Practical Experience & Proposal for eCTD Implementation

Regulatory Information and & Technology Expert Group

European Federation of Pharmaceutical Industries and Associations
www.efpia.eu

eCTD Implemention in the ICH Region

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Agenda

- Deck objectives
- Summary Recommendations
- Background to eCTD
- CTD and eCTD Structure and Format
- eCTD global map of activity
- Implementation Perspectives and industry recommendations
- Handling Different Strengths and Dosage Forms
- eCTD for registered products
- Maintaining the eCTD
- Key Summary Recommendations

Objectives

Deck objectives

- This deck forms the basis of EFPIA (European Foundation of Pharmaceutical Industry and Associations) RITEG (Regulatory Information and Technology Expert Group) core deck that provides awareness and industry recommendations on the scope, adoption and implementation of eCTD (electronic Common Technical Document).

- The intent is to promote this deck as a “self serve” material for use by industry in communication with worldwide regulatory authorities.

- This deck is updated twice yearly in 1Q and 3Q.

Summary EFPIA Recommendations

- EFPIA fully supports the adoption of ICH eCTD and recognises the many benefits, including:
  - Better information management, document storage, retrieval, archiving
  - Electronic working, searching, cross referencing
  - Management of product information in the dossier over time
- EFPIA recommendations in these slides:
  - Collaboration – regulator<>industry<>software vendors
  - Timelines – allow time for transition (minimum 12 months)
  - Consistency with existing standards
  - Baselines recommended only
  - Maximise use of technology – electronic gateways and automated upload, use of metadata.

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Background to eCTD

International Conference on Harmonisation (ICH)

ICH Members

- Permanent Members:
  - Founding regulatory members: EC, Europe; MHLW/PMDA, Japan; FDA, US
  - Founding industry members: EFPIA, JPMA, PhRMA
- Standing Regulatory Members:
  - Health Canada, Canada; Swissmedic, Switzerland
- Regulatory Members:
  - ANVISA, Brazil; CFDA, China; MFDS, Republic of Korea
- Industy Members:
  - BIO; IGBA; WSMI

ICH Observers

- 23 Observers:
  - Including Roszrdravnadzor, Russia; IFPMA, WHO, TGA, Australia; EDQM, EU; APEC, ASEAN;

http://www.ich.org/

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CTD Definition

- The Common Technical Document (CTD) defines the organisation of a **paper** submission that is accepted by regulatory authorities in scope

- ICH Multidisciplinary Expert Working Group (M4 EWG) defines CTD

- Out of scope: Guidelines for local (national/regional) content requirements

eCTD Definition

- The electronic Common Technical Document (eCTD) is the **electronic presentation** of the CTD. It is a standard format for text, data, and images and facilitates electronic transmission of information from transmitter to receiver.

- ICH M8 Multidisciplinary Expert Working Group (EWG)/Implementation Working Group (IWG) defines eCTD format and specifications to manage common documentation
  - Current eCTD is v3.2.2
  - Next version of eCTD is v4.0 (global adoption from 2020 onwards)

- Out of Scope: Guidelines for regional requirements

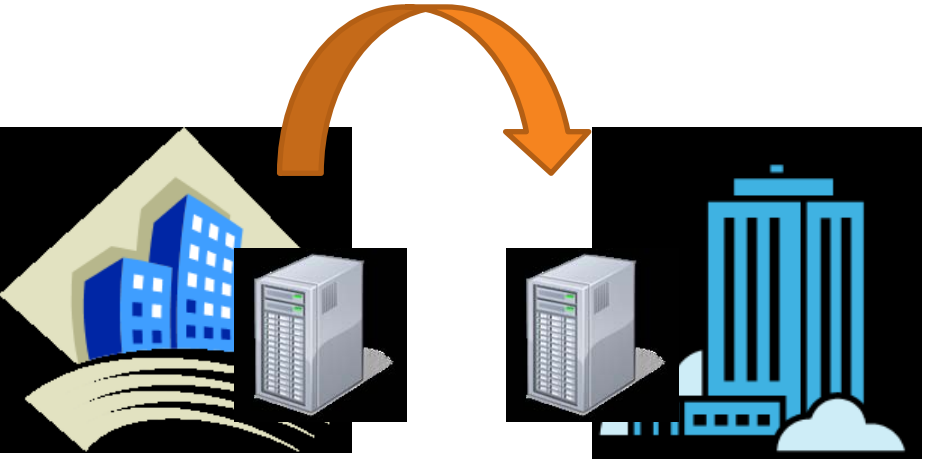
Before eCTD

CTD dossier in bookrack

Reviewer‘s desk

After eCTD

eCTD is a standard format for exchange of data and metadata



Industry - gateway/portal - Agency

eCTD dossier in server

Reviewer‘s desk

Benefits of eCTD

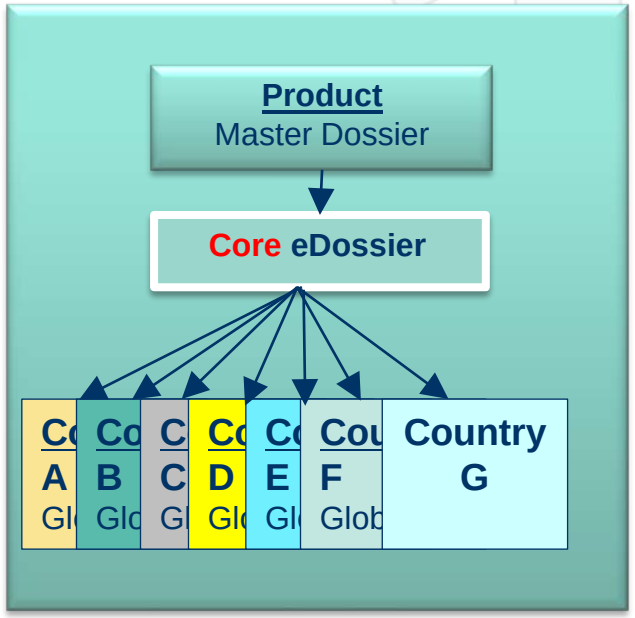
- Expectation was:
  - High availability
  - Easy view / navigation
  - Fast retrieval
  - Lifecycle support
  - Replaces paper
- Results are:
  - Expected advantages have been met
  - Contribute to improvement of:
    - Data quality
    - Reusability
    - Faster and secure access to dossiers via gateway or portal
    - Lifecycle management

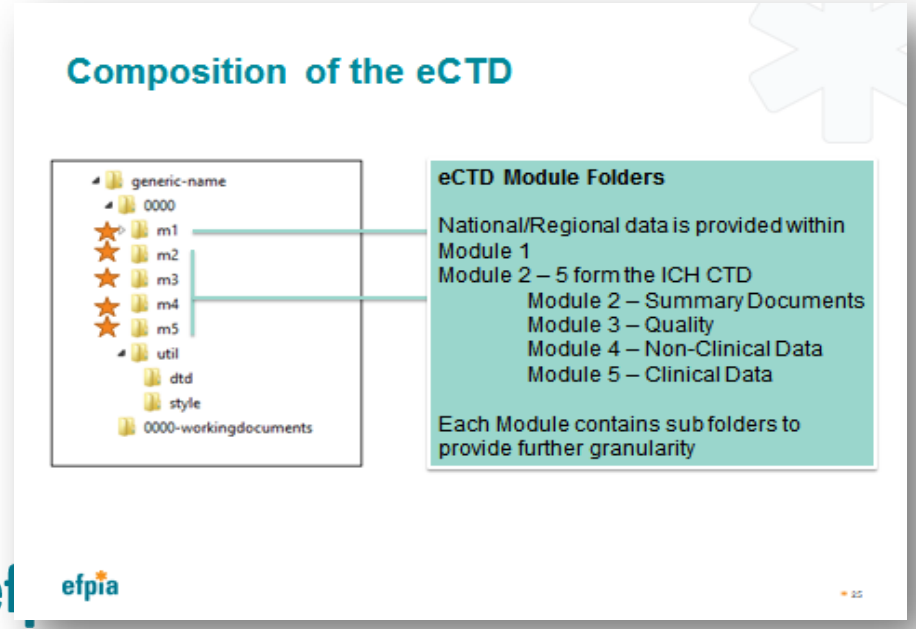
Challenges with eCTD

- eCTD adoption has provided Health Authorities and Industry with challenges;
  - Limited knowledge to its adoption that impacts uptake
  - Software / IT infrastructure / Interoperability
  - Transition plans for new and registered products
  - Clear communication and interpretation of requirements
  - Management and implementation of new specifications

Master Dossier Concept

- Initial submission in one or more markets
- Subsequent submissions sourced from this initial dossier (if available)
- Standards (ICH) enable cloning, targetted rework and customization





eCTD Module 1 enables customisation through location of country specific documentation

The CTD and eCTD

Structure and Format

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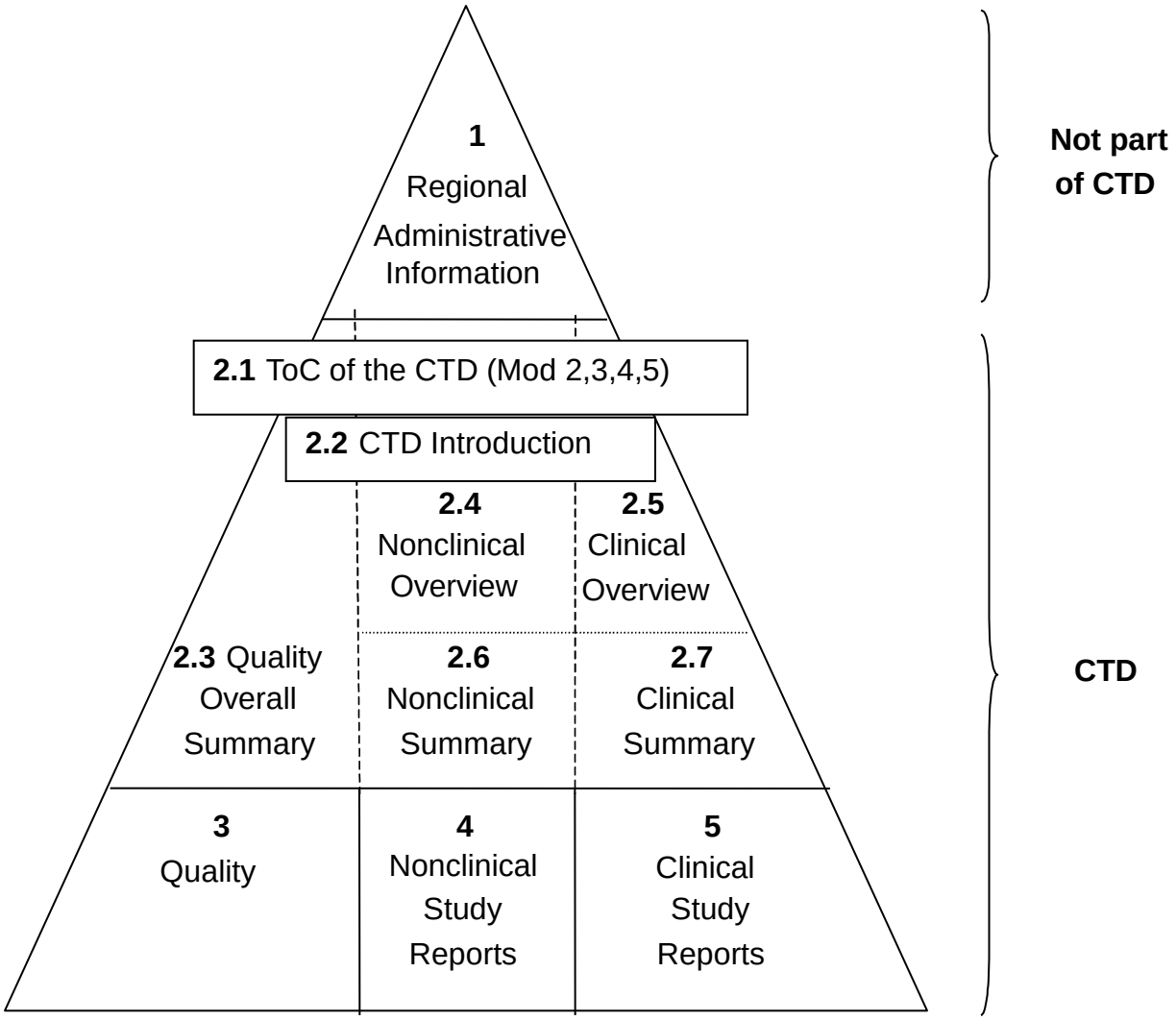
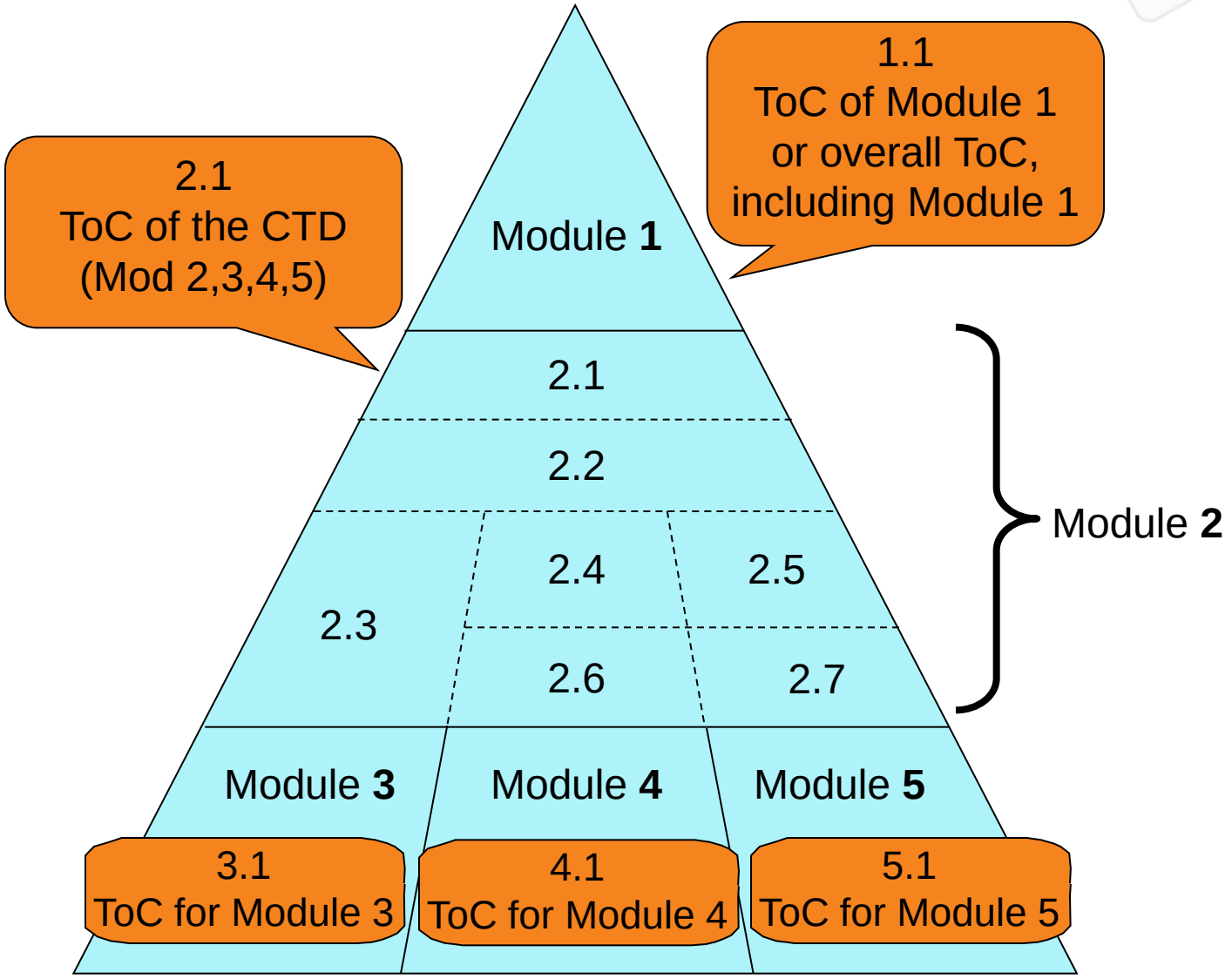
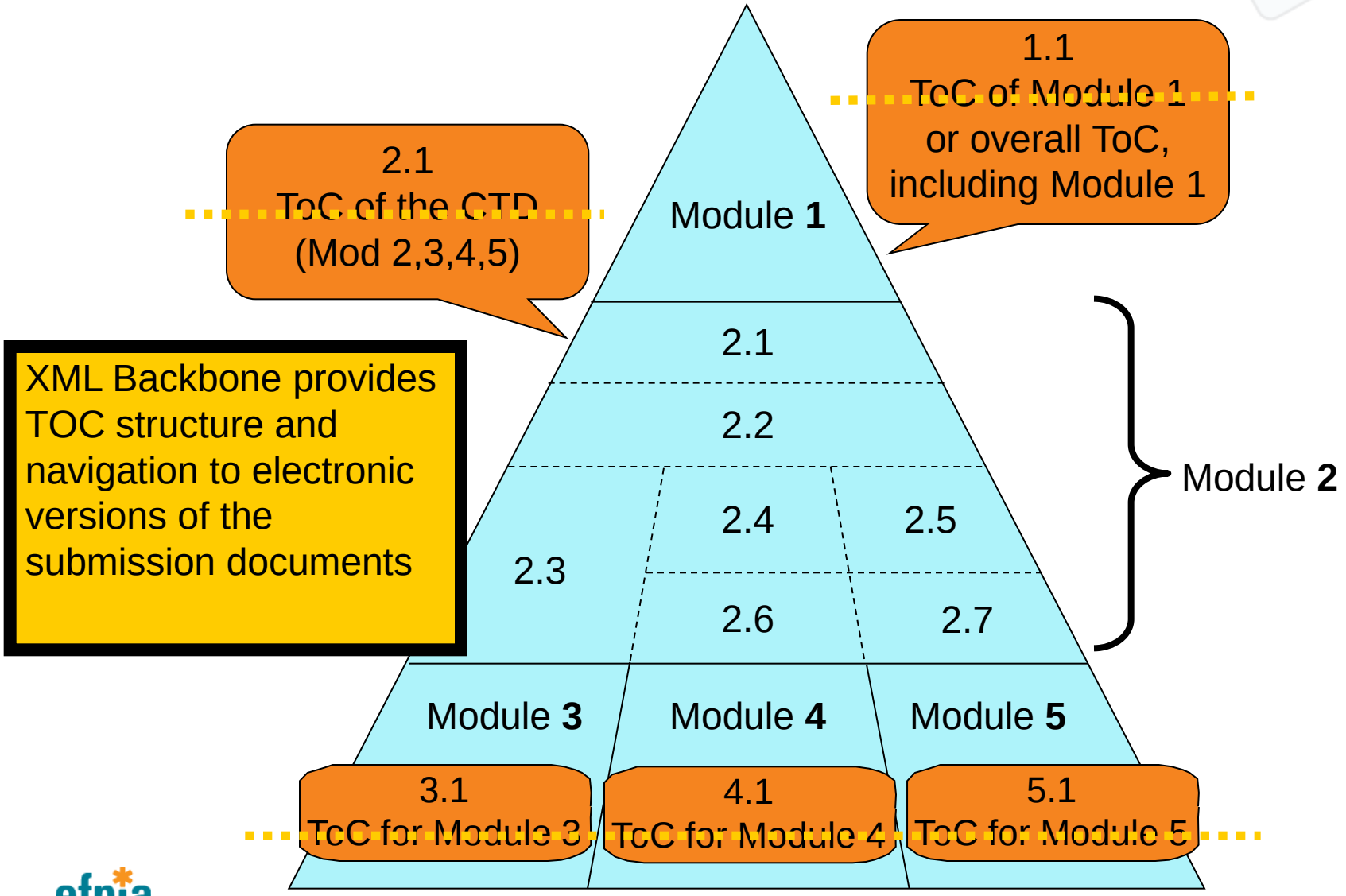
The CTD Pyramid



The CTD Pyramid

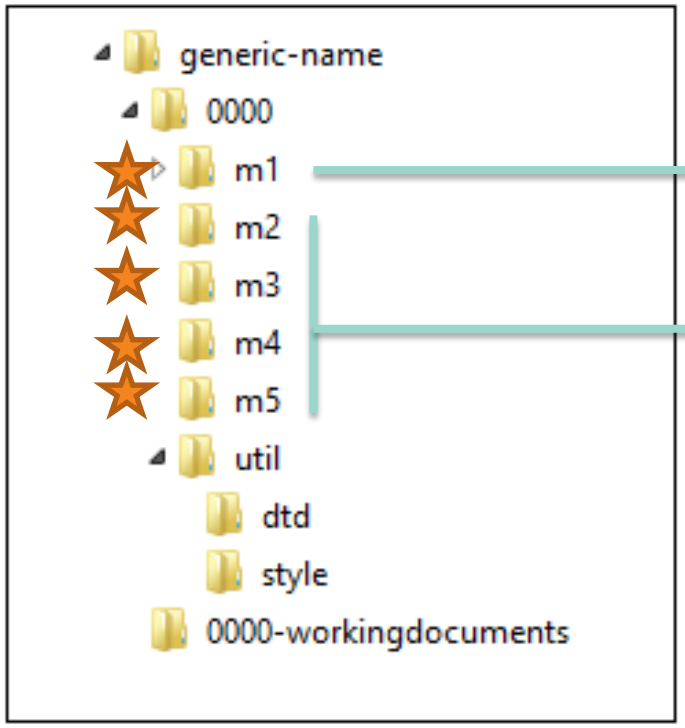


The eCTD



XML Backbone provides TOC structure and navigation to electronic versions of the submission documents

Composition of the eCTD



eCTD Module Folders

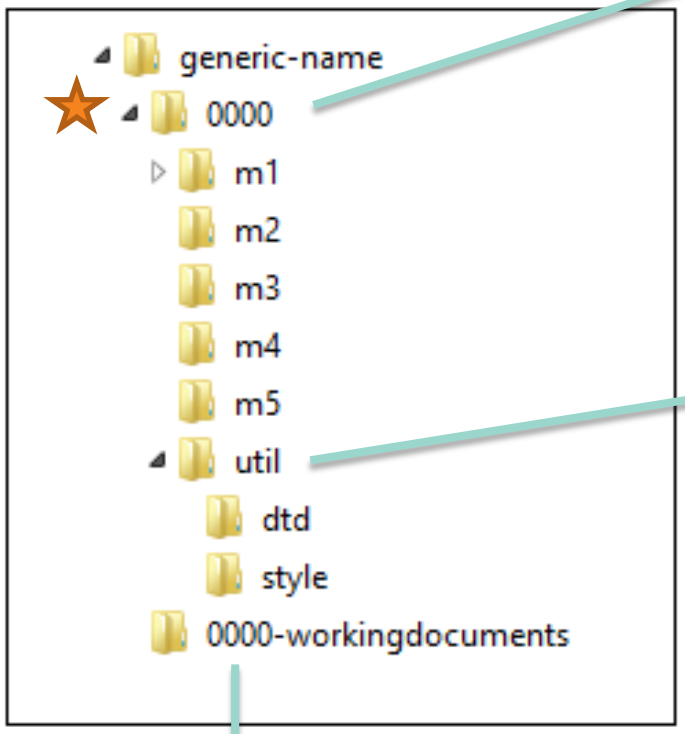
National/Regional data is provided within Module 1

Module 2 – 5 form the ICH CTD

- Module 2 – Summary Documents
- Module 3 – Quality
- Module 4 – Non-Clinical Data
- Module 5 – Clinical Data

Each Module contains sub folders to provide further granularity

Composition of the eCTD



eCTD Sequence Number

The initial submission submitted to eCTD format is generally 0000 (0001 in the US with most recent specification).

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Subsequent Responses and Lifecycle maintenance submissions are sequentially numbered 0001, 0002 etc. and form their own submission packages

eCTD Util Folder

dtd

Contains the ICH and Regional DTD/schema files covering Module 2 to 5 and Module 1 respectively

style

Contains the ICH and Regional stylesheets covering Module 2 to 5 and Module 1 respectively

Note: the Working Documents concept is not a global standard but primarily used in the EU processes

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eCTD XML Files

- Each eCTD contains two XML files forming the Table of Contents, metadata about the submission, documents and structure of the eCTD
  - index.xml backbone of Modules 2 to 5 located in nnnn folder (four digits), template defined by ICH
  - Regional xml template is defined by region using ICH principles
    - Regional template defines content including metadata
    - located in the \nnnn\m1\xx\ folder (where xx is the two letter country/region code)
    - xx-regional.xml can also contain 'Envelope' information providing further details about the submission

Lifecycle Operation Attributes

- All documents (leafs) in an eCTD must have a lifecycle operation

Operation	Meaning/Use
new	Used to identify a leaf that has never been submitted for this product before
replace	Used to replace a previous version of a leaf with a new version
delete	Used to hide from view a leaf that is no longer relevant to the review or was submitted in error
append	Used to associate a leaf with another leaf that has already been submitted **Important Note: Append is generally recommended not to use** (except for STF in the US) - Due to complications that this causes to the lifecycle management of the eCTD e.g. Can you append to an append & what if the document that was appended to is deleted?

Language of the eCTD

- XML (eXtensible Markup Language)
  - A structured data exchange standard that is both human and machine readable
- Backbone
  - Table of Contents in XML format
- Leaf
  - Contains information about a document in the eCTD
  - Will reference to a physical file on the file system
- Node
  - A section in the eCTD e.g. 3.2.S.4.1
  - Contains Leaf documents
- eCTD filename
  - Physical filename linked to from contents page by including the file path (e.g. 0000\m1\eu\10-cover\ema\ema-cover.pdf)
- Leaf title or eCTD title
  - Document Name that will be displayed to the reviewer e.g. ‘Cover Letter’
- eCTD Sequence
  - A four digit sequential number that identifies a particular submission e.g. 0000

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Language of the eCTD

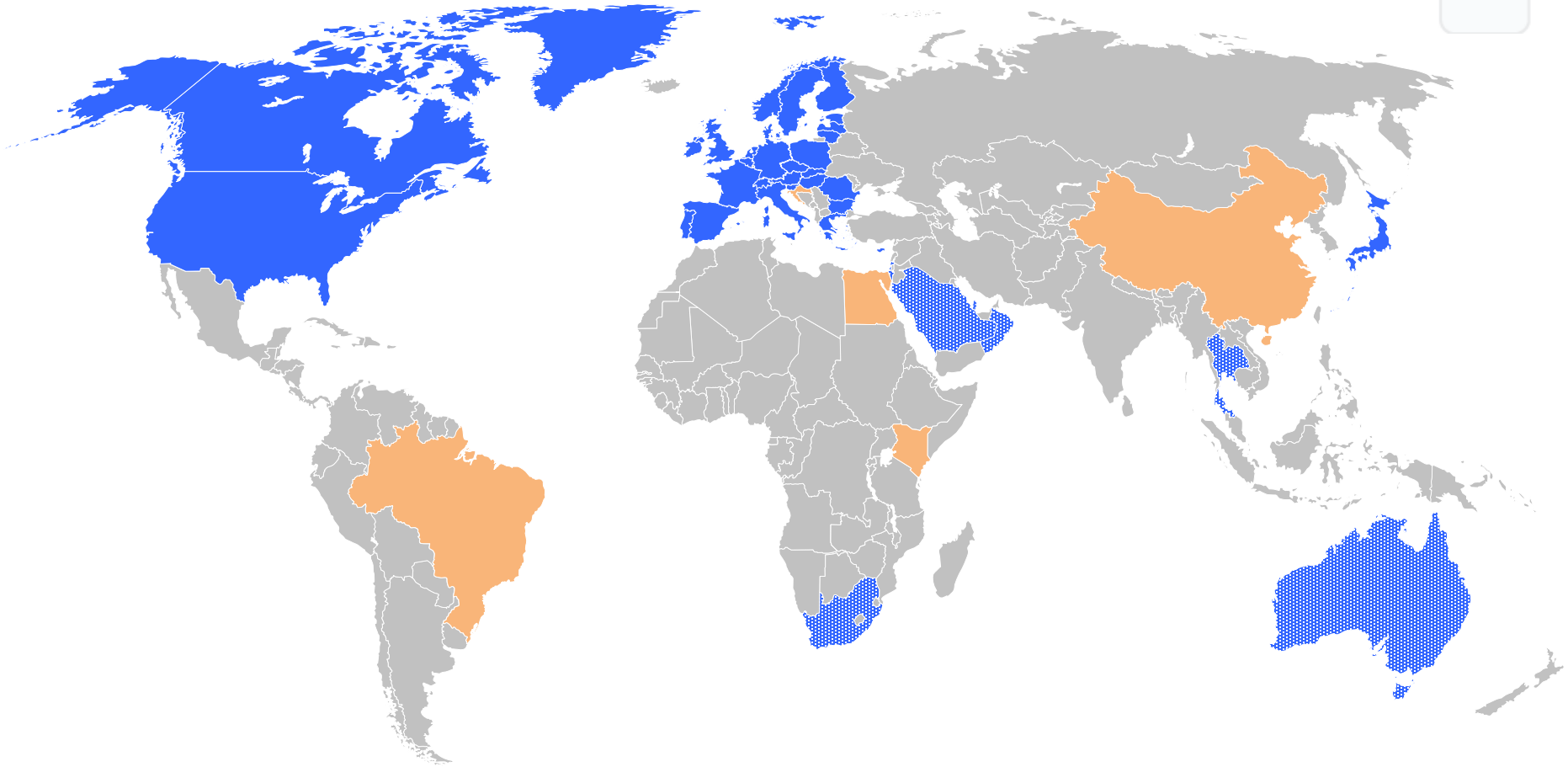
- Lifecycle
  - Submission Lifecycle – Relationship between eCTD sequences using the Related Sequence metadata
  - Document Lifecycle – Relationship between document versions using Lifecycle operations (New, Replace, Delete & Append)
- ICH eCTD Metadata
  - Information used to define the contents of submission sections e.g. indication, substance, manufacturer
- Regional (m1) Metadata
  - Information in the XML that describes the submission
- MD5 Checksum
  - Unique calculated value of a document used to determine if it has been changed
- Baseline
  - Providing part or all of the current registered submission documents (normally as an initial eCTD sequence, but can be provided later in the lifecycle)
  - Many Health Authorities highly recommend baselines being provided, but industry position is that they should not be mandated
- Current View
  - Displaying just those documents across all sequences that are current (i.e. not Deleted/Replaced)

Language of the eCTD

- Regulatory Activity
  - A collection of eCTD sequences related to the same regulatory step e.g. A variation sequence and associated response sequences
- Document Reuse
  - Ability to reference a document previously submitted by hypertext linking to it
  - Also can be possible to re-include documents in another section or another eCTD sequence or application without physically re-providing the file
- STF (Study Tagging File)
  - Provides metadata to categorise study reports in Module 4 & 5 (required by US, encouraged in Canada)
  - Not allowed in Japan and not required by other HAs, but if included STF will be validated
- Node Extension
  - Provides ability to create a node at the lowest level of the eCTD only, to help keep content together
  - Used in many regions as an alternative to STF
- Schema/DTD
  - Provides rules on how the XML must be structured
- Stylesheet
  - Used to display the eCTD XML in a user friendly manner

eCTD global map of activity

Visual of eCTD Adoption mid 2016



Early eCTD adopters (Main ICH region) – Canada, Europe (CP), Japan, USA

More recent eCTD adoption – Australia, Bahrain, Oman (2017), Saudi Arabia (2017), South Africa, Switzerland, Thailand, United Arab Emirates

eCTD planned – Brazil, China, Egypt, Jordan, Kenya, Serbia, Singapore

Questions?

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