



U.S. Food and Drug Administration

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Electronic Submissions and the Electronic Common Technical Document eCTD

Gary M Gensinger, MBA
CDER Office of Business Informatics
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 CANDE



Electronic
NDA/ANDA
Supported by
Paper



Electronic
Only
IND, NDA,
BLA,
ANDA, MF

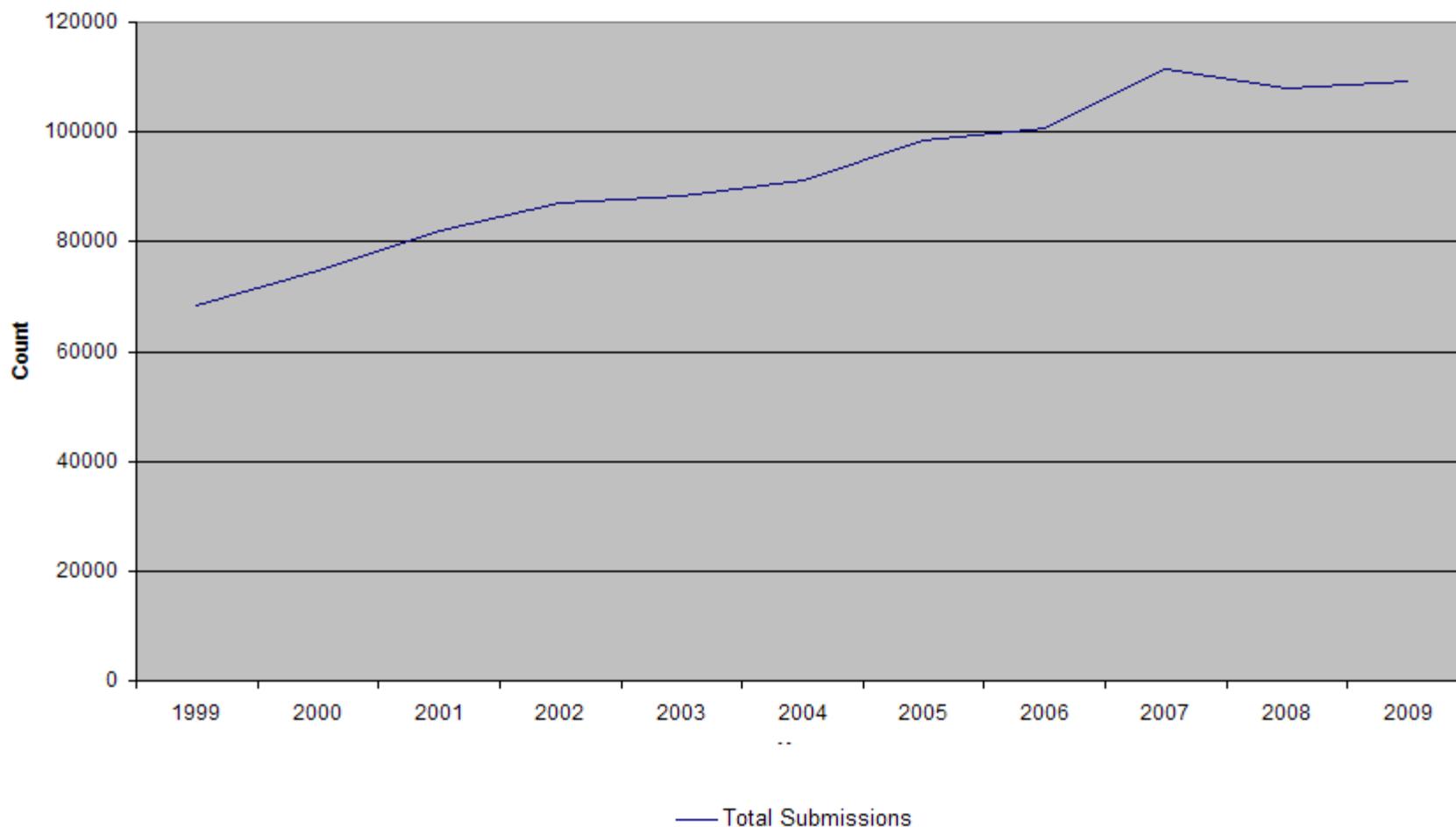
Paper Remains an Issue





Growth of IND/NDA Submissions

FY1999 through FY2009



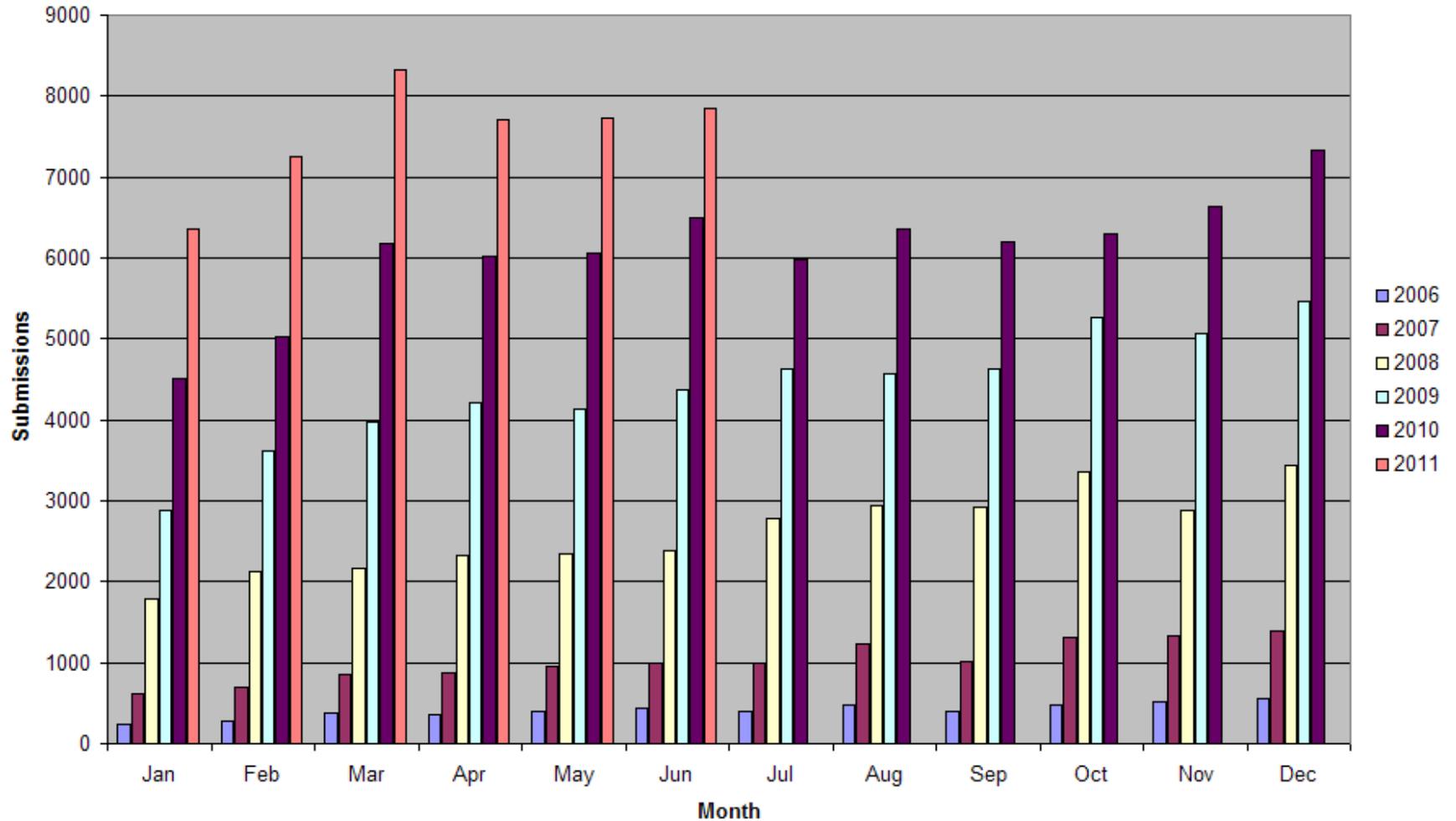


eCTD Submissions
as of June 30, 2011

Application	No. of Applications	No. of Sequences
IND	3,691	122,274
NDA	1,894	46,707
ANDA	5,390	35,830
BLA	193	14,146
MF	826	3,379
FDA Internal	684	1,231
Total	12,688	223,566



eCTD Submissions January 2006 through June 2011





CDER Investigational New Drugs

	FY2006	FY2007	FY2008	FY2009	FY2010	FY2011*
IND Research	11,749	13,236	11,833	12,863	14,816	11,922
IND Commercial	67,800	74,898	73,784	74,163	77,402	57,699
IND Total	79,549	88,134	85,617	87,026	92,218	69,621
IND Research Electronic	21	114	307	456	721	918
IND Commercial Electronic	1,535	6,960	13,006	24,913	36,794	35,286
IND Electronic Total	1,556	7,074	13,313	25,369	37,515	36,204
IND Electronic %	1.96%	8.03%	15.55%	29.15%	40.68%	52.00%
IND Research eCTD	26	66	217	326	595	783
IND Commercial eCTD	2,215	5,525	12,338	24,448	36,219	34,851
IND eCTD	2,241	5,591	12,555	24,774	36,814	35,634
eCTD % of Total	2.82%	6.34%	14.66%	28.47%	39.92%	51.12%
eCTD % of Electronic	144.02%	79.04%	94.31%	97.66%	98.13%	98.43%

* Through 6/30/2011



CDER New Drug Applications

Original, Supplement, Miscellaneous

	FY2006	FY2007	FY2008	FY2009	FY2010	FY2011*
NDA Total	21,217	23,310	22,308	22,148	22,443	17,293
NDA Electronic	5,689	8,771	11,272	13,297	15,497	12,904
NDA Electronic %	26.81%	37.63%	50.53%	60.04%	69.05%	74.62%
NDA eCTD	2,225	2,085	7,410	11,146	14,007	11,775
NDA eCTD % of Total	10.49%	8.94%	33.22%	50.33%	62.41%	68.09%
NDA eCTD % of Electronic	39.11%	23.77%	65.74%	83.82%	90.39%	91.25%

* 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

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>

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 leafs 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 leafs 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

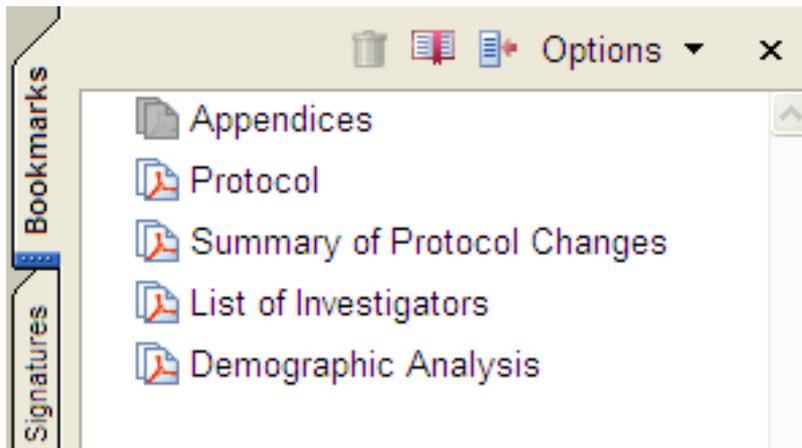
- CDER: Office of New Drugs
 - ALL electronic submissions for original applications, supplements, and amendments, must be sent to the Central Document Room
- CDER: Office of Generic Drugs
 - All electronic submission to the OGD document room
- Send only ONE copy of the electronic submission
- Use the correct electronic media and choose type appropriate to size of submission

Submitting Electronic Submissions Continued...

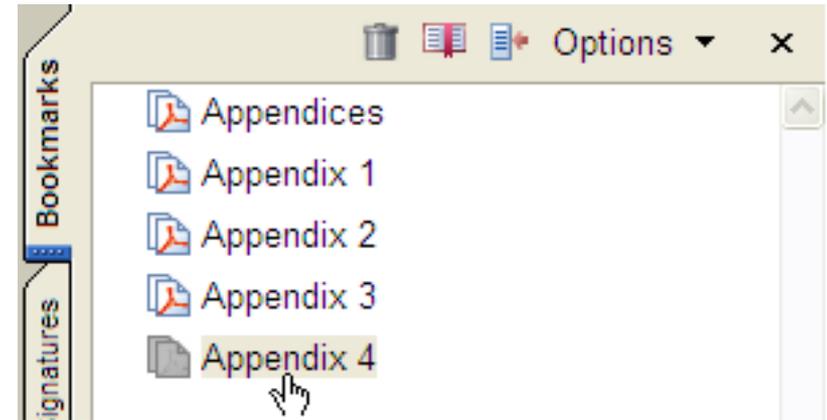
- eCTD
 - Should not include any paper
 - If Part 11 compliant electronic signatures are available otherwise only documents requiring original signatures
 - Only exception is Briefing Packages
 - Include all required eCTD files
 - Include all required forms, letters, and certifications
 - Be sure ALL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

Provide Bookmarks with Intuitive Names

- Good

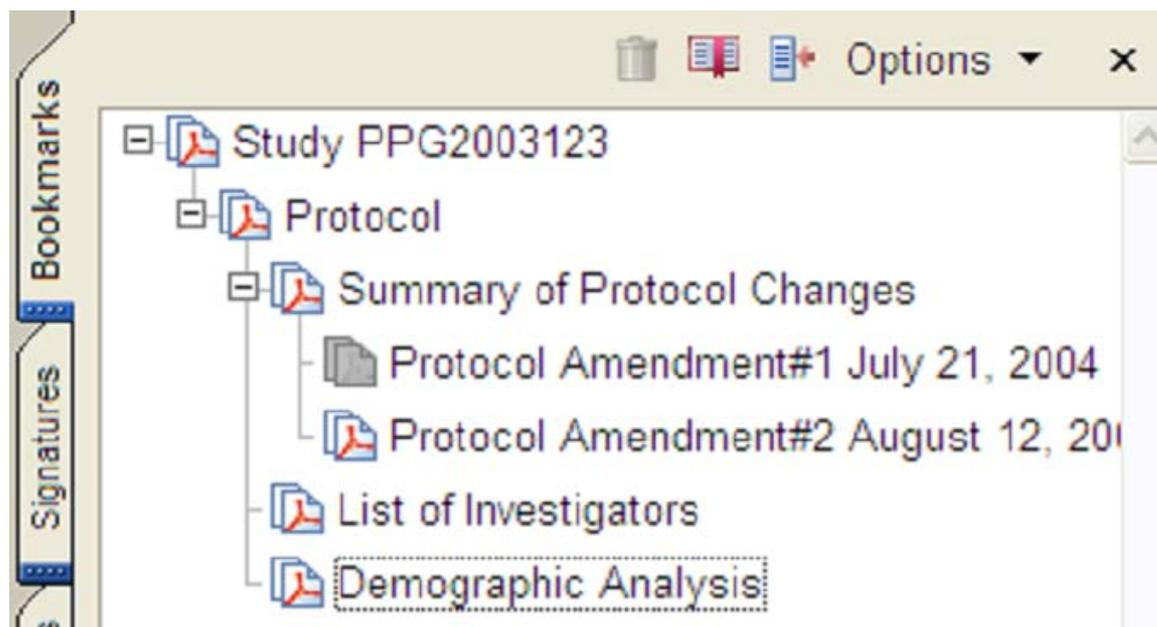


- Bad



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
 - http://wiki.hl7.org/index.php?title=Regulated_Product_Submissions

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



Gary M Gensinger
gary.gensinger@fda.hhs.gov
301.796.0589