Electronic Submissions and the Electronic Common Technical Document eCTD

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Deputy Director
Overview

• FDA’s Vision
• Background: The history of Electronic Submissions at CDER
• eCTD Basics
• eCTD Future Updates
• Standards Activities
• Standards Development Activities
A standards based end-to-end fully electronic receipt, review, and dissemination environment
Why the push towards Electronic Submissions

- Operate seven (7) DRs at five (5) different and dispersed geographical locations
- Processes on average, 20,000 submissions per month across several regulatory programs
- Manage over 170,000 linear feet of paper records (32.2 miles) Processes 6 different and unique submission types
The Evolution of Electronic Submissions

- Informal and reviewer driven
  - Early Activities in 1980s
- Computer Aided New Drug Applications
  - Known as CANDAs
  - Largely during the 1990s
  - Ad-Hoc designs
- 1999 eNDA Guidance Issued
  - Formal eSubmission Program
  - Lowered burden to submit in paper
The Evolution of Electronic Submissions

- 2002 eANDA Guidance Issued
- 2003 eCTD Guidance Issued
  - Following development of eCTD by ICH
  - Start of transition to standards based submission
  - Provided support for all application types including IND, NDA, BLA, ANDA, and Master Files
- 2005 Electronic Labeling
- 2006 Withdrawal of eNDA and eANDA guidances
  - Beginning January 1, 2008 all electronic submissions must be in eCTD format
The Evolution of Electronic Submissions

Paper Only

Paper Supported by CANDA

Electronic NDA/ANDA Supported by Paper

Electronic Only

IND, NDA, BLA, ANDA, MF
Paper Remains an Issue
Growth of IND/NDA Submissions
FY1999 through FY2009

Count

Total Submissions
# eCTD Submissions

as of June 30, 2011

<table>
<thead>
<tr>
<th>Application</th>
<th>No. of Applications</th>
<th>No. of Sequences</th>
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<tbody>
<tr>
<td>IND</td>
<td>3,691</td>
<td>122,274</td>
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<tr>
<td>NDA</td>
<td>1,894</td>
<td>46,707</td>
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<tr>
<td>ANDA</td>
<td>5,390</td>
<td>35,830</td>
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<td>BLA</td>
<td>193</td>
<td>14,146</td>
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<tr>
<td>MF</td>
<td>826</td>
<td>3,379</td>
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<tr>
<td>FDA Internal</td>
<td>684</td>
<td>1,231</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>12,688</strong></td>
<td><strong>223,566</strong></td>
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eCTD Submissions
January 2006 through June 2011
## CDER Investigational New Drugs

<table>
<thead>
<tr>
<th></th>
<th>FY2006</th>
<th>FY2007</th>
<th>FY2008</th>
<th>FY2009</th>
<th>FY2010</th>
<th>FY2011*</th>
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</thead>
<tbody>
<tr>
<td>IND Research</td>
<td>11,749</td>
<td>13,236</td>
<td>11,833</td>
<td>12,863</td>
<td>14,816</td>
<td>11,922</td>
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<tr>
<td>IND Commercial</td>
<td>67,800</td>
<td>74,898</td>
<td>73,784</td>
<td>74,163</td>
<td>77,402</td>
<td>57,699</td>
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<tr>
<td>IND Total</td>
<td>79,549</td>
<td>88,134</td>
<td>85,617</td>
<td>87,026</td>
<td>92,218</td>
<td>69,621</td>
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<tr>
<td>IND Research Electronic</td>
<td>21</td>
<td>114</td>
<td>307</td>
<td>456</td>
<td>721</td>
<td>918</td>
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<tr>
<td>IND Commercial Electronic</td>
<td>1,535</td>
<td>6,960</td>
<td>13,006</td>
<td>24,913</td>
<td>36,794</td>
<td>35,286</td>
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<tr>
<td>IND Electronic Total</td>
<td>1,556</td>
<td>7,074</td>
<td>13,313</td>
<td>25,369</td>
<td>37,515</td>
<td>36,204</td>
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<tr>
<td>IND Electronic %</td>
<td>1.96%</td>
<td>8.03%</td>
<td>15.55%</td>
<td>29.15%</td>
<td>40.68%</td>
<td>52.00%</td>
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<tr>
<td>IND Research eCTD</td>
<td>26</td>
<td>66</td>
<td>217</td>
<td>326</td>
<td>595</td>
<td>783</td>
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<tr>
<td>IND Commercial eCTD</td>
<td>2,215</td>
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<td>35,634</td>
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<td>eCTD % of Total</td>
<td>2.82%</td>
<td>6.34%</td>
<td>14.66%</td>
<td>28.47%</td>
<td>39.92%</td>
<td>51.12%</td>
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<tr>
<td>eCTD % of Electronic</td>
<td>144.02%</td>
<td>79.04%</td>
<td>94.31%</td>
<td>97.66%</td>
<td>98.13%</td>
<td>98.43%</td>
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</tbody>
</table>

* Through 6/30/2011
## CDER New Drug Applications

*Original, Supplement, Miscellaneous*

<table>
<thead>
<tr>
<th></th>
<th>FY2006</th>
<th>FY2007</th>
<th>FY2008</th>
<th>FY2009</th>
<th>FY2010</th>
<th>FY2011*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA Total</td>
<td>21,217</td>
<td>23,310</td>
<td>22,308</td>
<td>22,148</td>
<td>22,443</td>
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<td>NDA Electronic</td>
<td>5,689</td>
<td>8,771</td>
<td>11,272</td>
<td>13,297</td>
<td>15,497</td>
<td>12,904</td>
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<td>NDA Electronic %</td>
<td>26.81%</td>
<td>37.63%</td>
<td>50.53%</td>
<td>60.04%</td>
<td>69.05%</td>
<td>74.62%</td>
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<tr>
<td>NDA eCTD</td>
<td>2,225</td>
<td>2,085</td>
<td>7,410</td>
<td>11,146</td>
<td>14,007</td>
<td>11,775</td>
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<tr>
<td>NDA eCTD % of Total</td>
<td>10.49%</td>
<td>8.94%</td>
<td>33.22%</td>
<td>50.33%</td>
<td>62.41%</td>
<td>68.09%</td>
</tr>
<tr>
<td>NDA eCTD % of Electronic</td>
<td>39.11%</td>
<td>23.77%</td>
<td>65.74%</td>
<td>83.82%</td>
<td>90.39%</td>
<td>91.25%</td>
</tr>
</tbody>
</table>

* Through 6/30/2011
eCTD – Making the Transition
Where are we today…

• FDA has become a standards based organization
  – eCTD is just one standard we have adopted
• Accepting IND, NDA, ANDA, BLA, DMF and related submissions in eCTD format
• Actively support secure electronic transmission of eCTD submission through ESG
Where are we going…

• Required submission of IND, NDAs, and BLAs in eCTD format in 2014/2015

• Begin accepting DDMAC submissions in 2012 (look for announcement)
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,
  – Last Published as Final June 2008
• Preferred Format for Submissions
eCTD Specifications

• eCTD Specifications
  – FDA Module 1 Specification
  – FDA Modules 2 to 5 Specification
  – Study Tagging File Specification
• FDA eCTD Table of Contents Headings and Hierarchy
• Documentation Available On-Line
  
What doesn’t change

• Data files submitted in SAS XPORT format
• Documents submitted in PDF Format
  – PDF 1.4 through PDF 1.7
• PDF should be text-based
  – Understandable that aged legacy reports are scanned
  – Recommend contracts with CROs for current documents should require receipt of reports in text-based electronic format, e.g., MS Word or text-based PDF
• Draft labeling still submitted in MS Word
What Does Change… Continued

- XML-based eCTD Backbone replaces PDF Tables of Content
  - Backbone defines what can be submitted, not what must be submitted
- Increased document granularity in accordance with ICH eCTD agreements
- No requirement to submit technical sections or study reports in paper
- 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
What Does Change

• GSValidate performs rigid validation of backbone against DTD
  – Requires strict adherence to specifications
  – Do not add or modify leaves within the backbone
  – Validation criteria can be found on FDA Website

• Once a submission is sent in eCTD format all future submissions for the application should be in eCTD format
A Few Validation Examples

• Your application number is 6 numeric characters
  – 99-909 is bad
  – 099909 is good

• Your sequence number is 4 numeric digits
  – 909 is bad
  – 0909 is good

• Your sequence number must be unique
Making the Transition

• Convert to eCTD-based submissions at any time
• Starting sequence is sponsor decision
  – Can start at 0000 or next available sequence
• Make move from paper-based to eCTD-based or eNDA-based to eCTD-based
• No requirement to resubmit material previously submitted in paper
• Look for revised specifications for mapping to specifications
• Change is difficult for all
• Communication is key to success
How to Create a Successful Submission
Remember!

• One of your goals is communication
  – Clarity improves reviewability
  – Consider application from reviewer’s standpoint
  – Create document level Tables of Content with appropriate bookmarks
  – Use meaningful file names
  – Use clear concise leaf titles
Have a Pre-Meeting to Discuss the Electronic Submission

• Schedule prior to assembling application, e.g., 6 to 12 months prior to submission of NDA

• Discuss data, datasets, format
Contact Electronic Submission Coordinator

• Initiate contact prior to assembling application
• Arrange participation in eCTD Pilot
• Clarify Guidance questions
• Contact addresses:
  cder-edata@fda.hhs.gov
  esub@fda.hhs.gov
  esubprep@fda.hhs.gov
Submitting Electronic Submissions

• CDER: Office of New Drugs
  – ALL electronic submissions for original applications, supplements, and amendments, must be sent to the Central Document Room

• CDER: Office of Generic Drugs
  – All electronic submission to the OGD document room

• Send only ONE copy of the electronic submission

• Use the correct electronic media and choose type appropriate to size of submission
Submitting Electronic Submissions

• eCTD
  – Should not include any paper
    • If Part 11 compliant electronic signatures are available otherwise only documents requiring original signatures
    • Only exception is Briefing Packages
  – Include all required eCTD files
  – Include all required forms, letters, and certifications
  – Be sure ALL files submitted are referenced in XML backbone
  – Do not use Node extensions
Provide Bookmarks with Intuitive Names

- Good
- Bad
Bookmarks

• Useful to have a bookmarks arranged hierarchically
Provide Hypertext Links

• They enhance navigation and improve reviewability.

• When to provide them?
  – Anytime the text refers to a reference (table, figure, etc.) that is not on the same page.
Updates to eCTD Module 1
Module 1 Updates

• Provide updates based on experience of receiving eCTD submissions since 2003
  – Reorganize and update Administrative Information
    • Including applying one submission to multiple applications
  – Table of Contents

• Changes are consistent with the eCTD NMV Standard

• Allow CDER DDMAC to accept eCTD submissions
Admin Updates

• Added
  – Company id
  – Submission description
  – Contact information (e.g., regulatory, technical)
  – Submission type values
  – Submission sub-type
  – Supplement effective date type
  – Submission id and Submission unit id

• Removed
  – Date of submission
  – Sequence number & Related sequence number
Admin Updates

• New Submissions types
  – Post-marketing requirements and commitments
  – Safety reports
  – Promotional labeling advertising
  – Product correspondence

• Added Submission sub-type to match business requirements
  – Submission sub-types include; presubmission, application, amendment, resubmission
  – Valid Submission sub-type will be based on the Application Type and Submission Type
    – Example
      • nda / labeling-supplement / presubmission
      • nda / labeling-supplement / application
      • nda / labeling-supplement / amendment
      • nda / labeling-supplement / amendment

• Added supplement effective date type (PAS, CBE, CBE-30)
Admin Updates

- Submission numbering
  - Added submission id and submission unit id to replace related sequence number and sequence number
    - Submission id replaces related sequence number
    - Submission unit id = sequence number
    - Submission unit id can be a maximum of six digits
  - For each application number
    - Each “new” submission type: submission id will equal the submission unit id that creates the submission type
      - The submission id will remain the same during the review of the submission type (e.g., original-application, labeling-supplement)
    - Each submission unit id will begin with 1 for an application and will be incremented for each submission to the application
Grouped Submissions

• Will allow for multiple application numbers per submission instance

• One set of documents related to multiple applications

• Currently handled differently by CDER and CBER
Headings & Hierarchy

• Heading attributes
  – Form attribute – will include 3674 form
  – Promotional Material attributes
    • Audience (professional or consumer)
    • Document Type (e.g., request for advisory launch, promotional 503b)
    • Material Type (e.g., print ad, tv, direct mail)

• New Headings
  – Tropical disease priority review voucher
  – Correspondence regarding fast track/rolling review
  – Multiple information amendment
  – Orphan drug designation
  – Development safety update report
  – Postmarketing studies
  – Proprietary names
  – Pre-EUA and EUA
  – General investigational plan for initial IND

• Updates to clarify headings
1.15 Promotional Section

• Additional headings and attributes that will allow for the identification of:
  – Professional Promotional Materials and Consumer Promotional Materials
  – Consumer and Professional material types (e.g., audio, direct mail, kit, print advertisement, television, internet social media, etc.)
  – Type of submission (e.g. advisory, 2253, accelerated approval presubmission)
Tasks & Schedule

• Currently reviewing M1 updates
  – FDA eCTD Table of Contents Headings and Hierarchy
  – eCTD Backbone Files Specification for Module 1
  – US regional DTD

• Public Announcement
  – Federal Register (FR) Notice
  – Comment Period
  – Public Meeting
    • Address comments and answer vendor questions

• Guidance Updates
• Implement new software & begin receiving submissions using new DTD
  – NOTE: DDMAC submissions will require updated M1
eCTD Next Major Version
4.0
eCTD v4

• **eCTD v4 will use the Regulated Product Submission (RPS) exchange message**
  – Health Level Seven (HL7) exchange standard
  – Regulated Product Submission
    • Create one standard (exchange message) that can be used for the submission of any regulated product
    • Scope
      – Animal and Human products
        Including but not limited to food additives, human therapeutics, veterinary products, and medical devices
      – Worldwide use
        Same model for all product types to all regulatory authorities
      – Out of Scope - Document content

• **eCTD v4 is a subset of RPS implemented specifically for human pharmaceuticals**
International Conference on Harmonisation (ICH)
Development of the eCTD v4

• In late 2007, the ICH Steering Committee approved gathering business requirements for the Next Major Version (NMV) of the eCTD

• In October 2008, the SC endorsed the decision to develop the eCTD NMV with a Standards Development Organisation (SDO)
  – Specifically Health Level 7 (HL7), with agreement that the standard must become an ISO/CEN standard
Major Change Items for the eCTD

• A review by ICH M2 resulted in major business requirements being identified
  – Create a two way electronic interaction
  – Have a message structure that better matches the business needs (managing regulatory activities, regulatory status, managing metadata)
  – Better manage current lifecycle model

• FDA
  – Document Reuse / Cross-referencing
Regulated Product Submission

• **Release 1**
  – Develop exchange standard to handle any regulated product
  – HL7 Normative Standard
  – ANSI Standard

• **Release 2**
  – Draft Standard for Trial Use (DSTU)
    • Incorporate FDA PDUFA requirements and additional medical device requirements
    • HL7 Draft Standard for Trial Use (DSTU 1) – January 2010
  – DSTU 2
    • Incorporate ICH requirements and ICH regional requirements
    • DSTU 2 Ballot September 2011

• HL7 RPS documentation and activities posted on RPS HL7 wiki
RPS Message Capabilities

- **RPS Release 1 and Release 2 DSTU 1**
  - Standardize submission format/structure
  - Cross-reference previously submitted material
  - Handle Submission/Document Lifecycle (e.g. append, replace, delete)
  - Handle bundled/global/grouped supplements
  - Correct/modify attributes (keywords)
  - Two-way communication - The regulatory authority (e.g. FDA) will use RPS to send correspondence to the submitter
  - Exchange additional Submission metadata
    - Contact information
    - Submission status
    - Classify submission content/purpose
      - From Sponsor/Applicant (e.g. Meeting Request, New Protocol, Response to Hold)
      - From Regulator (e.g. Information Request, Response to Meeting Request, Approval)

- **RPS Release 2 DSTU 2**
  - ICH and Regional requirements
    - Additional product information
    - Multi-regulator submissions
  - Ability to handle multi-component documents
  - Incorporate RPS R2 DSTU recommendations
RPS 2 DSTU Testing

• HL7 RPS R2 DSTU Subgroup
  – Objectives
    • Create RPS 2 messages to test RPS functionality
      – Identify test scenarios and controlled vocabulary
    • Ensure software vendor participation
    • Determine if modifications are required to the RPS message and Identify issues/questions for implementation
  – Scope: US eCTD human pharmaceuticals
RPS 2 DSTU Testing

• Test scenarios
  – Creation of a DMF (Drug Master File) and three NDAs and supplements through approval
  – CMC Supplement that applies to the three NDAs and the withdraw of one of the supplements before approval
  – Included communication from FDA
  – Testing metadata changes

• Creation of single set of ("source of truth") RPS messages
  – Ensure common understanding on message creation
  – Avoid each vendor developing messages that only can be processed by the vendor software
Implementation of eCTD v4

• Development of Implementation Guides
  – How to use RPS to create eCTD messages
    • ICH Implementation Guide for the eCTD v4
      – The ICH IG is the key document to mark the ICH adoption of the eCTD v4/RPS
    • Regional (e.g. FDA) Implementation Guides
      – Key document that defines the Module 1 implementation specifications for each region
      – Draft ICH & Regional Implementation Guides in development; target completion is November 2011

• Testing (June 2011 – June 2012)

• Normative Ballot (January 2013)

• FDA target implementation for accepting RPS based eCTD submissions is 1st quarter 2014
Standards Development
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)
    - Clinical Data Interchange Standards Consortium (CDISC)
  - US standards adoption initiatives
    - Consolidate Health Informatics (CHI)
    - Health Information Technology Standards Panel (HITSP)
  - Others
    - 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
What Will Standards Mean to FDA?
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
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