Update on Regulatory Developments around the eCTD in Europe and the Quantum Leap ahead for South Africa

SAPRAA

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Agenda

- Introduction
- Developments in 2012
- Paperless Regulatory Authorities
- Software Vendors
- Submission Ready Documents

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Introduction

- Acknowledgements:
  - Knowledge shared today is knowledge gained at Lorenz' User Conference in Ireland in September 2012 and through the work we do at MRA Regulatory Consultants (MRA) on a daily basis.
  - Thank you SAPRAA for the opportunity to present here today.
- MRA is a docuBridge user and snapshots of builder images are taken from our compilation environment.

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Developments in 2012

- In fact – not just in Europe… - ICH driven activity = Global
  - USA
  - Canada
  - Other regions
- eCTD 4 / eCTD NMV – ICH M8, Endorsed 11 Nov. 2010
  - eCTD 4 = The next major version (NMV) of the eCTD
  - The challenge: to continue supporting the current ICH eCTD v3.2.2 and STF v2.6.1 requirements
  - Implementation Plan for eCTD4 – in 4 Steps
    - Currently in Step 2 – Testing of the ICH eCTD v4.0 DRAFT Implementation Guide v1.0 as of June 2012 – March 2013.
  - Subgroup to M2 Expert Working Group (EWG) responsible for the eCTD Specifications

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eCTD 4 / eCTD NMV & Regulated Product Submission (RPS)

- Setting the scene for document reusability, interoperability between builders and shared review (- the brave new world…)
  - Universally Unique Identifiers (UUI)
    - for sequences in each application
    - for each individual file
    - for communication between Agency and Applicant – portal environment
  - Controlled Vocabulary (CV) – harmonising terminology
    - Drug Substance, Active Substance, Active Ingredient
    - Drug Product, Finished Product

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eCTD 4 / eCTD NMV & Regulated Product Submission (RPS)

- Functional improvements
  - Sequence Replication – content reusability
  - Regulatory Activity – grouping sequences that apply to one activity
  - Access to the entire application from any part of the application
  - Capability to identify which eCTD sequence was used at which step of agency review
  - Cross-referencing files across different sequences in one product's lifecycle and, or across different products
  - Compatibility across regions and across the regional lifecycling methodology / philosophy

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eCTD 4 / eCTD NMV & Regulated Product Submission (RPS)

- Maintaining similarity to the current eCTD file-leaf model in the eCTD NMV with the following exceptions:
  - Lifecycle changes to existing documents will allow only:
    - New
    - Replace
    - Delete
    - Appending documents will no longer be possible.
  - Supporting changes in granularity.

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eCTD 4 / eCTD NMV & Regulated Product Submission (RPS)

- Validation improvements:
  - ensure that the document specification (DTD) remains unchanged – MD5 checksums
  - Should ensure that all files submitted are defined and referenced
  - Support the use of controlled vocabularies for both harmonised metadata and regional metadata
  - Specify date values in an unambiguous manner
  - Integrity of electronic files within an instance
  - Will not negate previous versions of the eCTD. These should remain valid submissions and reviewing tools should be able to review submissions made in terms of eCTD 3.2x specifications even if they are enabled for eCTD NMV.

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eCTD 4 / eCTD NMV & Regulated Product Submission (RPS)

- Data transfer
  - Applicant ➔ Regulatory Authority / Regulatory Authority ➔ Applicant
    - No restriction on mechanism for transmitting - media type/network
    - Supporting 2-way communication
    - Enabling acknowledgement of receipt
    - Traceability and relationship between activities and sequence submission

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ETICS III

- **eCTD Tools Interoperability and Compliance Study**
  - **ICH study of eCTD tools to look at the issues of:**
    - Interoperability:
      - Can an eCTD created by one tool be opened and used by another?
    - Compliance:
      - Is the eCTD compliant with ICH and regional requirements?
  - **11 Tools were tested**

ETICS III

- **Launched February 2010 as a project of the IRISS Interoperability Group**

IRISS = Implementation of Regulatory Information Submission Standards

- Questions/departure points for ETICS III:
  - How are systems, that are capable of meeting regulatory requirements, enable collaboration and establish traceability of content, enabled?

ETICS III

- Current IT technology advances such as Cloud-based systems and mobile devices, are emerging to enable globally-distributed staff to acquire, create, and manage regulated content that is universally accessible, reportable, and is extensible.

- ETICS III is qualifying the interoperability and validation capabilities of current regulatory submission technologies – the CTD builders (as we know them).

Further Developments in Europe - 2012

XEVPRM / XEVMPD

- Late in 2010, EC Directives were implemented in an effort to improve the safeguards to public health.
- The regulations mandated that the EU Agencies have and maintain databases for medicinal products that:
  - Provide access to the approved package leaflets in language that is considered to be understandable to the reader.
  - Access must be granted to:
    - all Member States
    - the general public
    - health-care professionals
    - marketing authorisation holders (MAH)

Further Developments in 2012

XEVPRM / XEVMPD

- 2 July 2012 was the deadline for MAHs to electronically submit the required information to the Agencies
- The technical specifications of which were published in March 2012 by the EMA – all 401 pages of it…
- 2 Technical Environments:
  - EudraVigilance Production Environment
  - EudraVigilance External Compliance Testing (XCOMP) Environment

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Further Developments in 2012

XEVPRM / XEVMPD

- The database generated enables:
  - traceability of any of the following - in the event of a technical concern, counterfeit alert, adverse reaction / pharmacovigilance issue:
    - Active Substances
    - Excipients
    - Manufacturers
    - Marketing Authorisation Holders
  - corrective and preventive action to be taken by an Agency where for example; suspect quality of an active substance can be traced to all products that could potentially be affected - throughout the European Region.

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Further Developments in 2012

AMNOG

- Nutzendossier (Value Dossier) – Germany
  - Requires the submission of pharmaco-economic studies and data as motivation for the need for the product in the market place
  - To be submitted at the time of submitting an application for registration
  - Currently not a requirement for submissions made into the EMA – Centralised Procedure for Mutual Recognition

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Further Developments in 2012

END OF THE PAPER ERA IN EUROPE …?

- By 2013 the German Regulatory Authorities will no longer accept paper submissions.
- What will this mean for the EMA for whom the German Authority is a vitally important Rapporteur and technical resource.
- EDQM has been paperless since 2010.
- The NEES seems finally to have been abandoned.

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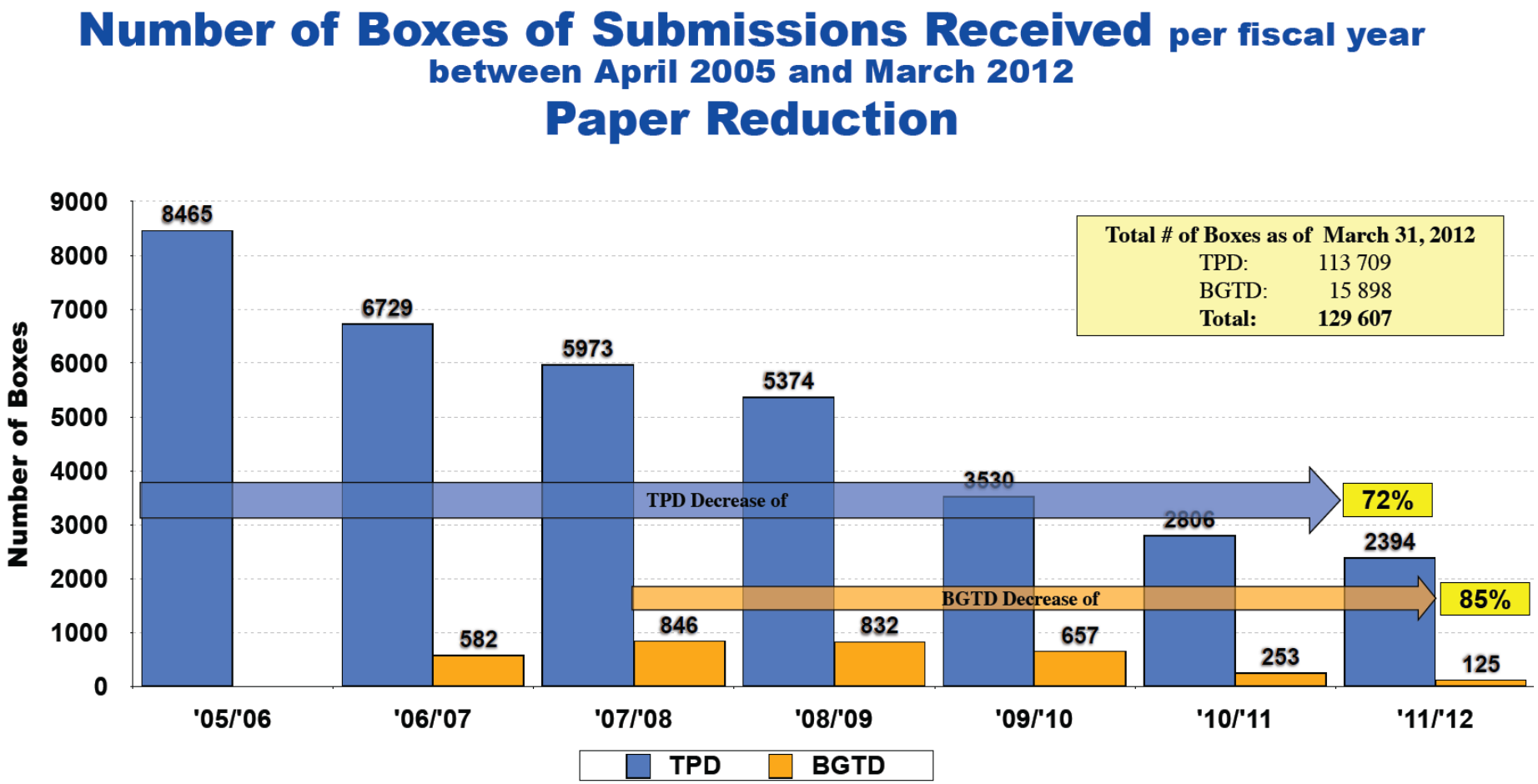
The eCTD in CANADA



TPD = Therapeutic Products Directorate
BGTD = Biologics & Genetic Therapies Directorate

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Software Vendors

- CTD builders are critical in alleviating the admin burden involved in compiling submissions. They reduce mistakes and allow us to reuse our data.
- Manage to integrate the ever-changing submission requirements globally into their tools.
- Keep up to date with the regional specifications and provide the validation tools.
- Provide databases that are customised to the regulatory environment and help us manage the information that we are the custodians of.
- Provide valuable training from a “futuristic” perspective which helps us to think and plan ahead.

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Submission Ready Documents

- Think of the future - Think eCTD!
- Granulate and name in accordance with ICH requirements and the regional requirements.
- Ensure that you will not need to rework documents unnecessarily in the future.
- It may take a little bit more time to do this, but you can train administrative assistants to help with this work.

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Module 3

Module 3 Note 1	3.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD		
	3.2	3.2.S Note 2	3.2.S.1	3.2.S.1.1
				3.2.S.1.2
				3.2.S.1.3
			3.2.S.2	3.2.S.2.1
				3.2.S.2.2
				3.2.S.2.3
				3.2.S.2.4
				3.2.S.2.5
				3.2.S.2.6
			3.2.S.3	3.2.S.3.1
				3.2.S.3.2
			3.2.S.4	3.2.S.4.1

60	Number	
	Title	*Analytical Procedure-3*
	Element	m3-2-s-4-2-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s42-analyt-proc/*analytical-procedure-3.pdf*
	Comment	
61	Number	3.2.S.4.3
	Title	Validation of Analytical Procedures
	Element	m3-2-s-4-3-validation-of-analytical-procedures (name, manufacturer)
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc
	Comment	The example below shows how a multiple file approach, where a separate file is provided for each analytical procedure, can be organized. CTD numbering is not defined below this level (e.g., 3.2.S.4.3.1).
62	Number	
	Title	*Validation of Analytical Procedure-1*
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc/*validation-analyt-procedure-1.pdf*
	Comment	
63	Number	
	Title	*Validation of Analytical Procedure-2*
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc/*validation-analyt-procedure-2.pdf*
	Comment	
64	Number	
	Title	*Validation of Analytical Procedure-3*
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc/*validation-analyt-procedure-3.pdf*
	Comment	
65	Number	3.2.S.4.4
	Title	Batch Analyses (name, manufacturer)
	Element	m3-2-s-4-4-batch-analyses
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s44-batch-analys
	Comment	
66	Number	3.2.S.4.4

Submission Ready Documents - ICH

- **PDF:**
  - Version 1.4 – Agencies don't need additional software to view documents
  - Should be rendered not images/scans
  - Optical Character Recognition (OCR) enabled
  - Not secured / password protected
    - one should be able to select, copy and paste sections out of a document into another document if needed.
    - Secured/protected documents fail validation!
  - Minimum resolution – text 300 dpi (dots per inch); photos 600 dpi
  - Do not shrink documents/reduce size at the cost of legibility or quality.
  - Compress for storage or transfer purposes if needed.

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Submission Ready Documents - ICH

- **Fonts:**
  - Ensure that only standard fonts are used
  - Embed fonts
  - Text size – minimum size equivalent to Times New Roman 12
  - Table text size – minimum size equivalent to Times New Roman 10

Company logos are not to be inserted into headers/footers. - Even if the logo is only 5b in size, imagine that multiplied across a 50 000 page submission.

Company logos are acceptable on letterheads and signed reports.

The Quantum Leap…

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Current Master Outline

0000 | 1 - 3

- 0008
  - 1 Administrative Information and Prescribing Information
    - European Union (v1.4)
      - 1.0 Cover Letter
        - Cover Letter by Country
          - Cover Letter
          - Cover Letter 0001
          - Cover Letter 0002
          - Cover Letter 0003
          - Cover Letter 0004
          - Cover Letter 0005
          - Cover Letter 0006
          - Cover Letter 0007
          - Cover Letter 0008
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country
      - 1.2 Application Form
        - Application Form by Country
        - Application Form by Country
        - Application Form by Country
        - Application Form by Country
        - Application Form by Country
        - Application Form by Country
        - Application Form by Country
        - Application Form by Country
        - Application Form by Country
      - 1.3 Product Information
      - 1.4 Information about the Experts
      - 1.5 Specific Requirements for Different Types of Applications
      - 1.6 Environmental Risk Assessment
      - 1.7 Information relating to Orphan Market Exclusivity
      - 1.8 Information relating to Pharmacovigilance
      - 1.9 Information relating to Clinical Trials
      - 1.10 Information relating to Paediatrics

Sequence Master Outline

- 0000
  - 1 Administrative Information and Prescribing Information
    - European Union (v1.3)
      - 1.0 Cover Letter
        - Cover Letter by Country
          - Cover Letter
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country
      - 1.2 Application Form
      - 1.3 Product Information
      - 1.4 Information about the Experts
      - 1.5 Specific Requirements for Different Types of Applications
      - 1.6 Environmental Risk Assessment
      - 1.7 Information relating to Orphan Market Exclusivity
      - 1.8 Information relating to Pharmacovigilance
      - 1.9 Information relating to Clinical Trials
      - 1.10 Information relating to Paediatrics
      - Additional Data
  - 2 Common Technical Document Summaries
  - 3 Quality
  - 4 Nonclinical Study Reports
  - 5 Clinical Study Reports
- 0001
- 0002
- 0003
- 0004
- 0005
- 0006
- 0007
- 0008
  - 1 Administrative Information and Prescribing Information
    - European Union (v1.4)
      - 1.0 Cover Letter
        - Cover Letter by Country
          - Cover Letter 0008
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country
        - Cover Letter by Country

The Quantum Leap…

A change in perspective… and a change in attitude!

The future of regulatory compliance is the eCTD.

We need to ensure that we have the right tools and the right people to do the work in an ever-evolving environment.

It's time to engage!

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Thank You!

Questions?

Or maybe later…

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