

Abstract

CDRH, FDA's center for medical devices, receives data in regulatory submissions in many structures and formats.

Regulatory mandates imposed by MDUFA III on CDRH also require ever decreasing time for reviews as numbers of covered submissions increase. Together, these result in challenges that can significantly delay reviews.

CDISC's standards cover much of the clinical data in device submissions, including device-centric data (SDTMIG-MD).

CDISC standards have been mandated for CDER submissions, and while devices have many unique attributes, experience suggests that there are also many similarities.

This poster describes some of CDRH's challenges, and how the CDISC standards can increase the efficiency of the device review process

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Source

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CDRH: Current Situation

- 46 marketing applications per year received for high-risk devices and additional lower risk devices (PMA/510(k))
- MDUFA III: each year, current requirements shorten review times and increase the number of covered submissions
- Applications are typically an e-copy (PDF of paper copy), often with no subject- or device-level data
- When data are submitted, any format is accepted (i.e., no data standardization)
- Lack of standards significantly slows review process and ability to deal with late-breaking issues

CDISC *Data* Standards Include...

- **CDASH:** Data capture (CRF), begin by collecting data in standard structure
- **SDTM:** Regulatory submission of subject- and device-level data (tabulations)
- **ADaM:** Statistical analysis datasets
- **Controlled Terminology:** code lists
- **Define-xml:** comprehensive metadata for each study dataset and variable
- **And more** [REDACTED]

CDISC *Device* Standards Include...

- **Device Identifiers:** Supports UDI/GUDID
- **Device Properties:** Unchanging, e.g., composition, coil type, size
- **Device-in-Use:** Settings used with device, e.g., magnetic field strength
- **Device Tracking:** Location and disposition of device; flexible granularity
- **Device Events:** What happens to the device, e.g., malfunctions, calibrations
- **Device Exposure:** Characteristics of subject/device interface, e.g., dates

CDISC SOLUTIONS FOR CDRH ISSUES

Industry-wide standards can address many of the current challenges

Protocol Deviations
Issue
➤ Hard to identify, determine impact
CDRH Reviewer Requests
➤ Summary tables by type of deviation (major/minor)
➤ Protocol deviations by investigational site
CDISC Solution
➤ SDTM: designed to facilitate summary table production;
➤ CDASH: defines deviation data capture, including narratives; facilitates categorization

Data Traceability
Issue
➤ Lack of data traceability means cannot assess data validity
CDRH Reviewer Request
➤ Provide mechanism to trace each data point from the study report back to the CRF
CDISC Solution
➤ ADaM, SDTM, associated define-xml and CDASH-conformant CRFs are specifically designed for this: hyperlink each variable to associated algorithm(s), source dataset(s), controlled terms and annotated CRF(s)

Missing data
Issue
➤ May impact validity of conclusions, choice of statistical model
CDRH Reviewer Requests
➤ Show why and when data are missing (missed visits, value not recorded, etc.)
➤ No undisclosed data omissions; justify all data omissions
➤ Clearly note all imputed data
CDISC Solution
➤ SDTM and ADaM define-xml:
➤ Origin of each variable is defined as collected, derived or imputed
➤ Algorithms for all derivations and imputations included
➤ Can show what data were included or omitted and why
➤ CDASH can indicate what data were missing, with associated dates

Patient Accountability
Issue
➤ Hard to determine accountability for all subjects
CDRH Reviewer Request
➤ Provide patient accountability charts with discussions of missing data
CDISC Solution
➤ CDASH and SDTM: Subject Disposition domain captures status of each subject at each defined time point, which can be used to produce accountability charts; see also "Missing Data" box

Missing coding tools
Issue
➤ Hard to identify, determine impact
CDRH Reviewer Request
➤ Include Proc Format program that creates the format catalog
CDISC Solution
➤ Controlled Terminology contains standard "formats"
➤ define-XML contains customized ones and external terms

Trial Data Issues
CDRH Reviewer Requests
➤ Include electronic datasets in PMA submission
➤ Adverse Event listings for medical reviewers
➤ Study endpoints analysis dataset(s) and raw data to minimize complicated manipulations and merges required to validate results
➤ Analysis datasets to support key effectiveness/safety analyses
➤ Include basic demographic variables and important covariates in analysis datasets
➤ Define/README file for datasets and program files
➤ Document datasets and code sufficiently
CDISC Solution
➤ SDTM and ADaM provide subject- and device-level tabulation and analysis datasets
➤ Data transmitted in SAS transport files
➤ Standardized AE data support listings from data visualization tools
➤ ADaM defines key effectiveness/safety analyses and datasets, and permits inclusion of any/all relevant variables
➤ ADaM datasets are "one proc away" from running analyses
➤ Define-xml provides structure to document all datasets