BIOMEDICAL INFORMATICS AND CLINICAL DATA ANALYSIS

DIVISION OF PSYCHIATRY PRODUCTS

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
ISCTM 2018 Focus Today

• Study Data Standardization – Current
  – Regulations and Guidance
• Early Data Specifications
  – Data Collection
  – Reporting
  – Novel Data and Customized Methodologies
• Industry Engaging in Agency Data Standardization
  – Standards Developing Organizations (SDOs)
Review U.S. FDA Federal Code

- **Food, Drug, and Cosmetic Act** (abbreviated as FFDCA, FDCA, or FD&C), laws passed by Congress in 1938 giving authority to the U.S. Food and Drug Administration (FDA) to oversee the safety of food, drugs, and cosmetics
- **Food and Drug Administration Safety and Innovation Act** (FDASIA), July 9, 2012, expands the FDA’s authorities and strengthens the agency's ability to safeguard and advance public health
- **21st Century Cures Act** (Cures Act), December 13, 2016, designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently
- **Food and Drug Administration Reauthorization Act** (FDARA)
- **Prescription Drug User Fee Act** (PDUFA) I – VI
- **Health Information Technology for Economic and Clinical Health Act**, abbreviated HITECH Act, was enacted under Title XIII of the American Recovery and Reinvestment Act of 2009
Biomedical Informatics and Regulatory Review Science Program

- Safety Analysis and Review Support
- Data Standards
- Knowledge Management
- Professional Development/ Internal and External Outreach

Specialized activities: Working with OMP CTTI on innovative trial design (Mobile Clinical Trials) and Real world evidence related activities.

All Things Data !!!

- Jointly review New Drug Application (NDA)
- Data quality/integrity (NDA fileable?)
- Adverse event analyses (e.g., FDA MedDRA queries, time to event)
- Risk/benefit

- Innovation, alignment and feedback with Industry
- Therapeutic Areas (TAs) for psychiatry
- Review consistency and quality
- Standards and patient advocacy organizations
FDA Data Standards – Industry Home Page

FDA Resources for Data Standards

Data Standards Resources
- Structured Product Labeling
- Individual Case Safety Report
- Regulated Product Submission
- Study Data Standards
- Stability Data Standard
- Substance Registration System - Unique Ingredient Identifier (UNII)
- XForms

Data Standards Catalog (XLS) The spreadsheet provides a listing of supported and/or required standards, their uses, the date FDA will begin (or has begun) to support a particular standard, and the date support ends (or will end), the date the requirement to use a particular standard will begin (or has begun) and the date such requirement ends (or will end), as well as other pertinent information. For Centers other than CBER and CDER there may be additional supported standards, please check with the specific Center.

Please note that the first tab in the spreadsheet includes instructions.

Link: https://www.fda.gov/ForIndustry/DataStandards/default.htm
Current FDA Guidance

• 2012 FDASIA amendment
• Guidance
  – Data Standards Catalog (Domains, Terminology, Dictionaries)
  – Electronics Submissions
  – Study Data Technical Conformance Guide
  – FDA Specific SEND Validation Rules
  – FDA Specific SDTM Validation Rules

To make sure you have the most recent versions, please check:
http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
Current FDA Guidance (cont.)

- Adverse Events – MedDRA Dictionary, FDA MedDRA queries
- Medications – WHO Drug Dictionary
- Indications – SNOMed Dictionary
- Labs Tests – LOINC Dictionary
FDA Priority Therapeutic Areas for Development

- FDA, CDISC, and the Critical Path Institute are collaborating on efforts to support development of therapeutic area standards. FDA is also collaborating with HL7’s Clinical Interoperability Council and other consortia to define related clinical concepts. We encourage stakeholders to engage in and, where possible, support these data standardization efforts.
- Questions and comments can be forwarded to CDERDataStandards@fda.hhs.gov.
- PDUFA V Therapeutic Area Standards Initiative Summary Report NEW
- Roadmap for Development of Priority Therapeutic Area Standards (updated 3/20/2018)
- Table of Priority Therapeutic Area Standards (updated 3/19/2018)
- Therapeutic Area Project Plan
Therapeutic Areas Process

Projects follow these process steps as relevant to project scope:

1. Define Scope and Requirements
2. Analyze Alternatives
3. Use an Existing, Change, or Develop a Standard
4. Test Standard
5. Determine Data Standard Adoption
6. Implement Standard

External Processes

Initiation → Development → Internal Review → Public Review → Public Release

FDA SME Interaction

Industry Participation in Standards Testing (as appropriate)

Psychiatry Therapeutic Area Data

Data standards for clinical reviews – Therapeutics Areas (TA)

– 7 Therapeutic Areas (review/data guidance)
  • Schizophrenia ✓
  • Major Depressive Disorder ✓*
  • Bipolar Disorder
  • General Anxiety Disorder
  • Attention Deficit Hyperactivity Disorder (ADHD)
  • Traumatic Brain Injury ✓
  • Post Traumatic Stress Disorder (PTSD)

– Published on FDA external website under technical specifications related to therapeutic area in March 2018.
  • Downstream benefits: enhance efforts for data integration across applications

– PreNDA meeting requests related to standards
  • Standardized set of instructions, now a part of New Safety Review Process deliverable

– Clinical outcomes assessment data standards

Note: ✓ = TA Users Guide Completed, *
  = FDA Guidance Draft
## Psychiatry Therapeutic Areas

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<th>Therapeutic Area</th>
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<tr>
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<tr>
<td>Traumatic Brain Injury</td>
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<tr>
<td>Major Depression Disorder</td>
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Review Division Therapeutic Area
Standard Use Supported

5. THERAPEUTIC AREA STANDARDS

5.1 GENERAL

5.2 SUPPORTED THERAPEUTIC AREAS

5.2.1 Chronic Hepatitis C

5.2.2 Dyslipidemia

5.2.3 Diabetes

5.2.4 Diabetic Kidney Disease

5.2.5 Ebola

5.2.6 Influenza

5.2.7 Kidney Transplant

5.2.8 Malaria

5.2.9 QT Studies

5.2.10 Rheumatoid Arthritis

5.2.11 Tuberculosis

5.2.12 Virology

No Psychiatry Therapeutic Areas Yet !!!
MDD Schizophrenia Traumatic Brain Injury Coming Soon !!!
CDISC Standards Organization (SDO)

https://www.cdisc.org/standards/therapeutic-areas/major-depressive-disorder
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<td>In silico Deep Analytics</td>
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</tbody>
</table>

**Supporting Novel Data - Big Data Flow**
Backup Slides
Medical Officers – Questions and Answers

**Supplementals**
- Clinical Data Analyses
- Labeling
  - Label Tables, etc.
- Safety Issues/Signals Research

**Labeling Changes**
- Clinical Data Analyses
  - Label Tables, etc.

**Consults**
- Clinical Data Analyses
  - Psychiatry (e.g. Suicidality)

Point of contact for all Data related questions.
DPP Clinical Review Steps

New Molecular Entity (NME)

• Preliminary Review – EDR and GS Review (eCTD)
• Study Reports/SAPs/Protocols/Reviewers Guides
• Meet with assigned medical officer (MO)
  – Select Studies for Analyses
  – Compile Issues List
• Clinical Data Analyses – JMP Scripts/JMP Clinical
• Therapeutic Areas

All things Data!
NME – Clinical Review Steps (cont.)

• Assess Adverse Events coding with medical officers
• Adverse Event Analyses – FDA Tools
• Clinical Data Analyses – FDA Scripts
  • Customized Analyses (Treatment/Dose, Phases (OL/DB/FU, etc.)
  • Labeling – Tables, etc. with Clinical Reviewer
  • Tables/Figures/Tabulations (Labs, Vitals, Questionnaires, etc.)
• Research Identified Issues
• Integrated Summary of Safety (ISS)
• Special requests (management/medical officers)
NME – Clinical Review Steps (cont.)

- Per Study: Create Subject Disposition Data Flow – Visits Schedule
- Per Study: Clinical Data
  - SDTM Standards Review
  - ADaM Standards Review
  - Traceability – Study Reports >> ADaM >> SDTM
- Clinical Data Analyses – JMP Clinical – Customized Review

All things Data!
Data Standards: What are we doing?

Other activities: Working with OMP CTTI on Innovative trial design (Mobile Clinical Trials) and Real world evidence related activities, liaison with other offices.
What else are we doing?
Five main areas of work across divisions

- Safety Analysis and Review Support
- Data Standards
- Knowledge Management
- Professional Development/ Internal and External Outreach

Other activities: Working with OMP CTTI on Innovative trial design (Mobile Clinical Trials) and Real world evidence related activities, liaison with other offices (eg. OSP, OMP, OTS and OBI)
KM: Project Deliverables

• Harmonization efforts – future
  – CDISC trial and protocol related domains (~300 variables)
  – NIH/FDA template
  – EMA Enabling Technologies Project collaboration
  – Internal data harmonization

• Auto population of important elements (e.g. inclusion/exclusion criteria) into protocol review template
Consistent approach to improve efficiency of reviews

Safety Analysis and Review Support

Data Standards

Knowledge Management

Professional Development/Internal and External Outreach

Consistency, Efficiency, and Transparency with Data-Driven Approach
The ADBMI Scientific Pursuits

• Data savvy, experienced reviewers
• Mentoring role (asking the right questions, review approach, bridge to the Clinical Data Scientist role)
  – Clinical/review question experts: what are the most common challenging questions we face.
    • How can address these questions with data analyses?
    • What tools to use?
    • How to present that information into labeling?
• Change agents for safety review
• Subject matter expert user feedback for various IT systems development, new tools and technologies for Data analyses (TAs) and Knowledge management
• External facing: inform industry, public, other stakeholders of approach to safety review and data analysis
• Reviewer’s voice for biomedical informatics
Safety Analysis and Review Support

Goal: Establish best practices for safety analyses for consistency, transparency and efficiency

Supporting new safety review process working group

- FDA MedDRA Queries Project
- MIFIA Project
- Adverse event coding evaluation project
- Core tables and figures working group
- Clinical Review work stream
- Attachment B working group
- Data integrity working group
FDA MedDRA Query (FMQ) Project

**Goal:**
Develop standard queries for detecting and summarizing safety signals from clinical trial adverse event datasets

**Methods:**
- Prior efforts in this area were evaluated
  - None of the internal or external efforts met the need
- Develop FMQs based on most frequently labelled terms pulled from > 38,000 labels using natural language processing (NLP)
Adverse Event Coding Quality

- **Problem**: Safety review depends on quality of adverse event coding. Concerning examples are noted frequently, such as
  - Verbatim: ‘patient committed suicide by falling out of window’ coded as ‘Fall’
  - Verbatim: ‘Low grade temperature’ coded as ‘body temperature decreased’

Clinical expertise is needed to ensure accuracy of the mapping, but it is labor-intensive for every medical officer to evaluate thousands of records from clinical trials

- **Goal**: Develop an algorithm to accurately identify those adverse events that have been coded incorrectly

- **Methods**: Combine adverse event data from > 4000 clinical trials
  - Deep learning to develop algorithms medical officers use - subset (10-20%) of events
External Outreach

• American Medical Informatics Association (AMIA)
  – Partnership for Clinical Informatics Curriculum development and Board input

• CDISC (Clinical Data Interchange Standards Consortium)

• Pharmaceutical Users Software Exchange (PhUSE)
  – Study Data Standardization Plan (SDSP) template (published 02/2018)
  – Analysis Data Reviewer’s Guide (ADRG) template (reviewing FR comments)
  – Standard analysis and code sharing project team (white papers)
  – Industry experiences submitting standardized data to regulatory authorities
  – Adjudication working group

• Duke Cardiac Safety Research Consortium (CSRC)
  – Restricted Mean Survival Time project

• Industry outreach
  – At the request of the division, we attend industry meetings/professional society interactions to provide support for data standard related issues
  – e.g. The International Society CNS Clinical Trials and Methodology (ISCTM)

• NIH/NIST/CDC
  – International Natural Language Processing (text mining) challenge
  – Article published Jan 2018 (www.nature.com/scientificdata)
Biomedical Informatics: Review

• Jointly review New Drug Application (NDA)
  – Data quality / integrity (NDA fileable?)
  – AE analyses (e.g., FDA MedDRA queries, time to event)
  – Risk benefit
• Therapeutic Areas (TAs) for Psychiatry
• Innovation, alignment and feedback with Industry
• Share innovative approaches to improve efficiency
• Provide consistency in and across FDA Office of New Drugs review divisions and help produce higher quality reviews
• Nexus to Standards and Patient Advocacy Organizations

All things Data!
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<th>User Guide Section Number</th>
<th>Section Name</th>
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# Published TA User Guides

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Therapeutic Areas Related Guidance

- **Major Depressive Disorder: Developing Drugs for Treatment** (June 2018, Draft)
- **Clinical Trial Imaging Endpoint Process Standards** (April 2018)
- **Multiple Endpoints in Clinical Trials** (January 2017, Draft)
- **Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials** (April 2012, Draft)
- **Adaptive Designs for Clinical Trials of Drugs and Biologics** (September 2018, Draft)
- **Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims** (December 2009)
Division of Psychiatry

Therapeutic Areas – Specific Topics

• Behavior Markers
  – Study Instruments – described in TAUG
  – Patient Reported input – described in TAUG
  – Wearables data (geo/sleep) – data described in TAUG
Division of Psychiatry

Therapeutic Areas – Specific Topics

• Placebo Effect (responders)
  – Study Bias – methodology to compensate (TAUG)

• Drug Effect
  – Efficacy minus Placebo Bias – raise bar (TAUG)

• Dose Effect
  – Drug/Drug, Drug/Disease bias (TAUG)
    • Adjust Efficacy based on lowered dose titrations
Subject Matter Experts for Data Standards Development

• **Therapeutic area specific standards** (TA User Guide development with Coalition for Accelerating Standards and Therapies (CFAST) and Clinical Data Interchange Standards Consortium (CDISC))
  – Point of contact for SME input across OND Divisions
  – Standard analysis Change Control Boards (Across Offices e.g. OCS, OB, DCaRP)
  – Study Data Standardization plan working group

• **Representation on internal committees**
  – Universal Common Data Model: Center/agency level committees
  – PDUFA VI/V Analysis Data Standards committee
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Additional Data Topics

• Genomics Data
• Systems Biology Models (SBML)
• Proteomics Data
• Markers (Bio/Behavioral)
• Real World Evidence (RWE)
• Novel Study Designs
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• Study Design
  – Optimal Experimental Designs
  – Adaptive Designs

• Biomarkers
  – Scanning/Imaging (fMRI, PET, EEG) Data
  – Genetics Data