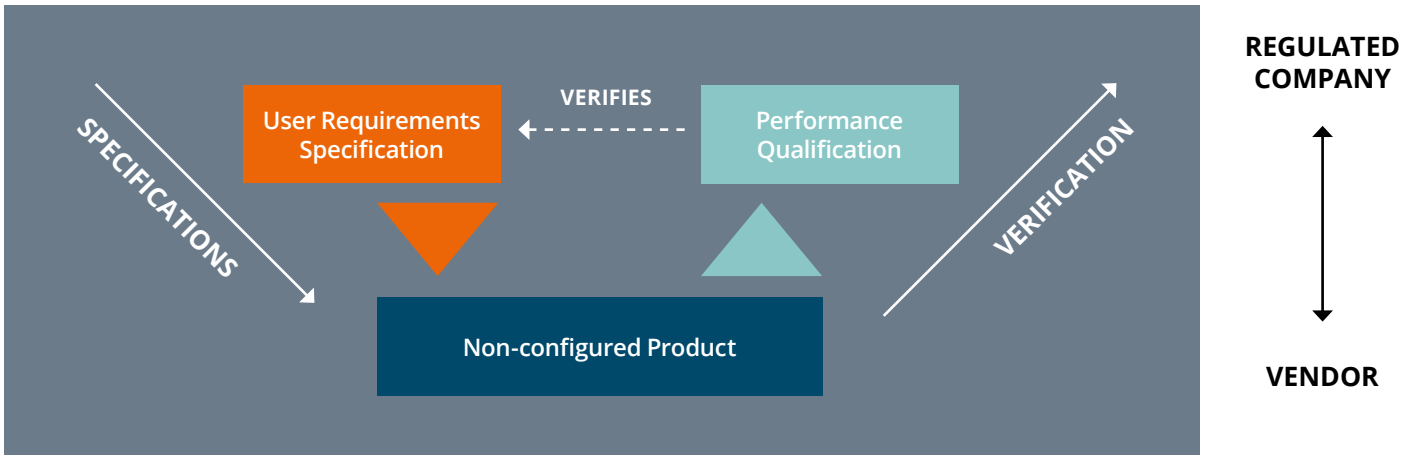
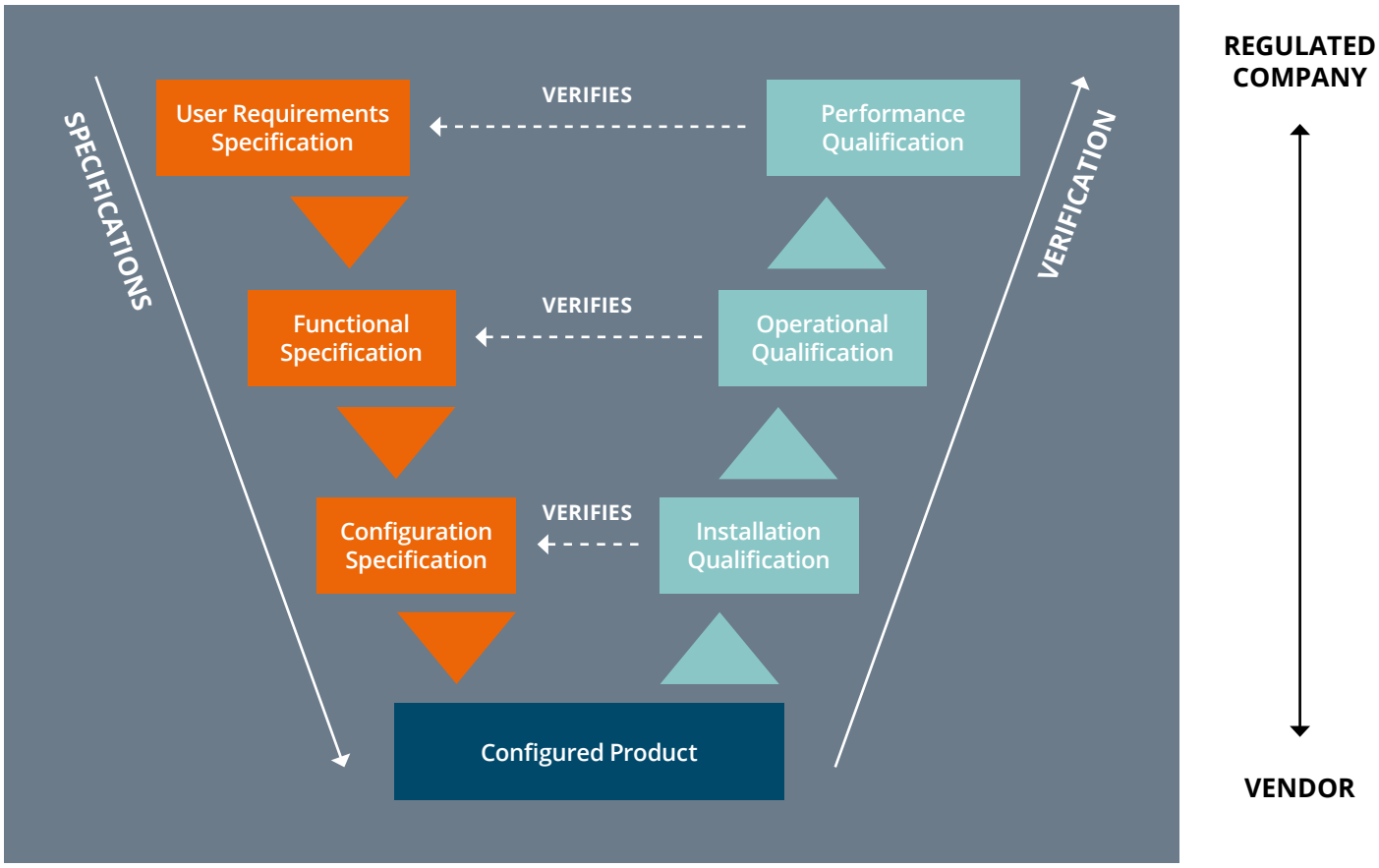


Figure 4 V-model approach for a GAMP 5 category 4 configured software



Conclusion

The establishment of study data standards not only promotes harmonization but also improves medical research across health authorities, research organizations and pharmaceutical/ biotech industry. Some health authorities such as EMA, US FDA and JP PMDA either require or endorse the submission of electronic study data that conform to CDISC standards.

CDISC data standards provide tools that support the acquisition, exchange, submission, and archiving of research medical data and metadata. Although the implementation of CDISC data standards can be resource- and cost-intensive, the long-term benefits manifested in swifter submission-ready data and regulatory reporting compliance outweigh the associated challenges.

Lastly, the validation of the CDISC validation tool plays a significant role in ensuring the tools are robust and perform as intended. Therefore, HGP[22] as a business consultancy specializing in life sciences, and having a wealth of knowledge, experience and expertise in CSV warrant strong consideration by CDISC implementers for the validation of CDISC validation tools.

Book an inspirational meeting

You are welcome to book a meeting with one of our consultants to discuss your unique position and situation. This provides the best foundation for maximizing your investment while reducing compliance and operational risk.

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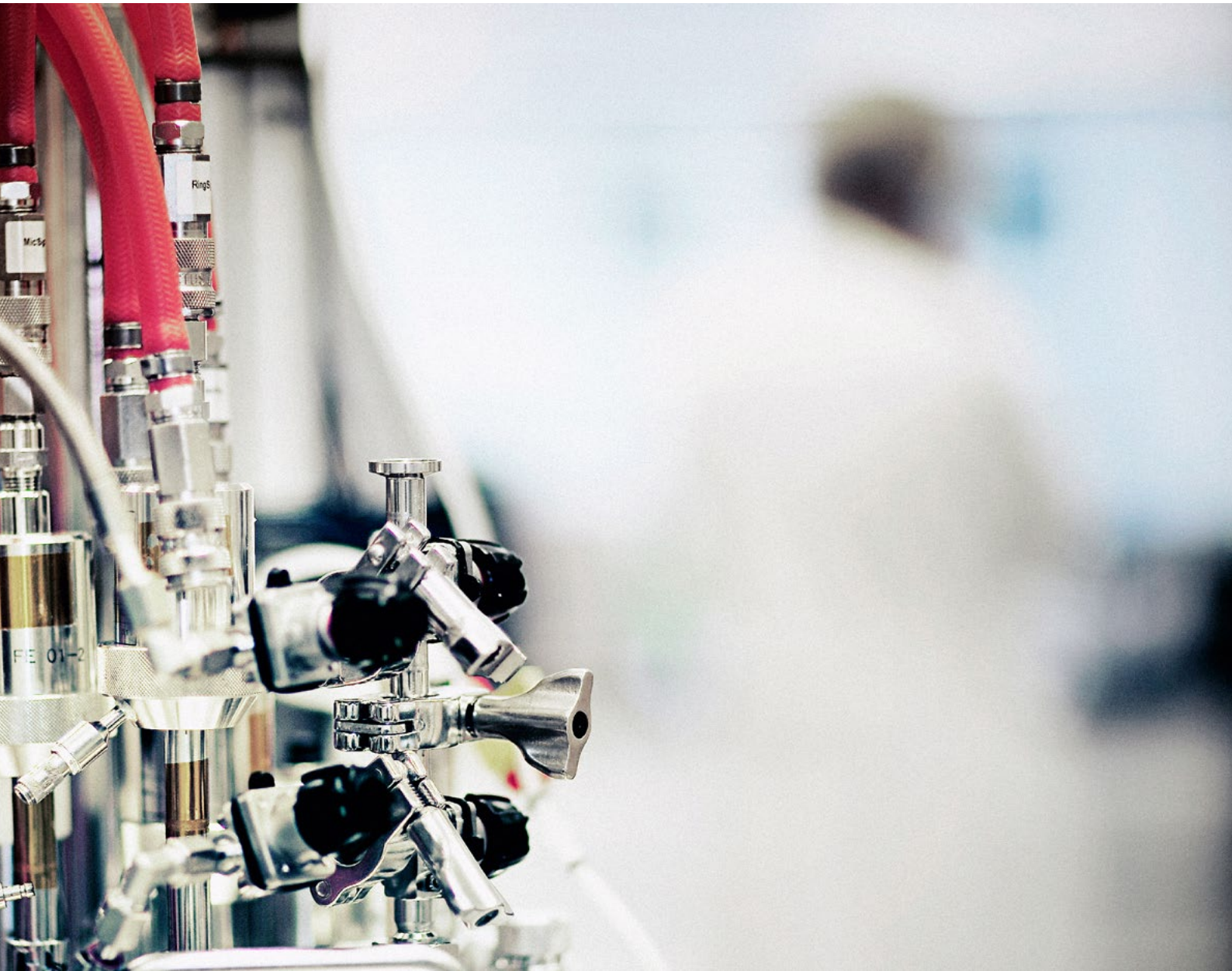

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Adhering to regulatory legislations when implementing Non-Clinical/Clinical IT systems and migrating non-clinical/ clinical data is of utmost importance. In order to stay compliant, up-to-date regulatory knowledge and experience in implementation and migration projects is key. NNIT's **GxP Compliance and Validation Advisory** is the very foundation to ensure a speedy implementation of robust IT systems that meet regulatory requirements.

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List of Abbreviations

ADAE	Adverse Events Analysis Dataset / Analysis Dataset for Adverse Events
ADaM	Analysis Data Model
ADaMIG	Analysis Data Model Implementation Guide
ADSL	Subject Level Analysis Dataset / Analysis Dataset for Subject Level
ARM	Analysis Results Metadata
BDS	Basic Data Structure
BRIDG	Biomedical Research Integrated Domain Group
CDASH	Clinical Data Acquisition Standards Harmonization
CDASHIG	Clinical Data Acquisition Standards Harmonization Implementation Guide
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CSV	Computer/Computerised System Validation
CT	Controlled Terminology
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GAMP	Good Automated Manufacturing Practice
GMP	Good Manufacturing Practice
HGP	Halfmann Goetsch Partner
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
JP	Japan
ODM	Operational Data Model
PMDA	Pharmaceuticals and Medical Devices Agency
PRM	Protocol Representation Model
QRS	Questionnaires, Ratings and Scales
SDM	Study Design Model
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SDTMIG-AP	Study Data Tabulation Model Implementation Guide: Associated Persons
SDTMIG-MD	Study Data Tabulation Model Implementation Guide for Medical Devices
SDTMIG-PGx	Study Data Tabulation Model Implementation Guide for Pharmacogenomics and Pharmacogenetics
SEND	Standard for Exchange of Non-clinical Data
SENDIG	Standard for Exchange of Non-clinical Data Implementation Guide
SHARE	Shared Health And Research Electronic library
TA	Therapeutic Area
US	United States
XML	Extensible Markup Language

About NNIT

NNIT is an international consultancy in the development, implementation, validation and operation of IT for the life sciences industry. We create value for our clients by treating their IT as if it was our own. And of course, we meet the industry's strictest regulatory requirements. We apply the latest advances in technology to make our clients' software, business processes and communication more effective.

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