International Update
22nd Annual Electronic Document Management

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U.S. Department of Health and Human Services
Food and Drug Administration

Overview

- Organizational Changes
- eCTD Activity
- eSubmission Progress & Validation
- HL 7 Regulated Product Submission Update
- Firebird Update
- Electronic Registration and Listing Update

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CDER Organizational Changes

- Reorganization of the Division of Regulatory Review Support
- Implementation of separate teams supporting eSubmission and eReview
  - EDR support staff re-aligned with eSubmission support staff
- Additional personnel resources dedicated to each team
  - Enhancing support for Office of Generic Drugs and Office of Compliance

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eCTD Submissions

May 31, 2006

Application	No. of Applications	No. of Sequences
Master Files	14	17
IND	119	1,312
NDA	71	1,194
ANDA	72	236
BLA	18	599
Total	285	3,358

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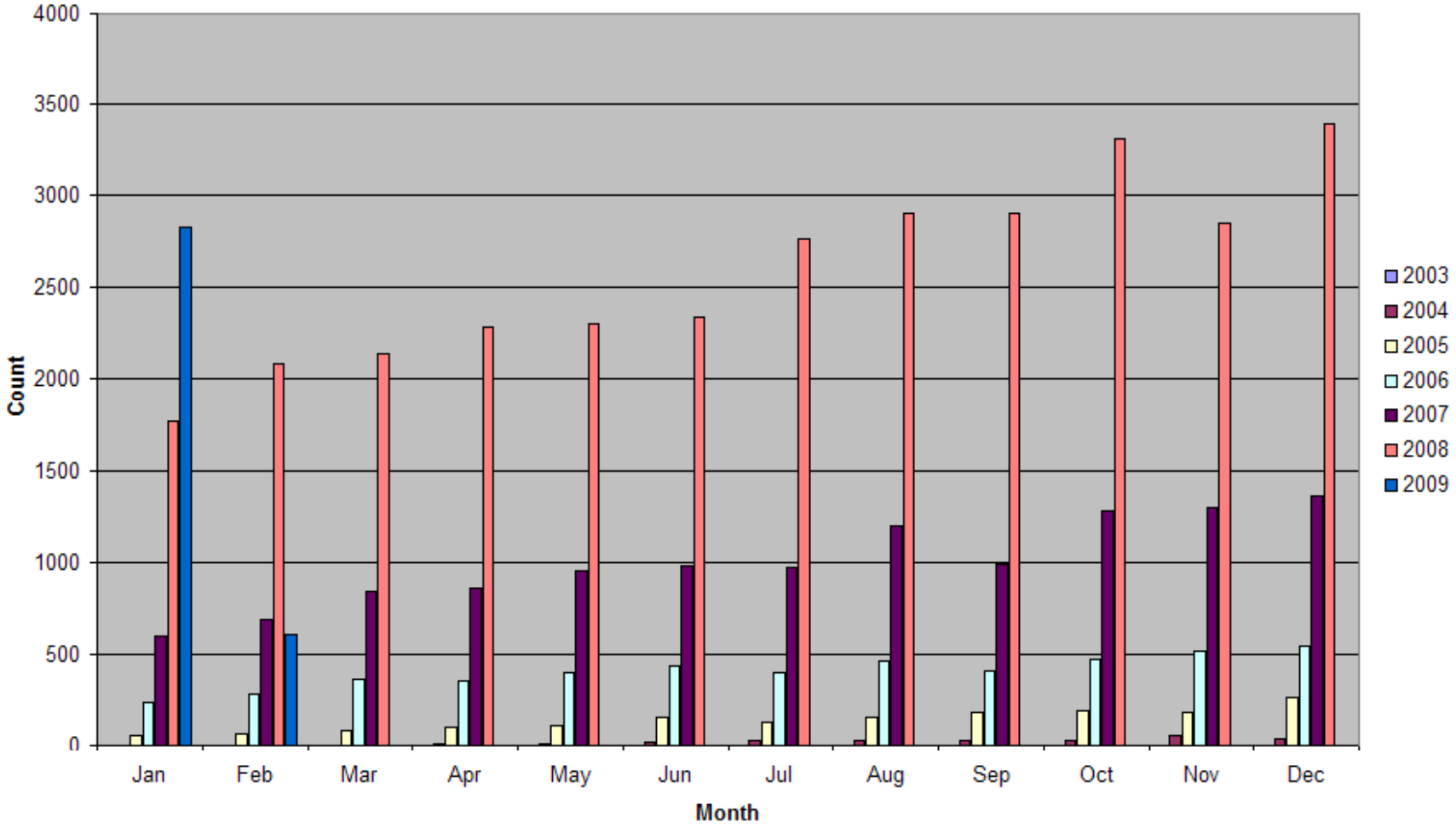
eCTD Submissions

February 9, 2009

Application	No. of Applications	No. of Sequences
IND	1,537	28,219
NDA	1,255	14,076
ANDA	1,550	6,234
BLA	97	4,280
MF	293	591
OTHER	304	570
Total	5,049	53,970

eCTD Submissions

October 2003 - January 2009



eSubmissions – A Larger Perspective

- For 2007
  - Total Submissions 167,490
  - Paper 136,556 (81%)
  - Mixed Paper/Electronic14,025 (8%)
  - Electronic Only 16909 (11%)

Successes and Opportunities

A Great Start

Type	Total	Paper		Mixed		Electronic	
NDA Original Initial	124	15	12.10%	70	**56.45%**	39	**31.45%**
NDA Efficacy Supplements Initial	159	17	10.69%	62	**38.99%**	80	**50.31%**

Progress is Still Needed

Type	Total	Paper		Mixed		Electronic	
IND Original	3241	3039	93.77%	82	**2.53%**	120	**3.70%**

eSubmission Validation

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eSubmission Validation – What is it?

- ASR Validation
- eCTD Tool Validation
- Qualitative Validation

Automated Submission Receipt (ASR)

- ASR
  - Processes your submission
  - Performs Initial Validation
  - Activates eCTD Validation
  - Loads the submission into CDER's tracking system
  - Notifies the Regulatory Project Manager

The Top ASR Validation Issues

- No Electronically Fillable Form Found
- No 356h, 1571, or 2252 Form Found
- Unable to determine location of form
- Application number in us-regional.xml and form do not match
- Mismatch between application type and form
  - Example, an NDA with a 1571.PDF

eCTD Tool Validation

- Identifies and rates the severity of the errors encountered
- Validation specifications have been published

  http://www.fda.gov/cder/regulatory/ersr/validation_specs.htm
- Receipt Date Guidance

  http://www.fda.gov/CDER/guidance/7627dft.htm

eCTD Validation Severity Levels

- High Errors: Submission cannot be accepted
- Medium Errors: Submission can be accepted but review issues may exist that result in submission not being accepted.
- Low Errors: Errors against specification; submission can be accepted

Division Quality Checks

- Hyperlinks/Bookmarks
- Datasets
- Table of Contents Issues

FDA RPS Update

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Schedule - HL7 RPS Release 2

- Divided into Lifecycles and Iterations to facilitate requirements gathering and implementation strategy
  - Lifecycle One – September 2008 through January 2010 Draft Standard for Trial Use (DSTU) – January 2010
  - Lifecycle Two (Release 2.x) – January 2010 -
- Normative Standard – TBD (minimum 6 months from DSTU and maximum 24 months)

FIREBIRD

Federal Investigator Registry of Biomedical Research Data

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FIREBIRD - Background

- FIREBIRD is the first module realized from the vision of the Interagency Oncology Task Force, a partnership of the National Cancer Institute (NCI) and the FDA, to create an electronic platform (e-Platform) for the exchange of clinical research data, to include the submission of regulatory data, as described in the PDUFA IV IT Plan.
- FIREBIRD will be used by investigators to register online when participating in government, academic, or industry trials with the NCI, FDA and other sponsors.
- FIREBIRD stakeholders include: NCI, FDA, Clinical Research Industry, Contract Research Organizations, Institutional Review Boards

FIREBIRD – Features & Benefits

- Automation of investigator registrations in a central database using a secure web-based interface and digital signatures
  - FDA Form 1572
  - Financial Disclosure Form
  - Curriculum Vitae
- Eliminates inefficiencies of paper-based manual processes
- Provides a single Agency-wide solution for multiple Centers
- Permits association of INDs, IDEs, protocols, investigators, CROs, IRBs, etc.
- Facilitates the collection and storage of certain inspection data for CBER, CDER and CDRH regulated studies

Third Party Host

- Federal Government wishes to explore options for further development, operations, and maintenance via a third party non-profit organization
- Discussions with CRIX International has led to formation of a public-private-partnership to create FIREBIRD Next Generation
  - Runs on CRIX Int'l e-platform
  - Expands NCI FIREBIRD
  - Meets NCI, FDA, and industry requirements

FIREBIRD – Progress & Next Steps

- FIREBIRD implemented at NCI – Sept. 2007
- Requirements & work flow for CBER, CDER, CDRH documented – Nov. 2007
- Review by Pre-Market BRB – Jan. 2008
- MOA with CRIX International to develop/host demonstration project drafted – Feb. 2008
- CRIX concept designs for FIREBIRD presented to FDA, NCI – Feb. 2008
- MOA with CRIX and NCI signed. Aug. 2008
- CRIX/FDA/NCI Kick-off Meeting – Sept. 2008
- Development/Testing – Q4 2008 and beyond

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Electronic Registration and Listing

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Electronic Registration and Listing Update

- Voluntary pilot began July 10, 2008.
- FDA has received dozens of official electronic drug establishment registration and drug listing submissions.
- FDA has held several training sessions
- Quality of submissions range from good to excellent
- FDA intends to only accept electronic drug establishment registration and drug listing information beginning June 1, 2009

http://www.fda.gov/cder/guidance/OC2008145(2).pdf

International Standards

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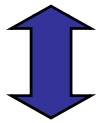
Bioinformatics Board and Data Standards Council

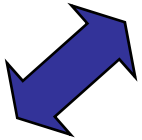
Bioinformatics Board

Identify data exchange or terminology standard need

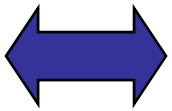


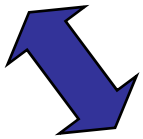
Data Standards Council

Coordinate adoption or development



Working group of FDA experts





Standard Development Organization

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Exchange Standards Organizations

- Development and adoption coordinated with other health-related organizations
  - Accredited, open consensus SDO
    - International Standards Organization (ISO)
    - American National Standards Institute (ANSI)
    - Health Level Seven (HL7)
    - National Council for Prescription Drug Programs (NCPDP)
  - US standards adoption initiatives
    - Consolidate Health Informatics (CHI)
    - Health Information Technology Standards Panel (HITSP)
  - Others
    - Clinical Data Interchange Standards Consortium (CDISC)
    - Global regulatory standards groups (ICH, VICH, GHTF)

HL7 Exchange Standards

- Submission Information
  - Regulated Product Submission Standard
- Product Labeling and Listing Information
  - Structured Product Labeling
- Manufacturing Information
  - Stability Data Standard
- Study Information
  - CDISC HL7 Standards
- Adverse Reaction Reports
  - Individual Case Safety Report Forms
- ECG Information
  - Annotated ECG Waveform Data standard

What Will Standards Mean to Industry?

- Improved harmony across Divisions and Centers
  - Focus is FDA-Wide
- Higher quality submission specifications
  - Formal standards development organizations (SDO), e.g., HL7, ANSI, CEN, have rigorous procedures to ensure the development of quality standards
- Increased ability to influence standards
  - SDOs employ an open process

Enhance FDA Operations

- Increase use of FDA Electronic Submission Gateway
- Leverage metadata accompanying eSubmissions
  - Automate receipt functions
  - Automate validation
  - Automate notification and routing

Enhance Review Capabilities

- Submission Content
  - Janus Study Data Warehouse
  - Integrated Electronic Document Room
- Review Tools
  - WebSDM
  - Patient Profile Viewer
  - iReview/jReview
  - ToxVision
  - GSReview

Enhance Review Capabilities

…Continued

- Improve Decision Support Tools
  - Data Mining
- Standardized Review Templates
  - SMART Template
- Supportive Documentation
  - Electronic Archive of FDA Documentation
  - Enhanced Search Tools
- Review Management Tools
  - Performance Tracking and Analysis
  - Reporting
  - Automated Workflow

Enhance Information Exchange

- Capture Investigator Information
  - Firebird
- Two-Way Communications
  - Use FDA ESG to provide two-way communication
  - SPL Collaboration Portal

Practical Implications

- Standards are specification driven
- Built to achieve interoperability
- Exchange of information requires validation
- Validation demands accuracy

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