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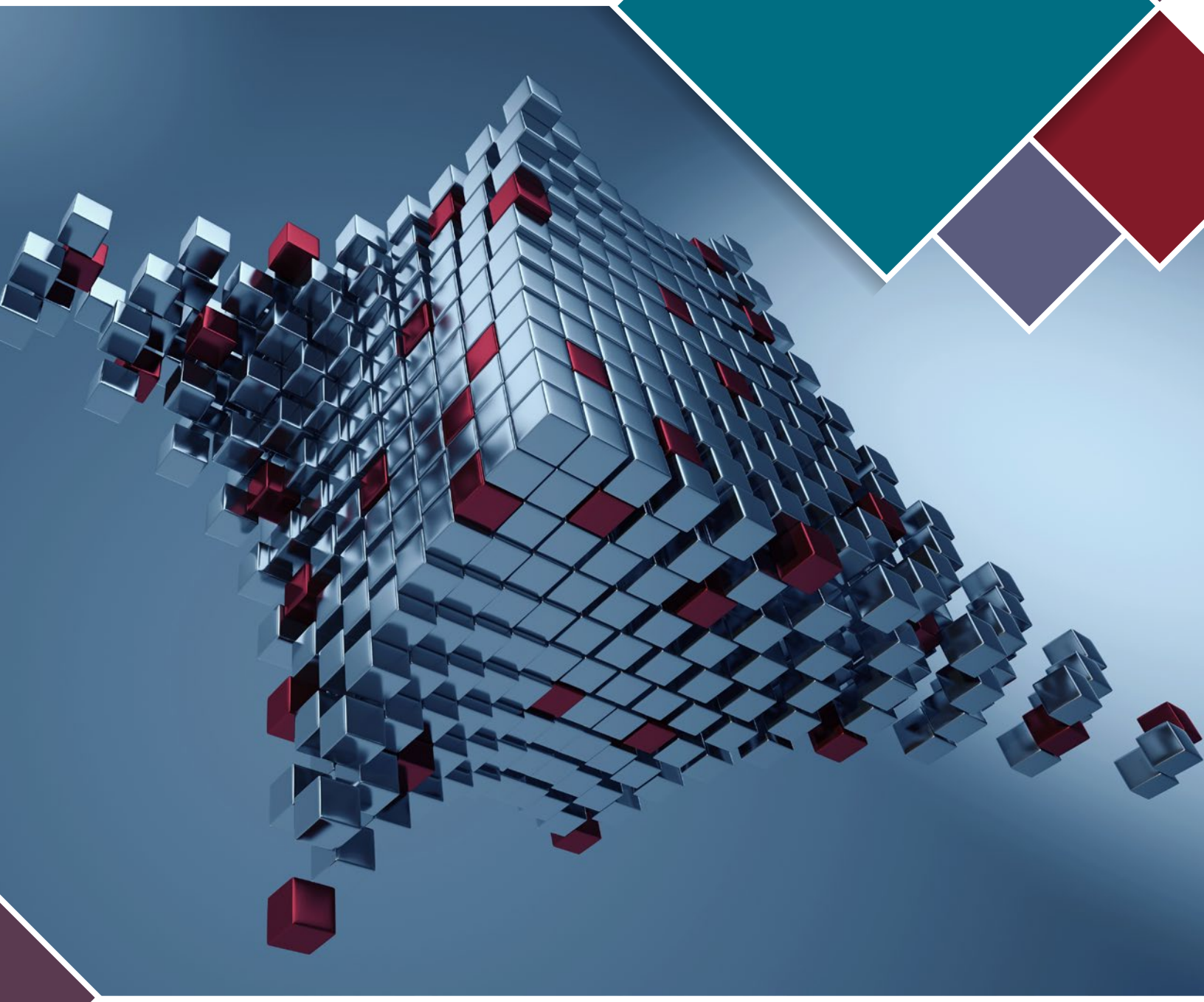


Streamline CDISC Electronic Data Submissions

Technology Solution for CDISC Pharmacokinetic (PK) Study Data

CDISC Registered Solutions Provider

Certara is a CDISC Registered Solutions Provider

Streamline CDISC Electronic Data Submissions

Certara CDISC Technology Solution for Preparation, Analysis, and Submittal of CDISC Pharmacokinetic (PK) Study Data

To better understand the new regulatory guidelines for electronic study data submissions, and to find out how Certara technology solutions can help streamline data preparation for CDISC-ready submissions, the following provides:

- An overview of the new guidelines
- Requirements for electronic submission of standardized study data
- A review of the CDISC SDTM/SEND standards and how they benefit your organization
- An overview of the solution Certara offers to streamline CDISC submissions
- How to develop a readiness plan to meet the regulatory CDISC electronic submission guidelines

Through our collaborations with regulatory agencies, and partnerships with global pharma, CROs and major nonprofit organizations, and as a CDISC Registered Solutions Provider, we continuously strive to provide up-to-date solutions to help streamline the drug development process and compliance requirements for our clients. The US Food and Drug Administration (FDA) and other regulatory agencies have implemented electronic submission guidelines using standards developed by the Clinical Data Interchange Standards Consortium (CDISC). These standards support acquisition, exchange, submission, and archiving of study data. CDISC Study Data Tabulation Model (SDTM) and Standard Exchange for Non-clinical Data (SEND) are examples of study data standards required by the FDA for electronic submission of tabulations data.[1]

What is CDISC?

The Clinical Data Interchange Standards Consortium (CDISC) is a global, multidisciplinary, non-profit organization that has established standards to support the acquisition, exchange, submission, and archive of non-clinical and clinical data. Since its formation in 1997, the CDISC mission is "to develop and support global, platform-independent data standards that enable information system interoperability, to improve medical research, and related areas of health care." CDISC provides data standards for the entire clinical trial process, from source to analysis/reporting and culminating in regulatory submission. This includes standards for Trial Design and Protocol Information, CRF and Subject Data, Analysis Datasets, and Regulatory Submissions.

What are the regulatory guidelines for the submission of CDISC non-clinical and clinical data?

The FDA requirement for using CDISC SDTM version 1.3 or earlier and SEND version 1.2 formats for electronic submission of data contained in New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Biologics License Applications (BLAs) to CDER and CBER went into effect on December 17, 2016.[2] Detailed information on submission guidelines for the FDA, EMA, PMDA and other regulatory agencies can be reviewed at CDISC and the agency websites.

What are the consequences if my organization does not follow the CDISC study data electronic submission guidelines?

Submissions that do not comply with CDISC requirements could potentially delay the regulatory review process. Furthermore, retroactively standardizing data can be a very complex and daunting task. Although these requirements will not impact IND submittals until December 17, 2017, CDER strongly encourages companies to consider the implementation and use of data standards for the submission of applications. Such implementation should occur as early as possible in the product development life cycle, so that data standards are accounted for in the design, conduct, and analysis of studies.

Why are data standards important, and how will these guidelines benefit my organization?

As outlined by the Critical Path Institute (C-PATH), CDISC specifies how to "structure data that has been collected in a dataset, not what should be collected nor how to conduct clinical assessments or protocols". When data content, structure and quality are standardized, it enables quality research. Standardizing the management of data sets within your organization, particularly those associated with large pre-clinical studies, can reduce the risk of data loss in the event of personnel changes, increase productivity through collaboration enabled by standard data structuring, and allow for easy exchange and review of pre-clinical and clinical trial data between pharmaceutical sponsors and CROs.

What are the CDISC data standards, and how is CDISC data organized?

The CDISC foundational data standards comprise a suite of standards that support clinical research processes from planning (Protocol Representation Model, Study Design) through data collection (CDASH, Lab) and data tabulation (SDTM, SEND) to statistical analysis (AdaM). CDISC data is organized into domains. For example, some of the relevant domains for PK analysis include demographic information (DM), exposure information (EX), pharmacokinetic concentration data (PC), and pharmacokinetic parameters (PP). Data content is structured using Study Data Tabulation Mode (SDTM), the general model for representing study tabulation data used in clinical research, which is then transported via the Operational Data Model (ODM). This approach retains data reporting consistency across the review and submission cycle.

How do the new standardization guidelines govern STDM and SEND electronic data submission?

Standard Exchange of Non-clinical Data (SEND) is an implementation of the CDISC Standard Data Tabulation Model (SDTM) for non-clinical studies. SEND compliance for the FDA went into effect on December 17, 2016. SEND compliance applies to general toxicology (single- and repeat-dose) and carcinogenic studies, with the goal to expand to other service areas (eg, safety pharmacology and DART/EFT). SEND provides guidance for the organization, structure, and format of standard non-clinical tabulation datasets for interchange between organizations such as sponsors and CROs and for submission to the FDA.

The CDISC STDM and SEND electronic formats provide the following benefits to streamline the submission and review of data:

- Minimizes delays in interpretation and sharing of massive data sets
- Results in greater standardization and consistent terminology for regulatory data review
- Provides a more robust data submission protocol
- Facilitates collaboration between sponsors and CROs through better data transfer between databases

Certara's CDISC tools and services have been developed as a set of "Best Practices" to:

- Accelerate SEND and SDTM data submissions using the CDISC guidelines
- Optimize R&D productivity
- Achieve regulatory compliance

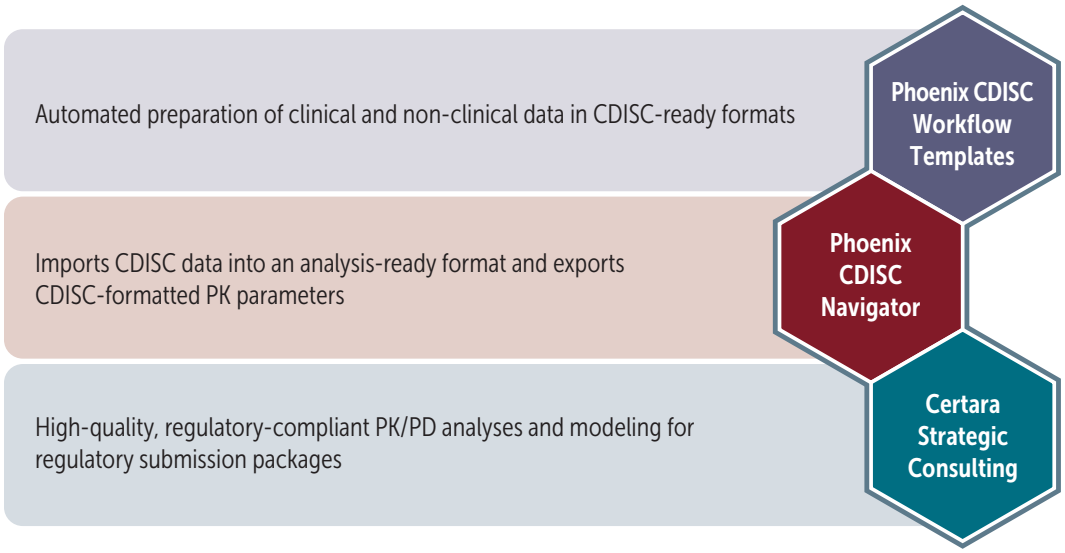
What are the additional benefits of using CDISC SDTM and SEND standards?

Depending on its length, non-clinical and clinical studies can amass extremely large amounts of data resulting in delays in interpretation and sharing of data sets. Many companies and service providers are already taking proactive measures to implement CDISC SDTM and SEND. The use of CDISC SDTM and SEND provides numerous benefits for regulatory agencies, industry, and software developers. For regulatory agencies, CDISC SDTM and SEND will provide better standardization for data review, more in-depth analysis of data, and consistent terminology. By providing a common framework, CDISC standards enable sponsors and CROs to better transfer data between databases, and ultimately provide a more robust submission protocol. CDISC STDM and SEND also foster development of new statistical and analysis tools.

Introducing Certara's Technology Solution for the Preparation, Analysis and Submittal of Pharmacokinetic Data

In addition to complying with CDISC data standards, companies need to ensure that their processes and documentation continue to meet Good Laboratory Practice (GLP). Certara offers a full end-to-end solution of tools and services that streamline routine PK data preparation for CDISC-ready submission, provide NCA-ready analysis of CDISC-formatted data in Phoenix, and eliminate the error-prone and time-consuming task of converting data to a CDISC format manually.

Certara CDISC Technology Solution for PK Data Preparation, Analysis and Submittal



Phoenix CDISC Workflow Templates are available for Phoenix users who require more routine automated preparation of NCA SDTM clinical and SEND non-clinical data sets into CDISC-ready formats.

Phoenix CDISC Navigator is an integrated solution to support the creation of NCA analysis-ready datasets from CDISC-formatted files received from external systems, vendors, or collaborators.

Certara Strategic Consulting provides a range of pharmacometric services, tailored to the specific needs of each client, ensuring that the modeling and simulation deliverables are embedded in the overall development workflow to optimize the impact of the work. These services support your strategic drug development decisions and new drug approvals through quantitative analysis and predictive models of diseases, drugs and clinical trials.

Certara Solutions for CDISC Data Preparation, Analysis and Submittal

Phoenix CDISC Navigator provides basic functionality to import CDISC-formatted data, prepare it for analysis, and then export results in CDISC-formatted datasets (PP and RelRec). This method is generally used when biostatistics groups are responsible for the final preparation and formatting of the CDISC domains. Enhanced functionality is provided by Phoenix CDISC Workflow Templates that allow full control over the formatting and export of submission-ready CDISC-formatted datasets. This method is preferred when the PK scientist is responsible for final CDISC domain preparations.

Certara has developed pre-defined Phoenix Workflow Templates and Plugins as a set of "best practices" to optimize R&D productivity and achieve regulatory compliance. The Phoenix CDISC Workflow Templates complete specific data transformation, analysis, and data preparation tasks to streamline routine analysis, maximize quality control output, and package data for submission for clinical PK, sparse and serial TK data sets. Phoenix has an extendable plugin framework which can be used to integrate the platform with both upstream and downstream systems such as LIMS, Study Protocol, Compound Management, Dosing/Treatment, Randomization, and CDISC Submission. The CDISC Export plugin provides the ability to export CDISC-formatted data from Phoenix to SDTM/SEND submission systems. The plugin also locks the data set so that it cannot be altered, but allows the user to add free form comments.

Use Case 1: Bioanalytical data received in CDISC SDTM and SEND format

Phoenix CDISC Navigator is used when bioanalytical data is received in a SDTM or SEND CDISC format from a CRO or internal biostatistics group. In this use case, the CDISC SDTM or SEND data is received as separate files, or CDISC domains. To complete pharmacokinetic analysis, CDISC domains containing Pharmacokinetic Concentration Data (PC), Demographic (DM) and Exposure (EX) Information, Pharmacokinetic parameters (PP), and other information, need to be merged together. The Data Preparer tool in Phoenix CDISC Navigator provides a user-friendly interface for merging CDISC domains into an analysis-ready dataset. The SDTM and SEND Export tools in Phoenix CDISC Navigator can be used to export PP, PC and Related Records (RELREC) domains.

References

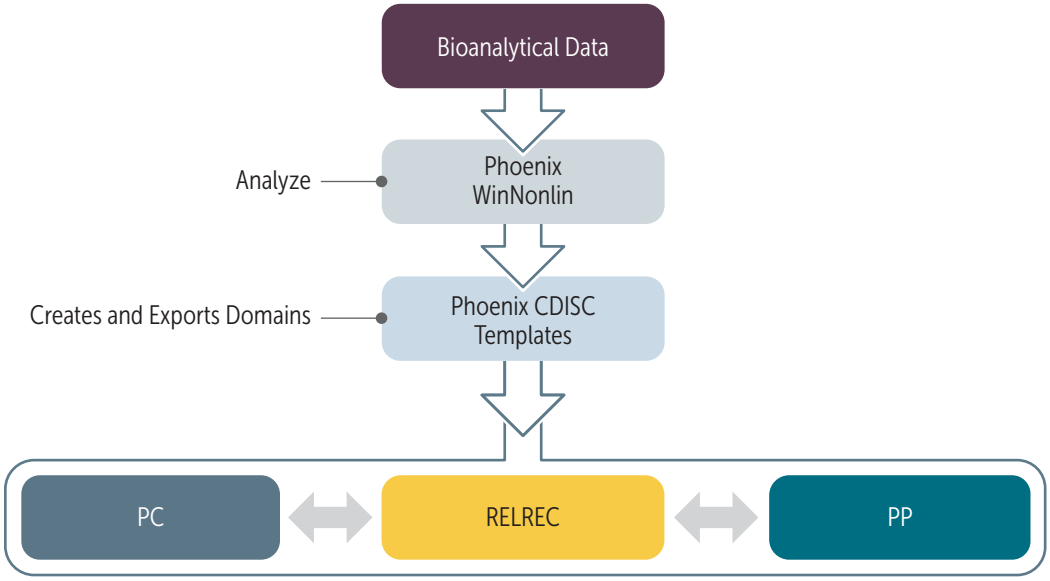
1. Providing Regulatory Submissions in Electronic Format – Standardized Study Data. Guidance for the Industry. US Department of Health and Human Services Food and Drug Administration. December 2014.

2. FDA Data Standards Catalog, v 4.5.1. August 31, 2016.

Use Case 2: Bioanalytical data needs to be converted to CDISC format

The diagram below illustrates how Phoenix CDISC Workflow Templates are used when bioanalytical data needs to be converted into SDTM or SEND CDISC format. In this use case, Phoenix WinNonlin analysis is completed according to normal operating procedures. The Phoenix CDISC Workflow Template can be used to take the output from WinNonlin and automate the creation of PP and PC domains. The CDISC Workflow Template then exports the PP, PC and RELREC domains.

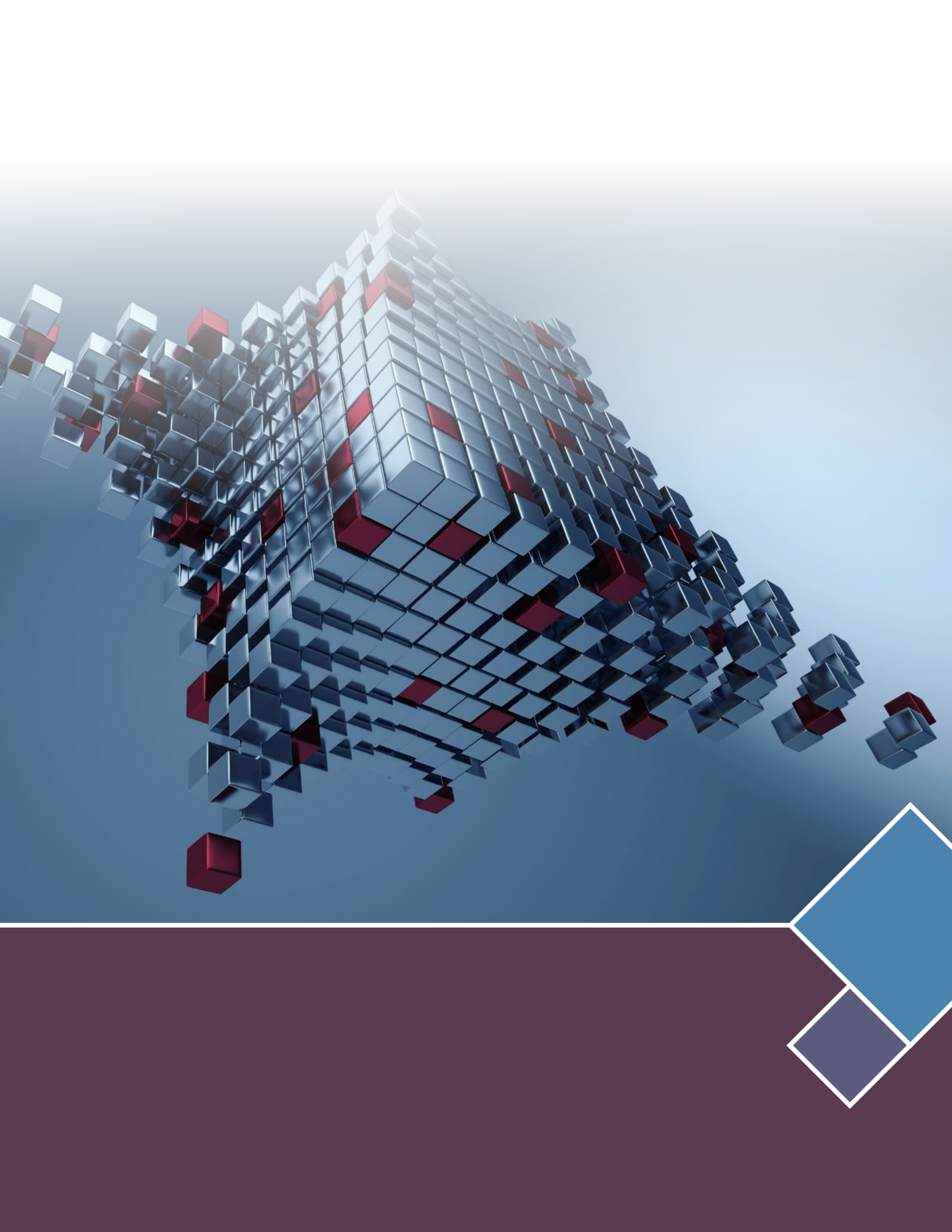
Use Case 2: Bioanalytical data needs to be converted to CDISC STDM or SEND format



Pharmacokinetic Concentration Data (PC), Pharmacokinetic Parameters (PP), Related Records (RELREC)

Summary

Understanding and complying with CDISC data standards is critical to satisfying electronic regulatory data submission requirements. Moreover, having data in a standard format provides numerous benefits to pharma and CROs by facilitating easier and faster collaboration on projects and by accelerating the review and approval process by regulatory agencies. Certara's tools and services streamline routine data preparation for CDISC-ready submission, provide NCA-ready analysis of CDISC-formatted data in Phoenix, and remove the error-prone and time-consuming task of converting data to a CDISC format manually. The result? Sponsors and CROs obtain more effective knowledge transfer between databases and robust regulatory electronic submission protocols.



About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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