

Written Notice of Participation by the Clinical Data Interchange Standards Consortium (CDISC) and Written Statement for Discussion Topics to be Addressed

In the FDA Public Hearing:

Electronic Submission of Regulatory Information, and Creating an Electronic Platform for Enhanced Information Management

Docket No. 2006N-0464

Date to be Held: December 18, 2006

The following CDISC Participants wish to have a total of 30 minutes to present their combined remarks at the Public Hearing on 18DEC06:

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Written Statements from the Clinical Data Interchange Standards Consortium (CDISC) for Discussion Topic in Section IV of FDA Notice of Hearing and Request for Comment: <http://www.fda.gov/OHRMS/DOCKETS/98fr/06n-0464-nhc0001.pdf>

Introductory Remarks

The Clinical Data Interchange Standards Consortium (CDISC) wishes to commend FDA for the regulations, guidance documents, specifications and their overall support for standards as part of their efforts to move toward electronic regulatory submissions.

CDISC (www.cdisc.org) is a global, open, multidisciplinary, non-profit organization that has developed standards to support the acquisition, exchange, submission and archive of clinical trial data and metadata. 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 healthcare. CDISC standards are vendor-neutral, platform-independent and freely available via the CDISC website.

CDISC is the leader in the development of data standards for clinical research. CDISC participants and stakeholders include more than 175 organizations representing academia, biopharmaceutical companies, technology and service providers, institutional review boards and others interested in streamlining biopharmaceutical product development and improving clinical data quality and healthcare. CDISC has joint memberships with HL7, HIMSS, AMIA and CPATH Institute. Additional information on CDISC can be found at www.cdisc.org.

CDISC endorses the FDA proposal to move to an all electronic submission environment for regulatory information and the creation of an electronic platform for enhanced information management across departments/divisions.

CDISC supports the belief that submissions in a *standard* electronic format will facilitate regulatory review processes at FDA and enable the use of common review tools that improve reviews. In addition, standards for electronic submissions enable data aggregation and the population of cross-study and cross-product databases that will vastly enhance the FDA's ability to perform safety assessments, identify trends and conduct product evaluations. Such knowledge repositories will not be feasible without the submission of logically and semantically consistent data and information by manufacturers in a standard electronic format.

The value of standards accrues to manufacturers as well. When applied from the start-up stage of a clinical study or program, standards have been shown to improve data quality and substantially reduce cost and time in the product development process for sponsors and other stakeholders in the industry. We will speak to these specifics later. Most importantly, CDISC believes the transition from paper to standard electronic submissions will lead to safer and more effective drug products to improve public health.

1. Transition from Paper Submissions to Electronic Submissions

One of the impediments to transitioning to an electronic submission environment is the requirement that this data/information must be in a standard format. Fortunately, industry has been actively involved with the Agency over the past decade to help develop and implement industry standards for the purpose of supporting electronic submissions.

CDISC is the leader in the development of data standards related to clinical research. Our members have contributed collaboratively to the consensus-based CDISC standards development process. Most stakeholders in the industry are either in the process of implementing or making plans to implement these standards

Broad-based technical knowledge and experience in the application of these standards are needed among all stakeholders, including industry and FDA personnel. Fortunately, both XML expertise and knowledge of the CDISC standards are increasingly prominent within the workforce. Education and training courses are readily available at a reasonable cost.

2. Cost & 3. Time

While the implementation of standards-based electronic submissions requires an investment of time and money, it also reduces operating cost and time to market once the standards are in place. CDISC recently partnered with Gartner Group, with support from PhRMA, to develop a business case analysis that estimates the costs and benefits of standards implementation. While these costs are very difficult to estimate (particularly because of the absence of baseline information), the business case metrics indicate that there are substantial reductions in cost and time related to capturing, cleaning, analyzing and reporting clinical trial data, especially when standards are used at the start up stage of a clinical trial or program.

Similarly, regulatory reviewers will be able to spend less time on data manipulation and more time on the science when data are submitted in a standard format. Communication will also improve between the Agency and manufacturers, such as by reducing time for follow up queries.

Over 50% of clinical trials involve a contract research organization (CRO) and an increasing number of trials involve electronic data capture (EDC) vendors. Communications and data exchange among sponsors, CROs, EDC vendors and even project team members become much more cost effective and easier when standards and electronic processes are employed.

CDISC supports the 2 year industry transition time that is stated in the proposed rule for electronic regulatory submission.

4. Implementation

Making the transition from paper to electronic submissions is hard work. CDISC would like to offer several recommendations to ease the transition.

FDA must take the strong position to drive manufactures to make all electronic submissions in XML containing data in the specified standard formats. The majority of industry organizations is prepared or is in the process of preparing to utilize CDISC standards for submission of clinical data for regulated biopharmaceutical products. This includes the CDISC Study Data Tabulation Model (SDTM), the Operational Data Model (ODM) and define.xml. SDTM can be submitted to FDA in the eCTD or the HL7 Regulated Product Submission format. We would like to see the FDA adopt the ODM for electronic CRF data submissions, in addition to using it as a transport format for define.xml metadata and SDTM and analysis data. This transport standard is already familiar to most industry stakeholders, and can also facilitate auditor reviews of electronic data capture environments at investigative sites.

CDISC is driven by a mission that supports electronic submissions and data exchange that will enable translational research. To that end, CDISC is working with industry and FDA on standards to support electronic submissions for devices, genomics data and animal data. CDISC has already published the SEND Standard for the Exchange of Non-

clinical (animal) Data. Both SEND and SDTM are cited in the Study Data Specifications for the final eCTD Guidance. Many view translational research as more rapidly bringing innovations from “bench to bedside”. For over five years, CDISC has had a formal relationship with Health Level Seven (HL7) to enable a link between clinical research and healthcare through standards. We strongly encourage FDA to continue its support of these standards development efforts, which are critical success factors for translational research and electronic submissions and data exchange.

Variation in terminology is a barrier to effective collaboration, data aggregation and multidisciplinary research. CDISC, through NIH Roadmap Grants in collaboration with Duke Clinical Research Institute, has work underway to develop therapeutic area terminology standards with the initial focus on cardiovascular and infectious diseases. CDISC also collaborates with the National Cancer Institute in a number of ways, including the development of standards relevant for oncology. FDA should continue its support of terminology standards.

CDISC is leading a Collaborative Group devoted to achieving Critical Path Opportunity #45 to standardize case report form data collection consistent with the SDTM standard. FDA should provide additional support to complete this work, which will provide tremendous value to investigators, clinical research associates/monitors, project leaders and others who work at the ‘front end’ of the clinical trial process. As mentioned earlier, this will cascade to provide significant downstream benefit for electronic submissions.

It goes without saying that the infrastructure to receive standardized electronic submissions is critical. So are standards.

Additional Standards

Before specifying additional standards, CDISC believes it is important to first apply the existing standards effectively, and to work to harmonize standards to support semantic interoperability within clinical research and between research and healthcare (electronic health records). Significant progress has been made in this area with the Biomedical Research Integrated Domain Group (BRIDG) model, which was initiated by CDISC and is now an open source model governed by FDA, CDISC, NCI and HL7.

Further harmonization support is needed in specific areas, including the following:

- a) to harmonize the multiple standards related to adverse event reporting (SDTM – AE domain, HL7 (ICH) Individual Case Safety Report, NIH-BAER, EMEA – SUSAR, NCI caAERS and others);
- b) to complete and ensure compatibility with implementations of the CDISC-HL7 Protocol Representation Standard (including Trial Design);

c) to harmonize the Protocol Representation Standard and SDTM with the needs of other regulatory agencies and global organizations, e.g. EMEA's EudraCT and the WHO International Clinical Trial Registry Platform and results reporting projects.

Global pharmaceutical companies will appreciate the efficiencies they will gain if there is harmonization of requirements and a single, consistent set of standards used across multiple groups such as FDA, EMEA, WHO, and NIH. These groups are requesting trial registry information and results reporting subsets for multiple purposes. If these data formats are designed to support semantic interoperability, there will be cost and time saving for all stakeholders globally.

We ask that FDA recognize and support CDISC's continued leadership of these standards enhancement and harmonization efforts.

5. Third Party Entities

CDISC supports the use of a third party entity especially if that accelerates the decision by FDA to require electronic submissions in a standard format. We believe the benefits to patient care and all stakeholders far exceed the initial cost.