A Critique of Implementing the Submission Data Tabulation Model (SDTM) for Drugs and Medical Devices

Presenter

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- Carey has more than 30 years of SAS statistical programming experience!
- He has successfully programmed/managed more than 20 regulatory submissions which have resulted in clearance / approval of FDA products!
- He also has more than 40 publications and is a frequent speaker at conferences / meetings!
- Carey is also the co-founder and co-leader of CDISC Device team!

Overview

- CDISC Background
- Study Data Tabulation Model (SDTM)
- Therapeutic Area User Guides (TAUGs)
- Medical Devices
- TAUGs and Medical Devices
- Associated Persons Implementation Guide (SDTMIG-AP)
- Putting it All Together

Section 1:

CDISC Background

Section 1: CDISC Background

- *"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."*
  - www.cdisc.org/about

Section 1: CDISC Background

- The FDA now requires industry sponsor companies to comply with submission of standardized electronic data for studies starting after 17Dec2016.
  - www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
  - The Japanese PDMA also requires similar electronic data standards as of 01Oct2016.
  - Thus adoption of CDISC standards by industry sponsor companies needs to happen quickly.

Section 1: CDISC Background

- Why industry should adopt CDISC standards:
  - Communication among project teams and partners is easier.
  - There is a greater level of accuracy and less training with a constant process.
  - Decision making is simplified.
  - Scientists can do the science rather than being concerned with the data.
  - Promotes easier transfer of data between partners.
  - They open up a wider choice of tools/technology.

Section 1: CDISC Background

- Why industry should adopt CDISC standards (continued):
  - Research has shown that when CDISC standards are adopted at the beginning of a research study that companies can save 70-90% of the time and resources in the Study Start-up Stage (time to first patient enrolled).
  - Companies can also save approximately 75% of the time and resources on the non-patient time for Study Conduct and Analysis.

Section 1: CDISC Background

- Why industry should adopt CDISC standards (continued):
  - Furthermore, for a typical 12-year investment in drug development, up to two years of time can be saved by the adoption of CDISC standards at the earliest phase of clinical research.
  - ~ $180 million dollars could be saved per drug submission.
  - See Executive Summary of the Business Case for CDISC Standards, Stage V, 2014 Update at:
    - www.cdisc.org/system/files/all/article/PDF/2014%20Business%20Case_Executive%20Summary.pdf.

Section 2:

Study Data Tabulation Model (SDTM)

Section 2: SDTM

- The CDISC foundational standards include:
  - CDASH – Clinical Data Acquisition Standard Harmonization – data collection
  - ***SDTM – Study Data Tabulation Model – data tabulation***
  - ADaM – Analysis Data Model – data analysis
  - Other models
  - The CDISC foundation standards are located at:
    - www.cdisc.org/standards/foundational

Section 2: SDTM

- The SDTM is the most well-known of the CDISC standards since it describes the format for submitting data tabulations to a regulatory authority.
  - The SDTMIG organizes and formats data to help streamline data collection and data analysis.
  - The latest versions of the SDTM and SDTMIG can be downloaded from the CDISC website:
    - www.cdisc.org/standards/foundational/sdtm and www.cdisc.org/standards/foundational/sdtmig

Section 2: SDTM

- The basic components of the SDTMIG are ***domains***, ***observations***, and ***observation classes***.
  - ***Domains*** are group of observations which have a common topic. Usually, SAS® datasets and domains are equivalent.
  - ***Observations*** may be described as a series of named variables which typically correspond to columns in a dataset.
  - An example of a domain is Vital Signs, and within this domain are tests such as heart rate.
  - A test within this domain could be the collection of heart rate at the baseline visit for a particular subject.

Section 2: SDTM

- ***Findings*** Observation Class:
  - Findings are observations that result from planned evaluations during the conduct of a study. Examples of Findings data are vital signs, labs, and ECGs.
  - The Findings domains contains one record (row in a dataset) per finding result or measurement.
  - Thus if temperature, heart rate, systolic blood pressure, and diastolic blood pressure were collected at a particular visit for each subject then there would be four records (one record per vital sign measurement) per subject for that visit.

Section 2: SDTM

- ***Events*** Observation Class:
  - Events are occurrences or incidents that happen independent of planned evaluations during the conduct of a clinical trial.
  - For example, the occurrence of an adverse event may not occur at the time of scheduled visit during the clinical trial.
  - In Event domains, there is one record per event.

Section 2: SDTM

- ***Interventions*** Observation Class:
  - Interventions are investigational treatments, therapeutic treatments or procedures that given to or taken by the subjects during the conduct of a clinical trial.
  - For example, if a subject had an adverse event, and a drug was administered to alleviate the symptoms then the drug (non-investigational) would be represented as a record in the domain called Concomitant Medications.
  - Interventions domains contain one record per intervention or constant-dosing interval.

Section 2: SDTM

- Other Domains:
  - Special-purpose domains
    - Demographics (DM), Comments (CO), Subject Elements (SE) and Subject Visits (SV)
  - Findings About (FA) domain
  - Trial Design domains
    - Trial Arms (TA), Trial Elements (TE), Trial Visits (TV), Trial Inclusion / Exclusion Criteria (TI) and Trial Summary (TS)
  - Relationship domains
    - Supplemental Qualifiers (SUPPQUAL) and Related Records (RELREC)

Section 2: SDTM

- SDTM Domains (SDTMIG 3.2) – ***Interventions***
  - CM - Concomitant and Prior Medications
  - EX – Exposure
  - EC - Exposure as Collected
  - PR – Procedures
  - SU - Substance Use

- SDTM Domains (SDTMIG 3.2) - ***Events***
  - AE - Adverse Events
  - CE - Clinical Events
  - DS – Disposition
  - DV - Protocol Deviations
  - HO - Healthcare Encounters
  - MH - Medical History

Section 2: SDTM

- SDTM Domains (SDTMIG 3.2) - ***Findings***
  - DA - Drug Accountability
  - DD- Death Details
  - EG - ECG Test Results
  - IE - Inclusion / Exclusion Criterion Not Met
  - IS - Immunogenicity Specimen Assessments
  - LB - Laboratory Test Results
  - MB -Microbiology Specimen
  - MS - Microbiology Susceptibility Test
  - MI - Microscopic Findings
  - MO- Morphology

Section 2: SDTM

- ***Findings*** (Continued)
  - PC - PK Concentrations
  - PP - PK Parameters
  - PE - Physical Examination
  - QS – Questionnaires
  - RP - Reproductive System
  - SC - Subject Characteristics
  - SS - Subject Status
  - TU - Tumor Identification
  - TR - Tumor Response
  - SR - Disease Response
  - VS - Vital Signs

Section 3:

Therapeutic Area User Guides (TAUGs)

Section 3: TAUGs

- The purpose of the Therapeutic Area User Guides (TAUGs) is to facilitate solutions using the various CDISC standards for specific diseases or conditions.
  - Typically, the TAUGs provide ***advice, examples, and explanations*** regarding the use of CDASH, SDTM, and/or ADaM standards within the context of the specific therapeutic area.
  - TAUGs can be found on the CDISC website at:
    - www.cdisc.org/standards/therapeutic-areas

Section 3: TAUGs

- Developing TAUGs involves finding companies interested in the specific Therapeutic Area (TA), and asking them to provide examples of data elements collected in that TA (e.g., Case Report Forms (CRFs)).
  - These elements then get mapped to CDASH domains and questions as well as SDTM-based domains and variables.
  - New variables and/or domains may be developed by the TA team. They then go through the SDTM Governance process and the CDISC Standards Review Council.
  - Once approved, they are incorporated into future SDTMIGs.

Section 3: TAUGs

- An important concept that has come out of the TAUGs is the Disease Milestone concept.
  - The Diabetes TAUG provides a good example of Disease Milestones. Hypoglycemic events may have data collected across several domains:
    - data about the hypoglycemic event as a whole would be in CE
    - the blood glucose level would be in LB
    - the last dose of study medication prior to the hypoglycemic event would be submitted in EX
    - the last meal prior to the hypoglycemic event would be in ML
    - any medications taken would be in CM

Section 3: TAUGs

- Disease Milestones (continued)
  - Prior to the Diabetes TAUG this data would have been handled by Time-Point Variables and Reference Time Points in the SDTM-based datasets.
    - However, the Diabetes TAUG introduced a new variable, MIDS, which can be added to the relevant domains to link the data from each hypoglycemic event together.
    - MIDS is somewhat analogous to VISIT in that it is a Timing variable that allows data to be grouped. Rather than a scheduled visit, however, MIDS is a “trigger event” that, when it occurs triggers data collection across multiple domains.

Section 3: TAUGs

Current List of TAUGs

- Alzheimer's Disease
- Asthma
- Breast Cancer
- Chronic Obstructive Pulmonary Disease (COPD)
- Cardiovascular
- Diabetes
- Diabetes Kidney Disease
- Dyslipidemia
- Ebola
- Hepatitis C
- Influenza
- Kidney Transplant
- Major Depressive Disorder

Section 3: TAUGs

Current List of TAUGs (continued)

- Malaria
- Multiple Sclerosis
- Polycystic Kidney Disease
- Pain
- Parkinson's Disease
- Prostate Cancer
- QT Studies
- Rheumatoid Arthritis
- Schizophrenia
- Traumatic Brain Injury
- Tuberculosis
- Virology

Section 4:

Medical Devices

Section 4: Medical Devices

- The ISO 14155 Medical Devices Good Clinical Practices standard defines a “device” as follows:
  - *Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used on human beings for the purpose of:*
    - *diagnosis, prevention, monitoring, treatment or alleviation of disease,*

Section 4: Medical Devices

- ISO 14155 (Continued):
  - *diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap,*
  - *investigation, replacement or modification of the anatomy or of a physiological process,*
  - *control of conception,*
- *and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.*

Section 4: Medical Devices

- Development of the SDTM Medical Device domains:
  - The Device domains are different from subject-based domains used in drug studies in that they were developed to capture information about entities other than the study subject or the trial itself.
    - They must also accommodate a more complex and variable set of data than those in typical drug development studies.
    - Thus Device domains are based on entities (devices) that are not typically required in most subject-related data.
    - The STDMIG-MD is available on the CDISC website:
      - www.cdisc.org/standards/foundational/sdtmig

Section 4: Medical Devices

- Device Identifiers (DI)
  - A special-purpose domain that identifies a specific device unit.
    - SPDEVID is a sponsor-defined variable for a specific device for linking data across Device domains.
    - DI depends upon what is needed to uniquely identify the device.
    - DI does not contain data about items that can change without affecting the identification of the device.
      - such as dial settings (e.g., imaging devices).
    - Device Identifiers data exists independently from subjects, and therefore the DI domain does not contain USUBJID.

Section 4: Medical Devices

- Device Properties (DO)
  - The DO domain is a Findings domain and is used to report characteristics of the device that are important to include in the submission, and that do not vary over the course of the study, but are not used to identify the device.
    - Examples include expiration date or shelf life.
    - Device Properties data exists independently from subjects and therefore the DO domain does not contain USUBJID.

Section 4: Medical Devices

- Device-In-Use (DU)
  - DU is a Findings domain that contains the values of measurements and settings that are intentionally set on a device when it is used, and may vary from subject to subject or other target.
    - These are characteristics that exist for the device, and have a specific setting for a use instance.
    - This is distinct from Device Properties, which describes the static characteristics of the device.
    - For example: Device Properties would capture that an MRI machine's field strength has a range from 0.2 to 3 Tesla, whereas the Device In-Use domain would capture that the field strength for the MRI scan for Subject 123 was 0.5 T.

Section 4: Medical Devices

- Device Exposure (DX)
  - DX is an Interventions domain that records the details of a subject's exposure to a medical device under study.
  - The device is prospectively defined as a test article within a study (via SPDEVD) and may be used by the subject, on the subject, or be implanted into the subject.
    - Examples include but are not limited to stents, drug delivery systems, and any other item under study that is defined as a device in the applicable regulations.

Section 4: Medical Devices

- Device Events (DE)
  - DE is an Events domain that contains information about various kinds of device-related events, such as malfunctions.
    - A device event may or may not be associated with a subject or a visit.
    - If a device event, such as a malfunction, results in an adverse event to a subject, then the AE-related information should be recorded in the Adverse Events (AE) domain.
    - The relationship between the AE and the device malfunction can be recorded using the SDTM RELREC table. The relationship between AEs and multiple devices is a work in progress and solution will be forthcoming.

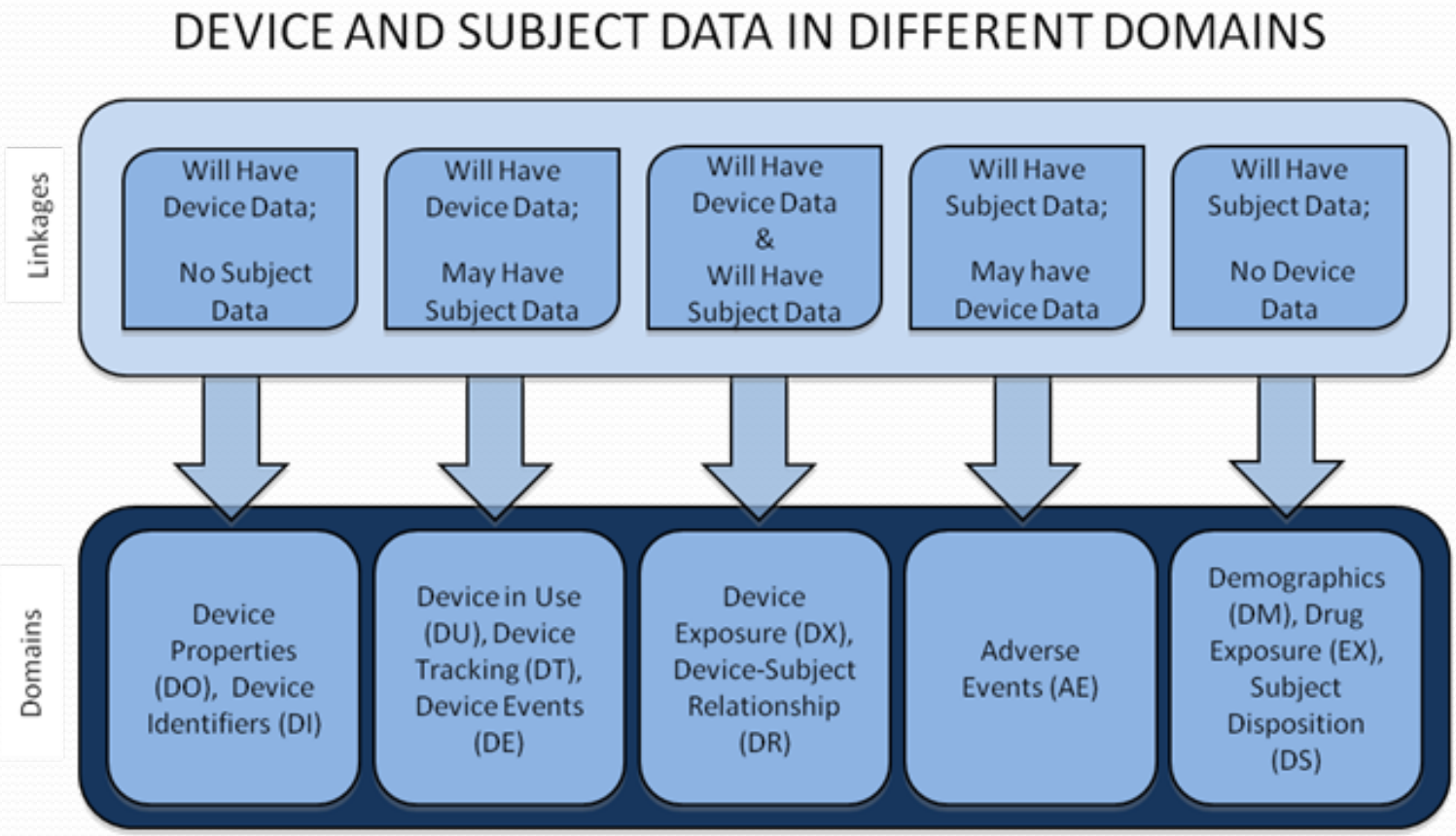
Section 4: Medical Devices

- Device Tracking and Disposition (DT)
  - The DT domain is an Events domain that represents a record of tracking events for a given device.
    - This could include initial shipment, deployment, return, destruction, etc.
    - The last record represents the final disposition of the device.
    - The sponsor decides upon the level of granularity that is appropriate for this domain, based on the type of device and agreements with the regulatory agencies.

Section 4: Medical Devices

- Device-Subject Relationships (DR)
  - The DR domain is a special-purpose domain that links each subject to the devices used in the study.
    - Information in this table may have been initially collected and submitted in other domains (e.g., Device Exposure, Device Tracking, Device Events).
    - However, this domain provides a single, consistent location to represent the relationship between a subject and a device, regardless of the device or the domain in which the subject-related data may have been submitted.

Section 4: Medical Devices



Section 4: Medical Devices

- The previous figure illustrates that device data can exist independent of subject data.
- While this may be a novel concept in the drug clinical trials, it is typical of device studies:
  - Approval of a heart stent requires collection of data (such as make, model, and lot number) that is not directly connected to a subject.

Section 4: Medical Devices

- Device data (continued):
  - A “lot” (lot number) of heart stents may be shipped to a clinical site for use in the device clinical trial.
    - Putting the lot number in a subject-based domain would be inefficient.
    - However, storing device data about the heart stent in domains like DI, DO and DU would be an efficient way to store the data.
    - On the other hand, including the serial number in a subject-based domain such as DX would be important.
    - The previous figure also illustrates where subject data (e.g., Demographics) may not have any relationship to the device.

Section 4: Medical Devices

- Drug-Device Studies
  - Examples
    - Combination Products
      - Patches that deliver a drug; drug eluting heart stent
    - Companion diagnostic devices and targeted drugs
  - SDTM
    - Required for the drug, but not for the device
      - Drug would be submitted to CDER / CBER
      - Device would be submitted to CDRH / CBER

Section 5:

TAUGs and Medical Devices

Section 5: TAUGs and Medical Devices

- 22 of the 25 TAUGs published use or should use one or more of the seven Medical Device domains.
  - The TAUGs illustrate the complexity of device data:
    - The software version of a device is captured in the DO domain for Parkinson's Disease, Polycystic Kidney Disease, and QT TAUGs, while it is represented in the DU domain for the Traumatic Brain Injury TAUG.
    - The distinction between DO and DU would be whether or not it is a static property (DO) of a device or varies based upon the subject or use instance of use (DU).

Section 5: TAUGs and Medical Devices

- Examples of use of Medical Device domains in TAUGs:
  - Alzheimer's Disease TAUG uses DI, DO and DU for imaging devices such as MRIs.
  - Breast Cancer TAUG uses DI, DO and DT for a tracer chip implanted for subsequent surgery.
  - Diabetes TAUG uses DI for identifying glucose meters and lancets.
  - Parkinson's Disease TAUG uses six Device domains for lead hardware from neurosurgery and diagnostic imaging.
  - QT Studies TAUG uses DI and DO from ECG devices.

Section 6:

Associated Persons Implementation Guide – SDTMIG-AP

Section 6: Associated Persons

- The Associated Persons Implementation Guide (SDTMIG-AP) was developed to model the submission of data collected about persons who are not directly enrolled in either drug or device clinical trials.
  - The SDTMIG-AP is available on CDISC website:
    - www.cdisc.org/standards/foundational/sdtmig
  - The key variable to link the non-subject data to SDTM is the Associated Person Identifier (APID).
  - Other important variables are the Related Subject (RSUBJID), Related Device (RDEVID), and Subject, Device or Study Relationship (SREL).

Section 6: Associated Persons

- Who are associated persons?
  - Data collected on family members or care-givers or data collected on persons who handle investigational device:
    - The original owners of donated organs, blood, tissues, etc.
    - A questionnaire administered to the caretaker of a study subject.
    - The demographics, sexual history, and/or pregnancy history of the sexual partner.
    - The collection of Adverse Events on lab operators of an investigational device.
    - A group of persons, e.g., pooled lab data.

Section 7:

Putting It All Together

Section 7: Putting It All Together

- SDTM Implementation Guides (SDTMIG) for both drug and device regulatory submissions exist.
  - However, drug regulatory submissions are far ahead of device regulatory submission in the adoption of CDISC standards such as SDTM.

Section 7: Putting It All Together

- The FDA now requires standardized electronic study data for submissions to CDER and CBER as of 17Dec2016.
  - Standards (SDTM and other standards) exist.
  - Therapeutic Area User Guides (TAUGs) also exist to assist with the ***advice, examples and explanations*** for submitting data in a particular therapeutic area.
  - Thus the pieces of the puzzle exist for pharmaceutical / biotech companies to meet this requirement.

Section 7: Putting It All Together

- Medical Devices
  - SDTM standards exist for medical devices.
  - However, adoption of these SDTM standards by medical device companies and CDRH has been slow.
  - Interestingly, the SDTM medical device standards are being adopted in the TAUGs.
    - Thus pharmaceutical / biotech companies are using the SDTM standards for medical devices used in drug studies.

Section 7: Putting It All Together

- What needs to be done to adopt SDTM standards for Medical Devices?
  - CDRH realizes the need for standards.
    - Presentation by CDRH statistician in 2014
  - Some sponsor companies are implementing these SDTM domains for medical devices.
  - More education on the benefits of standards for both CDRH and sponsor companies.

Section 7: Putting It All Together

Presentation by CDRH Statistician in 2014

- **CDRH Reviewer Requests**
  - Include electronic datasets in PMA submission.
  - Analysis datasets to support key efficacy/safety analyses.
  - 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.
  - ADaM defines key efficacy/safety analyses.
  - ADaM datasets are “one proc away” from running analyses.
  - Define-xml provides structure to document all datasets.

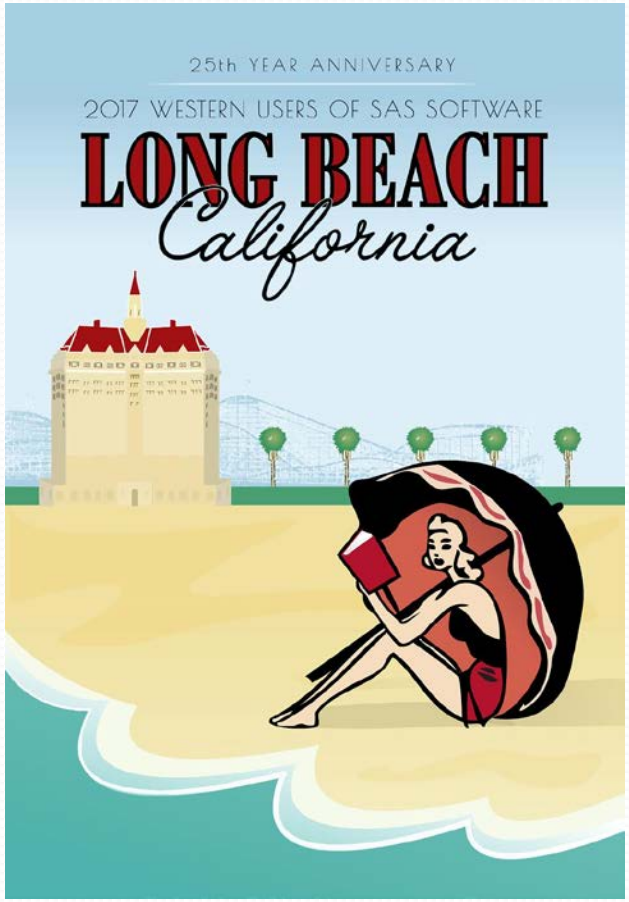
Section 8:

Conclusion

Section 8: Conclusion

- The pieces of the puzzle exist for drug submissions to meet the FDA requirement for standardized electronic data submission.
  - SDTM is an important piece of the puzzle.
- While SDTM standards exist for medical devices, much work still needs to be done for adoption of these standards by CDRH and sponsor companies.

Contact Information



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