Welcome to the American College of Toxicology's Webinar Series

We will begin at 11AM EDT

Preparing for Nonclinical eData Regulatory Submissions to the US FDA—"SEND" and Beyond

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Co-Sponsored by:
Society of Toxicologic Pathology

Presenters

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  US Food and Drug Administration

- **Shree Nath,** PhD, Vice President,
  PointCross Life Sciences

SEND (Standard for Exchange of Nonclinical Data)

- Processes, tools, and training in place for reviewers to use SEND submitted data
- Update on SEND submissions to date.

Validation rules for nonclinical datasets available

- The Validation Rules for SEND Formatted Studies is an Excel file that provides human readable description of a rule set for validation.
- Submitters of non-clinical study data can use this information to identify how FDA will validate submitted data.
- Available from the FDA Study Data Standards Resources webpage: http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm.

Validation rules

- The file contains a combination of conformance rules (i.e. how well the data conform to the standard) and business rules (i.e. quality checks; how well the data may support meaningful analysis).
- The file may be updated periodically as new or updated validation rules are developed.
  - The Change History tab will provide a descriptive change history of the document.

Technical conformance guidance

- Common errors over time will be consolidated to inform guidance given to sponsors

Test submissions and questions

- Highly recommended
- Participation in pre-IND/NDA/BLA meetings
- Contact edata@fda.hhs.gov before submission or with any questions

Topics

- Nonclinical e-Data Standardization & Submissions History
- Considerations for Regulatory e-Data Submissions
- What have we learnt from FDA NIMS e-Data submissions and from industry implementations?
- Future Directions:
  - Innovative ways to standardize studies for submission into NIMS: *Medical Countermeasures (MCM) as an example*
  - Protocol Design to drive downstream data collection & e-Data preparation
- Q&A

Nonclinical e-Data Standardization & Submissions History

2003 **2007** **2011** **2012** **2013**

SEND Initiation

Informal Pilot — SEND 2.3 IG

CRADA w/ PointCross for viewing & validation software (ToxVision)

CDER Regulatory Pilot — General Tox, Carc Studies — Safety Pharm, ReproTox

INHAND/CDISC/FDA Collaboration on Controlled Terminologies

SEND V3 IG

Draft Guidance

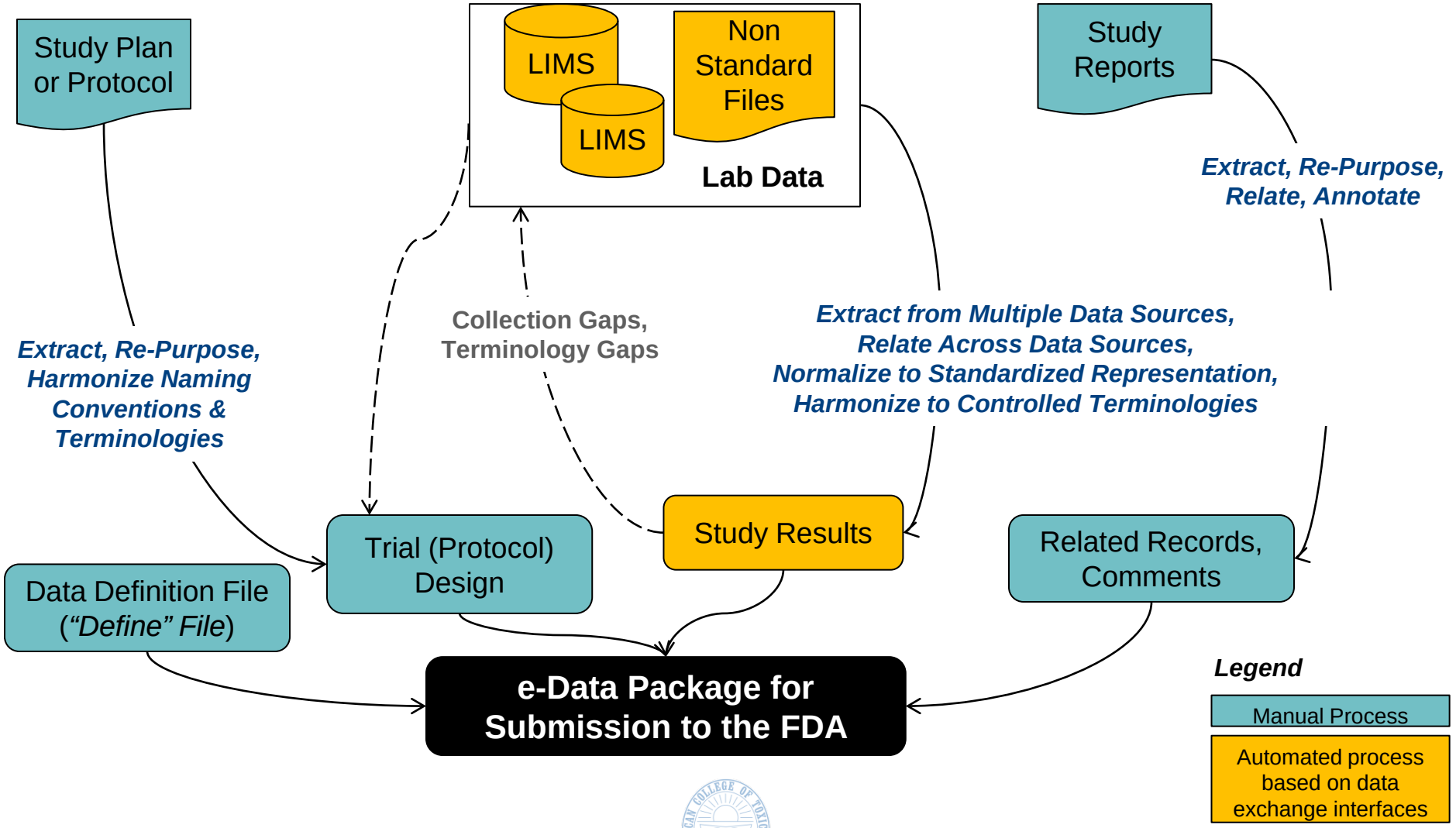
NIMS G0-Live

MCM Models

NIMS is the FDA's Nonclinical Information Management System

MCM stands for Medical Countermeasures used against CBRN Threat Agents. MCMs can be approved by the FDA without clinical trials under the *Animal Model* Rule.

Components of an e-Data Submission Package
(e.g., a "SEND" dataset for a study)



Experience with e-Data Submissions to Date

- One-off dataset compilation with a lot of manual intervention is possible at least by some sponsors & CROs
- Reliable and repeatable processes for routine compilation of submission ready e-datasets are non-existent
- Very few, if any, companies have submissions that successfully load in their entirety into NIMS

Challenges - Expertise and Knowledge Gaps

- Understanding of Standardized e-Data Models like SEND
- The SEND IG is open to subjective interpretation
- FDA Study Data Specification rules
- Requirements for Data Representation
  - Data organization - where & how should data be best represented?
  - Conventions – nomenclature, date formats, …
  - Use of controlled terminologies
  - Relating data represented in different categories or files
  - Dealing with missing data or those that are hard to find & extract

Companies can model the same kinds of datasets in different ways. This impacts both the FDA and Industry…

A Word on Controlled Terminologies (CTs)

- Collaborative effort among CDISC SEND Team, FDA and INHAND. FDA and STP are collaborating to adopt the INHAND nomenclature to standardize anatomic pathology findings – scientific expects from INHAND, sponsors, CROs and the FDA are on the SEND CT team
- CT's include protocol elements, clinical signs, clinical pathology, & macroscopic and microscopic findings
- CT's include both fixed and extensible lists
- Important to note that the original findings can be submitted *intact* to the FDA in the current e-Data models.
- CT's will allow for more effective cross-study analytics and signal detection

Challenges – Data Management & Collection Systems

- Study data can be scattered in as many as four sources:
  - In-life, Histopathology, PK systems *plus* Protocol Design files
- Generating reliable data extracts from some data collection sources can be a challenge
  - Same collection system exports different outputs for different studies!
- Relating data correctly across sources, often under GLP controls, and representing them in standardized formats requires new processes for data governance

No magic recipe for success. Software is not a panacea to address fundamental data management or process issues. GIGO (Garbage In, Garbage Out) will be the result ☺

Challenges – Beyond Standards like SEND

- Regulators and Sponsors both have an interest in building repositories of standardized e-Data
  - Applying analytics across “Big Data” for signal detection; increased efficiency; streamlining reporting & submission processes
- SEND is currently limited to General Tox & Carc Studies
  - What about Safety Pharm, ReproTox, Medical Countermeasure, Novel Protocols, Other Study Types?
- Standards development is lengthy – several years at best!

Addressing Immediate Term Challenges

- Initiate your e-Data standardization efforts ASAP and be both agile and flexible – **fly the plane as you build it**!
- Deep dive into your own and CRO generated datasets
- Work through the full lifecycle of compiling data for selected studies across all of your data sources/systems to determine requirements for both tools and processes
- Review CRO generated SEND datasets with the same level of rigor – *sponsors are ultimately accountable for datasets sent to the FDA!*
- Select vendors that combine expertise in tools & processes to compile complex data across disparate sources
- Get involved with initiatives like CDISC SEND & PhUSE

Novel Ways to Accelerate Standardized e-Data Representation – MCM as an example

- Draft Guidance for Animal Models—Essential Elements to Address Efficacy Under the Animal Rule released in 2009.
- Companies have started submitting studies to the FDA for approval of Medical Countermeasures (MCM).
- MCMs are needed to prevent or treat diseases or conditions caused by chemical, biological, radiological, or nuclear (CBRN) or emerging infectious disease threats.
- MCMs include medical products such as drugs, vaccines and/or combination therapies.

What is unique about MCM studies? And why current standards like SEND are insufficient

- Exposures: Subjects administered two kinds of Interventions
  - Change of state of a subject from a healthy state to an abnormal state by initial threat exposure and then again a reversal of state by administering MCM
- New Data Domains & Variables not typically in a tox study
  - New domains and variables like Disease/Threat Agent Characteristics, Pathogens Excluded, Antimicrobials (*Concomitant Medications*), Medical History & Protocol Deviations among others must be included in the data Models for MCM studies
  - Evolving study protocols require flexibility to further extend models

What is unique about MCM studies? (Contd.)

- Study Designs based on Adaptive Responses of Subjects
  - Many “unplanned elements” within the studies. E.g., The “trigger” or signals for intervention. Can vary from subject to subject.
  - Need to cluster subjects based on threat and MCM dosages
  - Assess efficacy in addition to safety
- Reporting of Findings
  - Assessment of responses may not always be against a fixed reference point

NIMS Data Model, Visualization & Analytics Extensions for MCM Studies

- 2012: The FDA initiated a NIMS extension for MCM studies
  - Data model, visualization and analytics in NIMS extended to handle representation of complex MCM studies
  - Selected studies submitted to the FDA have been standardized to this model and have been loaded by PointCross into NIMS
  - NIMS models are also being extended based on standardization of study data by sponsors
- Within a few months, an entirely new and complex type of study has been successfully modeled.

Agile, iterative modeling based on representative study data is an alternate to traditional standards development. Data schemas can eventually be published as a standard.

Future e-Protocol Design – why it matters…

- Standardized e-datasets today are being generated *ex post* without fundamental changes in protocol design and data management practices. Reliance on paper or PDF-based protocols does not fully realize the benefits of digital protocol designs.
- Clinical trials already use electronic case report forms (eCRF's) to specify and design data collection for the trial.
- If the industry adopts this concept for nonclinical studies:
  - It is possible to represent planned & actual protocols, and amendments/deviations electronically across the lifecycle of studies
  - Valuable for reviewers and researchers alike to evaluate results
  - Can also ensure that collected data will fit into the eventual data representation for e-data submissions bringing greater efficiency.

Conclusions

- Steep learning curve for the industry based on actual use cases is required – there is no time to waste.
- A knowledge base about the issues sponsors and CROs need to confront is developing slowly.
- Software tools are only a means to the end; not a panacea for poor data management processes & practices!
- Developing data models for new study types using actual study data can accelerate standards development.
- Novel ways for electronic protocol design can increase efficiency and reduce the effort in e-data preparation

Rapid adoption of e-Data initiatives for regulatory submissions and R&D will benefit both the FDA & Industry

Q&A

Contacts:

- FDA – edata@fda.hhs.gov
- PointCross – shree@pointcross.com

Other Resources:

- CDISC SEND
- PhUSE

Thank you for your participation in the American College of Toxicology Webinar!

We hope to see you at the 34th Annual Meeting of the American College of Toxicology

San Antonio Texas Hill Country,
November 3–6, 2013