WaDCCIN, CACIN, WACIN, WINCE, NCACIN, DCDISC, DCCDIN, CDDISC-IN, CDISC-INDC
Meeting

Steve Wilson
CDER/OTS/OB/DB III
SAS Institute, Rockville, MD
Tuesday, January 30, 2007
Steve’s Disclaimer

Views expressed in this presentation are those of the speaker and not, necessarily, of the Food and Drug Administration
Acknowledgements

• Bronwyn Collier, FDA
• Chuck Cooper, FDA
• Don Duggan, FDA
• Gary Gensinger, FDA
• Mark Gray, FDA
• Mina Hohlen, FDA
• Armando Oliva, FDA
• Ed Nevius, FDA
• Norman Stockbridge, FDA
• Ana Szarfman, FDA
• Virginia Ventura, FDA
• Feng Zhou, FDA
Outline

• Background/Motivation
• Strategy
  – eCTD
  – SDTM -- Data
    • SDS
    • Analysis
  – Tools
  – Next steps
• CDISC User Group?
abnl base ALT122/AST83,inc216/14
abnl base ALT49/42,inc ALT104, ha
nl base, rise ALT365/AST153,fall17
base abnl ALT121/AST49,rise 242
base ALT213/AST133PRE with el
base abnl ALT369/AST216, not n
nl base, inc ALT396/AST270,fall
abnl base, ALT243/AST142,fell
abnl base ALT198/ALP322,rise
abnl base ALT108/AST70,rise3
nl base, rise ALT160/AST172,
abnl base ALT173/AST83, not
hep C X15 years, ETOH and
sl base abnl , rise ALT112, th
abnl base ALT214/AST142
abnl base ALT84/AST38, in
C. Cooper, 2005
US Food & Drug Administration

“New” Mission Statement

- The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.

- The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.
FDA Critical Path Opportunities List

• “The Opportunities List outlines 76 Projects to bridge the gap between the quick pace of new biomedical discoveries and the slower pace at which those discoveries are currently developed into therapies.”

• Categories (6) include one called “Streamlining Clinical Trials”
  – (e.g. trial designs, patient response measurements, streamlining the clinical trial process) #34-53
  • Streamlining clinical trials #44 and #45
Critical Path Opportunities

• **Opportunity #44 – Development of Data Standards**
  
  “CDISC is paving the way by developing its Study Data Tabulation Model for describing observations in drug trials.¹ That model could someday encompass observations needed for other types of trials. Health Level 7 and CDISC are working to create standards that can be used for the exchange, management, and integration of electronic healthcare information to increase the effectiveness and efficiency of healthcare delivery².”

• **Opportunity #45 - Consensus on Standards for Case Report Forms**

¹ For more information on CDISC (the Clinical Data Interchange Standards Consortium), see http://www.cdisc.org.
² See also http://www.hl7.org.
Final Guidance for Industry

• Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications

• April 2006

• Public docket 92S-0251 … you then have the option of providing that submission type in electronic format according to FDA guidance …
ICH Guidances

• E3
• E6
• E9
• CTD
• eCTD
• Safety Reporting

<!-- CTD Backbone structures -->
============================================

<!ELEMENT m1-administrative-information-and-prescribing-information (leaf*)>
<!ATTLIST m1-administrative-information-and-prescribing-information %att;>

<!ELEMENT m2-common-technical-document-summaries (leaf*, m2-2-introduction?, m2-3-qualityoverall-summary?, m2-4-nonclinical-overview?, m2-5-clinical-overview?, m2-6-nonclinical-written-andtabulated-summaries?, m2-7-clinical-summary?)>
<!ATTLIST m2-common-technical-document-summaries %att;>

<!ELEMENT m2-2-introduction ((leaf | node-extension)*)>
<!ATTLIST m2-2-introduction %att;>

<!ELEMENT m2-3-quality-overall-summary (leaf*, m2-3-introduction?, m2-3-s-drug-substance*, m2-3-p-drug-product*, m2-3-a-appendices?, m2-3-r-regional-information?)>
Specifications

Many Arnolds

Adapted from S. Woollen
eCTD Guidance

• Reasoning and the CTD
• Structural Components
• Specifications and SDTM

http://www.fda.gov/cder/regulatory/ersr/ectd.htm
Study Reports

One PDF file each for: (E3 reference)

• Synopsis (2)
• Study Report (3 to 15)
• Appendices (16)
  – Protocol and amendments (16.1.1)
  – Sample Case Report Forms (16.1.2)
  – List of IECs IRBs (16.1.3) and consent forms
  – List/Description of Investigators/Sites (16.1.4)
  – Signatures of Principal Investigator…(16.1.5)
  – List/Patients receiving Test Drug/batch (16.1.6)

A. Oliva, 2006
- Randomisation Scheme (16.1.7)
- Audit certificates (16.1.8) and reports
- Statistical Methods (16.1.9)
- Inter-laboratory standardization method (16.1.10)
- Publications based on the study (16.1.11)
- References (16.1.12)
- Discontinued Patients (16.2.1)
- Protocol Deviations (16.2.2)
- Patients excluded from efficacy studies (16.2.3)
- Demographic Data (16.2.4)
- Compliance/drug concentration data (16.2.5)
- Individual Efficacy Response data (16.2.6)
- Adverse Event listings (16.2.7)
- Listing of individual laboratory measurement (16.2.8)

A. Oliva, 2006
• Case Report Forms (16.3)
• Individual patient data listings (16.4)
  – Data tabulations
  – Data listings
  – Analysis datasets
  – Annotated case report forms
  – Subject profiles
  – IND safety reports
Study Data: Folder Structure

- **{module}**
  - **datasets**
  - **{study}**
    - **analyses**
      - **programs**
    - **ecgs**
    - **listings**
    - **profiles**
    - **tabulations**

Replace with module name, e.g., m5

Replace with study identifier, e.g., 123-070
- Contains analysis datasets, annotated CRF, data definition
- Contains program files
- Contains annotated ECG waveform datasets
- Contains data listing datasets, annotated CRF, data definition
- Contains subject profiles
- Contains data tabulation datasets, annotated CRF, data definition

A. Oliva, 2006
Completing the Pyramid

Module 1: Regional Admin Information
- Regional Requirements

Module 2: Quality
- Quality Overall Summary

Module 3: Nonclinical Study Reports

Module 4: Nonclinical Summary
- Clinical Overview

Module 5: Clinical Study Reports
- The CTD

DATA
Current Guidance & Specifications

• Guidance
  – 1999, *Providing Regulatory Submissions in Electronic Format – General Considerations*
  – 2006, *Providing Regulatory Submissions in Electronic Format -- Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*

• Specifications
  – Documents/Files: ICH eCTD; 2006, *Study Data Specifications*
  – SDTM: CDISC
Study Data Specifications

Revision History

<table>
<thead>
<tr>
<th>Date</th>
<th>Version</th>
<th>Summary of Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004-07</td>
<td>1.0</td>
<td>Original version</td>
</tr>
<tr>
<td>2006-03-04</td>
<td>1.2</td>
<td>Update information on annotated ECG waveform data. Delete ecg folder under Specifications for Organizing the Datasets</td>
</tr>
</tbody>
</table>

• Available on ERSR Website
  – Posted 2006-03-04

• Support is currently limited to 3.1
  – Currently plan to support 3.1.1 in FY06 [“almost there”, SW]
FDA News

FOR IMMEDIATE RELEASE
P04-73
July 21, 2004

FDA Announces Standard Format That Drug Sponsors Can Use to Submit Human Drug Clinical Trial Data

The Food and Drug Administration (FDA) today announced a standard format, called the Study Data Tabulation Model (SDTM) developed by the Clinical Data Interchange Standards Consortium (CDISC), that sponsors of human drug clinical trials can use to submit data to the agency. It is expected that this step will lead to greater efficiencies in clinical research and FDA reviews of New Drug Applications (NDAs).
Submission Files

- **CRTs**
  - Data Submitted to FDA

- **Define**
  - Metadata Description Document

- **Data Tabulations**
  - Observations in SDTM Standard Format

- **Data Listings**
  - Domain views by subject, by visit

- **Patient Profiles**
  - Complete view of all subject data

- **Analysis Files**
  - Custom datasets to support an analysis
Study Data Specifications

• Individual subject data listings
  – Data tabulations
    + Data tabulations datasets
    + Data definitions
  – Data listing
    + Data listing datasets
    + Data definitions
  – Analysis datasets
    + Analysis datasets
    + Analysis programs
    + Data definitions
The mission of CDISC 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 in the “World of Standards” 2006

International Conference on Harmonization (ICH)
- EFPIA
- EMEA
- JPMA
- MHLW

U.S. Dept. of Health and Human Services (HHS)
- NIH/NCI
- CDC
- NLM

PhRMA

CDISC
- ADaM
- SDS
- ODM
- LAB

Health Level 7 (HL7)

Reference Information Model
- RIM

BRIDG Model
- Protocol Representation
- eCTD

MedDRA

SNOMED
- LOINC

CDA

World Health Organization (WHO)

= Organization
= Dictionary, Codelist
= Standard
= Model
= Document Standard, or Architecture
Critical Path Opportunities

• **Opportunity #44 – Development of Data Standards**
  - “CDISC is paving the way by developing its Study Data Tabulation Model for describing observations in drug trials.¹ That model could someday encompass observations needed for other types of trials. Health Level 7 and CDISC are working to create standards that can be used for the exchange, management, and integration of electronic healthcare information to increase the effectiveness and efficiency of healthcare delivery².”

• **Opportunity #45 - Consensus on Standards for Case Report Forms**

¹ For more information on CDISC (the Clinical Data Interchange Standards Consortium), see http://www.cdisc.org.
² See also http://www.hl7.org.
Submission Processes

- eCTD
- SDTM
Look at eCTD Guidance

• Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions
  – All submission types
    • NDA, ANDA, BLA, IND, DMF, Annual Reports, Periodic Safety Reports, Advertising and Promotional Labeling
  – Last Published as Final April 2006
  – Preferred Format for Submissions
eCTD Specifications

• eCTD Specifications
  – FDA eCTD Table of Contents Headings and Hierarchy
  – FDA Module 1 Specification
  – FDA Modules 2 to 5 Specification
  – Study Tagging File Specification

• Specifications Available On-Line
  http://www.fda.gov/cder/regulatory/ersr/default.htm
eCTD Changes

• XML-based eCTD Backbone replaces PDF
  Tables of Content

• Increased document granularity in accordance with ICH eCTD agreements

• No requirement to submit technical sections or study reports in paper
eCTD Changes

- EVS processor performs rigid validation of backbone against DTD
  - Requires strict adherence to specifications
  - Do not add or modify leaves within the backbone
- Once a submission is sent in eCTD format all future submissions for the application should be in eCTD format
- Opportunity to use Part 11 Compliant Electronic Signatures

G. Gensinger, 2006
What Doesn’t Change

• Data files submitted in SAS XPORT format
• Documents submitted in PDF Format
• Draft labeling submitted in MS Word
Implementing the Guidance

• Initial Pilot Phase
  – Contact CDER prior to generating pilot submission
  – Review process and make adjustments
• Pilot submission evaluated for technical compliance only unless directed otherwise
• Accepting all submission types, e.g., IND, NDA, Amendments, Master Files, Annual Reports…

G. Gensinger, 2006
## eCTD Submission Metrics

<table>
<thead>
<tr>
<th>Application Type</th>
<th>Applications</th>
<th>Submissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Master Files</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>IND</td>
<td>119</td>
<td>1,312</td>
</tr>
<tr>
<td>NDA</td>
<td>71</td>
<td>1,194</td>
</tr>
<tr>
<td>ANDA</td>
<td>72</td>
<td>236</td>
</tr>
<tr>
<td>BLA</td>
<td>18</td>
<td>599</td>
</tr>
<tr>
<td>Total</td>
<td>285</td>
<td>3,358</td>
</tr>
</tbody>
</table>

G. Gensinger, 2006
What is FDA Doing?

• Working to review & update guidance and specifications
• Working with ICH partners to develop clear interchange criteria
• Working with ICH partners to develop a more flexible eCTD
• Providing reviewer training and support as they need it

G. Gensinger, 2006
SDTM Dataset Considerations

• Submitted as SAS Transport Version 5
• Are not constrained by size limitations
  – Not subject to 100 mb size restriction
  – Do not split into multiple datasets
• Place in folder structure defined in specification

G. Gensinger, 2006
SDTM Dataset Considerations

...Continued

- eCTD Submissions
- eNDA Submissions

G. Gensinger, 2006
Getting Started with SDTM

• Contact CDER to arrange for sample
  – Contact through cder-edata@cder.fda.gov

• Prepare and submit sample
  – Sample is validated against WebSDM CDISC-SDTM Implementation
  – Issues identified prior to regulatory submission
  – Sample is not shared with review division
Your Regulatory Submission

• Discuss with review division well in advance
• Request attendance of OBPS staff at meetings discussing SDTM
• Remember that SDTM is new for everyone
  – Advance notice is critical to CDER’s training efforts.
Your Regulatory Submission

...Continued

• Be sure to include the following when submitting SDTM
  – Specify SDTM version – currently 3.1
  – Identify MEDRA version (if used)
  – Inclusion of annotated CRF very helpful

• Be sure not to include the following when submitting SDTM
  – CRF Listings
  – Patient Profiles
SDTM Implementation Status
June 2006

- Number of submissions increasing
- Most completed submissions in Neurology, Cardio-Renal and Anti-Infectives
- CBER evaluation of SDTM in progress
Issues Affecting Receipt & Review

• Reviewer acceptance of new formats
  – Reviewers like paper

• Failure to comply with specifications
  – Placement of SDTM files
  – Placement of SPL

G. Gensinger, 2006
What FDA Actually Does with eCTDs and the Data -- Review Tools
Prior Data Review Practices

• Analysis
  – Previous practice of analysis generally employed
    • Extensive SAS programming
    • Time intensive database management using tools such as Excel or JMP
  – Limitations
    • Limited number of analyses
    • Resources of statisticians
    • Lack of audit trail when using JMP, Excel
    • Great deal of time was spent by reviewers learning each new NDA’s submission data format and variable names
    • Dependant on user skill/ability
    • Majority of time spent analyzing data instead of interpreting and understanding results of data analyses

C. Cooper, 2005
ADaM Analysis Data

• Can review the study using internal review tool – eReview
• Can re-use the analysis programs
• ADaM analysis data modeling is the mirror of SAP (Statistical Analysis Plan)
• Provide metadata models and examples for analysis dataset used to generate the statistical results
Some Comments About Analysis Datasets

• How many records should be included in the analysis data file?
• It depends on the review needs. At the Pre-NDA meeting, review team and the sponsor agreed that the analysis data set should include the following records
• Example from review of anti-histamine
  • AM TNSS
  • PM TNSS
  • Average AM and PM TNSS
  • Individual TNSS scores

F. Zhou, 2006
Some Comments About the Analysis datasets

- We need SAS codes that created the ADaM data
  - The sponsor included the SDTM and ADaM data structures and sample data sets in the Pre-NDA meeting package.
  - If the source data is not SDTM data, better submit the internal data source.
  - After reviewing the meeting package, we pointed out some errors about data format and requested some new data sets.
  - Through the Pre-NDA meeting, we communicated with the sponsor and made things much easier at NDA review stage
FDA Data Review Tools

• Traditional Review Tools
  – SAS
  – JMP
  – Others, e.g., NONMEM, Excel, Access

• SDTM Review Tools
  – WebSDM
  – Patient Profile Viewer
  – iReview
WebSDM

- **Web-based Submission Data Manager**
- Provides Access, Displays of the Data
- Validates incoming files for conformance with SDTM
- Provides standard analyses of the data (customizable)
- Export data to various file types (.csv, .xpt, .sas, .xls)
WebSDM

...Continued

• Provides audit trail of transformation and reports created by reviewers
• Automatically joins data with other domains (DM, SUPPQUAL)
• Flips data for Findings into horizontal views (e.g., by visit or by test); easier to review
Patient Profile Viewer

- Allows graphical display of clinical trial data for a single patient
iReview

- Flexible analytical capabilities
- Flexible data selection options
  - Predefined
  - Shareable
- Flexible output options
  - Predefined
  - Shareable
  - Supports graphical output
  - Provides patient profile capability

G. Gensinger, 2006
iReview
...Continued
Tool Providers

• eCTD – Global Submit / Review
  – www.globalsubmit.org/

• WebSDM – Lincoln Technologies
  – www.lincolntechnologies.com

• Patient Profile Viewer – PPD
    cs/software/patient_profiles.htm

• i-Review – Integrated Clinical Systems
  – www.i-review.com

G. Gensinger, 2006
Getting Help at CDER
Office of Business Process Support (OBPS)

Regulatory Review Support Staff (RRSS)
White Oak

• Gary Gensinger, Sup.
  – Bob Berger -6th Fl
  – Don Duggan -2nd Fl
  – Don Collier -3rd Fl
  – Mina Hohlen -2nd Fl
  – Zei-Pao Huang -5th Fl
  – John O’Malley -6th Fl
  – Ginny Ventura -5th Fl
CDER- White Oak Campus
Helpful Links

• Electronic Regulatory Submissions and Review
  http://www.fda.gov/cder/regulatory/ersr

• SDTM Questions
  Cder-edata@cdrer.fda.gov

• eSubmission Questions
  esub@cdrer.fda.gov

• CDISC
  http://www.cdisc.org/

G. Gensinger, 2006
What’s Next

• Life Cycle
• Electronic Gateway
• Withdrawal of eNDA Guidance
• New Regulation
Electronic Gateway

• FR Notice: August 8th, 2006
• (FDA) is announcing the availability of the FDA Electronic Submissions Gateway (ESG) for the receipt and processing of electronic submissions provided so that the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH) can receive regulatory submissions electronically.
Electronic Gateway: Options

• Applicants with gateway systems.
  – simple mail transfer protocol (SMTP) with secure multipurpose internet mail extensions (S/MIME)
  – hypertext transfer protocol secure (HTTPS) to provide real-time Internet communication.

• For those without gateway systems
  – WebTrader submission option

• References: FR Notice and talk given by Mark Gray, included in your handouts
Withdrawal of eNDA Guidance
September 29, 2006

• The Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research is announcing the withdrawal of three guidances for industry: “Providing Submissions in Electronic Format—NDAs,” …
• These guidances are being withdrawn because they are no longer consistent with more recent guidance and no longer reflect the agency’s preferred format for receiving electronic submissions.
• Sunset Date: December 31, 2007
Electronic Regulatory Submissions and Review Webpage

www.fda.gov/cder/regulatory/ersr/default.htm#(NDAs)

New Drug Applications (NDAs)

- Regulatory Submissions in Electronic Format; General Considerations. (Issued 1/1999, Posted 1/27/1999)
- Sample Electronic NDA Submission
Insult to Injury?

Page Not Found

We're sorry, but we were unable to find the page you requested. The address of the page may have changed, the page may no longer exist, or you may have typed the address incorrectly.

First, check the URL you entered to be sure it is correct. Make sure that you are using forward slashes (/) and that there are no spaces in the name.

You might find the information you want by checking these locations on our Website:

- Our Home Page
- Our Site Map
- Our Website Index
- Our Search Engine
- The FDA Centers responsible for FDA-regulated products (listed at right)

You may also contact the FDA Website Management Staff to report any problems you have navigating our Website.
Will It Take New Regulation?

• HHS Regulatory Agenda - inventory of all rulemaking actions under development or review (Federal Register, vol. 68, No. 245, 72880)
  – Submission of Standardized Electronic Study Data from Clinical Studies Evaluating Human Drugs and Biologics

• Proposal would revise FDA regulations to require clinical study data to be provided in electronic format and require the use of standard data structure, terminology and code sets.

R. Levin, February, 2005