Transition to the eCTD

Trying to find the right road

Points to be Covered

- Description of GSK's implementation plan for the eCTD
  - Activity plan
  - Issues that emerge
- Submitting CTDs electronically (absent a Agency review tool)
- eIND as the preferred path for adoption of the eCTD

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eCTD Implementation

- Team formed with representation from USRA, UK, Canada, Germany and Belgium
  - Impact analysis of the eCTD
  - Develop prototype eCTD
  - Interface with the CTD Implementation team
  - Points of contact with external groups
    - PhRMA
    - EFPIA

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Impact Analysis

- Followed on the work already done by the CTD implementation team
- Senior Management endorsement of transition to CTD
- Impact Analysis
  - Authoring (document granularity)
  - Publishing – Table of Content builder
  - Document Management – considerations for meta-data

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Development of a Prototype

- Need to evaluate against representative document/file type rather than “placeholders”
- Need to move beyond the “simple” exercise of creating a table of contents and assess issues relating
  - Cross-references
  - Cross-document linking
  - Dossier navigation
  - Query ability
- Assess the impact of the transition to the eCTD against the existing functionality in eNDA, aMAA that we had prepared

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Development of a Prototype (2)

- Retrofit of a submitted NDA/MAA into CTD
  - Basis for decisions around document granularity, section numbering, cross-reference approach
  - Exercise help drive internal review of draft eCTD specification
  - Test files for the evaluation of tools
  - Intended for internal training
  - Intended for discussion with Agency reviewers

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Key Considerations for the eCTD

- Potential changes in cross-referencing strategies
  - Chem Abstracts vs Vancouver convention
  - Link to files (XML) versus link to pages (PDF)
- Need to consider the appropriate level of granularity for files
  - Clinical Summary (2.7) can be broken down into 6 files (for each major sub-section)
  - Non-Clinical Summary (2.6) can be broken down into 7 files (for each major sub-section)
  - Quality Summary (2.3) can be either provided as one file or as a collection of files (for each major sub-section)
  - Clinical Report is viewed as being comprised of 35 elements/files
- The approach should anticipate life-cycle maintenance and the need to modify or update files post-approval

Some key issues along the way

- Module 1 DTD undergoing change
- Available tools limited by the present (draft) state of the specifications
- Review tool(s) that will be used by Regulatory Authorities
- Interface with Regulatory reviewers – what are the expectations
- “Recommended but not required” in US and Canada
- If we create an eCTD, will the reviewers be ready for it?
- Managing present demands to supply electronic submissions (in CTD format) to the FDA

Electronic submission of CTDs (Interim)

- FDA Guidance document (Sep 2001) allowed for the electronic submission of CTD using NDA/BLA file folder structures
- Transitional model presents “interesting” challenges for dossier publishing
- Different electronic submissions for each region
- Despite limitations, The Interim solution may represent a viable bridging strategy

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Proposed Folder Structure -Module 1

Module	Description	Folder
Module 1	FDA form 356h Cover Letter	NDA Root Directory
Module 1	Comprehensive table of contents	NDA Root Directory
Module 1	**Administrative documents** • Patent Information • Patent Certification • Debarrment Certification • Field Copy Certification • User Fee Cover Sheet • Financial disclosure information • Foreign Marketing Experience • Risk Management Plan	**Other**

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Proposed Folder Structure –Module 1

Module	Description	Folder
Module 1	Prescribing information • Proposed labeling • Labeling History • Package Labeling • Container Labeling Annotated Labeling	Labeling

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Proposed Folder Structure – Module 2

Module	Description	Folder
Module 2	2.1 Table Of Contents 2.2 Introduction 2.3 Overall Quality Summary 2.4 Non-Clinical Overview 2.5 Clinical Overview 2.6.Non-Clinical Summary 2.7 Clinical Summary hypertext links will be provided to narratives, study synopses, and datasets in clinical study reports integrated datasets in Module 5	Summary

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Proposed Folder Structure

Module	Description	Folder
Module 3	Quality	CMC
Module 4	Non-Clinical Study Reports	PathTox

Proposed Folder Structure – Module 5

Module	Description	Folder
Module 5	5.1 Table of Contents 5.2 Tabular listing of studies	**Clinstat**
Module 5	5.3 Clinical Study Reports	
	5.3.1 Report of Biopharmaceutic Studies	**HPBIO**
	5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials	**HPBIO**
	5.3.3 Reports of Human Pharmaokinetic (PK) Studies	**HPBIO**
	5.3.4 Reports of Human Pharmacodynamic (PD) Studies	**Clinstat**

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Proposed Folder Structure – Module 5

Module	Description	Folder
Module 5	5.3.5 Reports of Efficacy and Safety Studies	Clinstat
Module 5	5.3.5.3 Reports of Analyses of Data from More Than One Study, Including Any Formal Integrated Analyses, Meta-analyses, and Bridging Analyses • Tables and listing that support the Clinical Safety Summary will be included. Integrated datasets will also be included in the CRT folder	Clinstat

Proposed Folder Structure – Module 5

Module	Description	Folder
Module 5	5.3.6 Reports of Post-Marketing Experience	Clinstat
Module 5	5.3.7 Case Report Forms and Individual Patient Listings • Datasets (individual study datasets and integrated safety datasets • CRFs	CRT CRF
Module 5	Literature References	Clinstat/Pubs

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Will the eCTD be ready for Prime Time?

- Concept needs to be translated into acceptable specifications
- No perceived loss in functionality (e.g., hypertext links)?
- FDA developing review tool for eCTD (Version 1: Spring 2003)
- Impact of different viewers adopted in different regions
- Will the transition to eCTD facilitate or impair ease of communication between Regulatory reviewers and internal sponsor staff (How did you get to that document?)
- Will the eCTD truly handle maintenance submission?
- Linkage between IND and NDA?

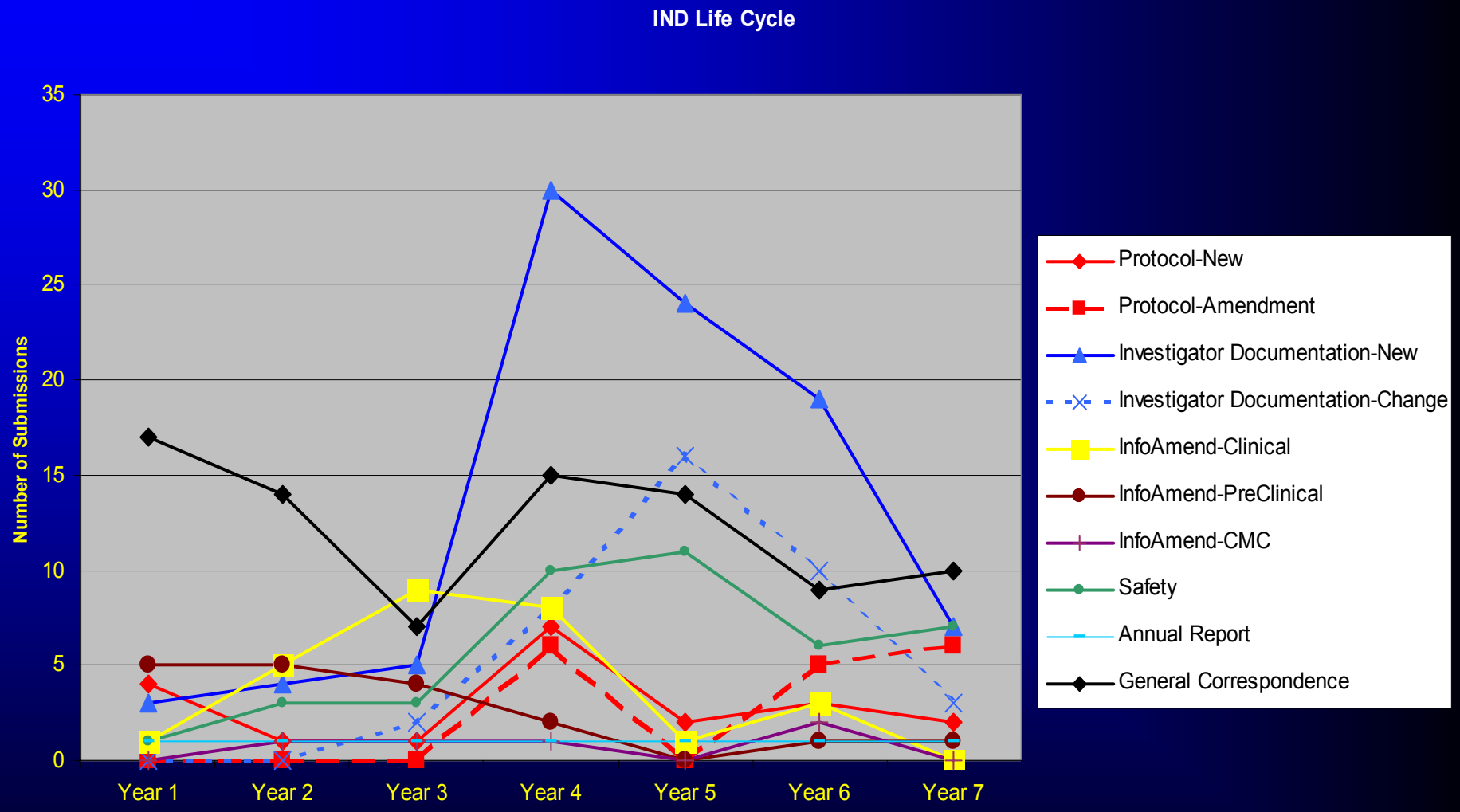
eIND as Transition to eCTD

- Possible resistance to change to the eCTD for NDA
  - Not required in the US
  - Feature comparison vs. eNDA
- eIND provides a stronger business case for the eCTD
  - Dynamic information exchanges
  - Stronger case for the need to re-use and re-present information
- View of the eIND as building the CTD marketing application over time

Case for the eIND

- The management of an “infobase” of product information during development
  - How is this information actively shared within the company?
  - How does the FDA track issues?
- The information can be re-used many times or requires minor modification
- Most of the information will be”resubmitted” as an NDA or BLA
  - How/what is the extent of rework?

IND Life Cycle



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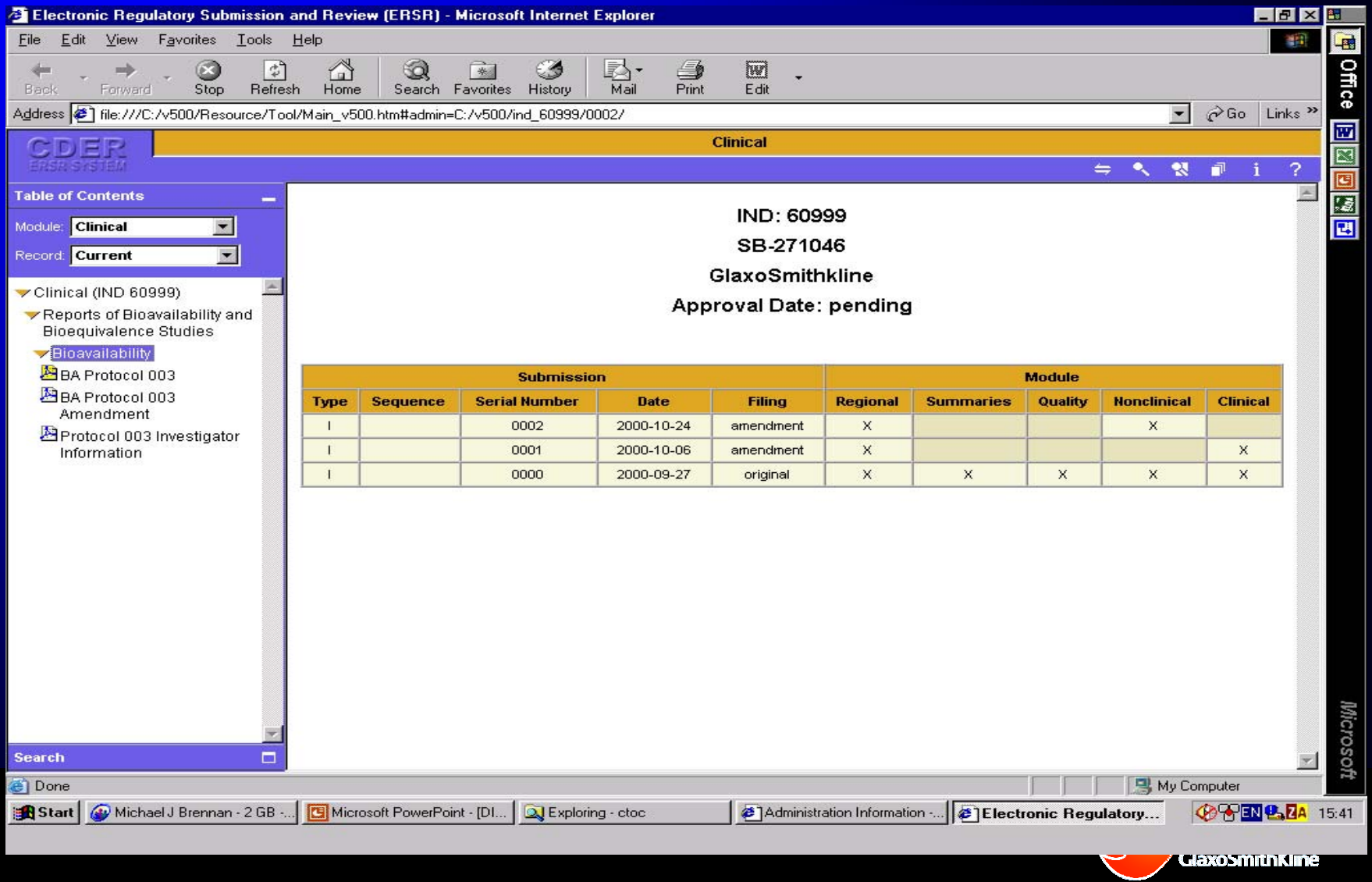
CDER CTOC Prototype for the eIND

- Introduced for consideration in a public meeting in January 2001
- Built around XML-based cumulative table of contents
- Meta data are associated with each file that is submitted
  - Date
  - Type of document
  - Status of document (new, amendment)
- Intended to anticipate the eCTD

Sample CDER CTOC eIND model



Module 1 Organization (July 2001)

m1-1-table-of-contents	
m1-2-reports-documents-summaries	m1-2-1-introductory-statement m1-2-2-financial-disclosure m1-2-3-letters-of-authorization m1-2-4-patents m1-2-5-postmarketing-commitments m1-2-6-user-fee m1-2-7-cover-letters m1-2-7-cover-letters m1-2-8-waivers
m1-3-prescribing-certifications	m1-3-1-Field copy m1-3-2-debarment
m1-4-forms	Form 356h, Form 1571
m1-5-labeling	m1-5-1-viewing-graphic m1-5-1-1-final m1-5-1-2-draft m1-5-1-2-text
m1-6-other	Risk Management, Foreign Marketing History, etc

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Module 1 (Jan 2003)

M1-1 Forms	1571, 356h, 2252, 2253, 3397, 3316,3331
M1-2	Cover Letter
M1-3 Administrative Information	1-3-1 applicant-information , 1-3-2 field-copy-certification, 1-3-3debarment-certification, 1-3-4 financial-certification-disclosure, 1-3-5 patent-exclusivity
m1-4-references	m1-4-1-letter-authorization, m1-4-2-statement-right-reference, m1-4-3-list-of-authorized-persons-to-incorporate-by-reference, m1-4-4-cross-reference-other-applications
m1-5-application-status	m1-5-1-withdrawal-request , m1-5-2-inactivation-request , m1-5-3-reactivation-request , m1-5-4-reinstatement-request , m1-5-5-withdrawal-unapproved-nda , m1-5-6-withdrawal-of-listed-drug , m1-5-7-request-withdrawal-application-approval
m1-6-meetings	m1-6-1-meeting-request , m1-6-2-meeting-background-materials , m1-6-3-correspondence-regarding-meetings

Module 1 (Jan 2003) cont

m1-7-fast-track	m1-7-1-fast-track-designation-request , m1-7-2-fast-track-designation-withdrawal-request , m1-7-3-rolling-review-request
m1-8-special-protocol-assessment-request	m1-8-1-clinical-study , m1-8-2-carcinogenicity-study , m1-8-3-stability-study
m1-9-pediatric-administrative-information	m1-9-1-request-waiver-pediatric-studies , m1-9-2-request-deferral-pediatric-studies , m1-9-3-request-pediatric-exclusivity-determination , m1-9-4-proposed-pediatric-study-request-amendments , m1-9-5-proposal-written-agreement , m1-9-6-other-correspondence-regarding-pediatric-exclusivity-study-plans
m1-10-dispute-resolution	m1-10-1-request-for-dispute-resolution , m1-10-2-correspondence-related-to-dispute-resolution

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Module 1 (Jan 2003) Cont

m1-12-other-correspondence	m1-12-1-pre-ind-correspondence , m1-12-2-request-charge , m1-12-3-notification-charging-under-treatment-ind , m1-12-4-request-comments-advice-ind , m1-12-5-request-waiver , m1-12-6-exemption-informed-consent-emergency-research , m1-12-7-public-disclosure-statement-emergency-care-research , m1-12-8-correspondence-regarding-emergency-care-research , m1-12-9-notification-discontinuation-clinical-trial , m1-12-10-generic-drug-enforcement-act-statement , m1-12-11-basis-submission-statement , m1-12-12-comparison-generic-drug-reference-listed-drug , m1-12-13-request-waiver-vivo-studies , m1-12-14-request-for-comments-for-promotional-material , m1-12-15-environmental-analysis , m1-12-16-request-waiver-vivo-bioavailability-studies , m1-12-17-field-alert-reports , m1-12-18-risk-management-plans

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Module 1 (Jan 2003) Cont

m1-13-annual-report	m1-13-1-summary-nonclinical-studies , m1-13-2-summary-clinical-pharmacology-information , m1-13-3-summary-safety-information , m1-13-4-summary-labeling-changes , m1-13-5-summary-other-significant-new-information , m1-13-6-individual-study-information , m1-13-7-general-investigational-plan , m1-13-8-foreign-marketing-history , m1-13-9-distribution-data , m1-13-10-status-postmarketing-study-commitments , m1-13-11-status-other-postmarketing-studies , m1-13-12-log-outstanding-regulatory-business
m1-14-labeling	m1-14-1-draft-labeling , m1-14-2-final-labeling , m1-14-3-listed-drug-labeling , m1-14-4-investigational-drug-labeling , m1-14-5-foreign-labeling

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Questions as we look ahead

- How will a transition to an “e-cumulative” model impact in-licensing decisions?
  - Documentation completeness and standards needs to be addressed upfront rather than waiting for surprises
  - Who within the organization should be making this assessment?

Questions as we look ahead

- Do we have the right organizations in place to respond to the challenges of fully electronic submissions?
  - What expectations need to be set for document authors?
  - Can Regulatory Affairs be a passive observer in the transition to fully electronic submissions?
  - Do we defer all decisions about hypertext linking to electronic document publishers?

Summary

- Where are we now? – Agreed specifications and and robust viewer (in the wings?)
- Need to look beyond this transition as solely a technology problem – Can we convince reviewers (and sponsor staff) that the eCTD is the way to go?
- Can we build the business case around major marketing applications (NDA, BLA, NDS) or should we look to more dynamic transactional submissions to highlight the benefits of the eCTD?

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