eCTD implementation: steps for success industry perspective & implementation in EU - necessary level of infrastructure development.

Lessons learned and how to optimize the resources

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About me

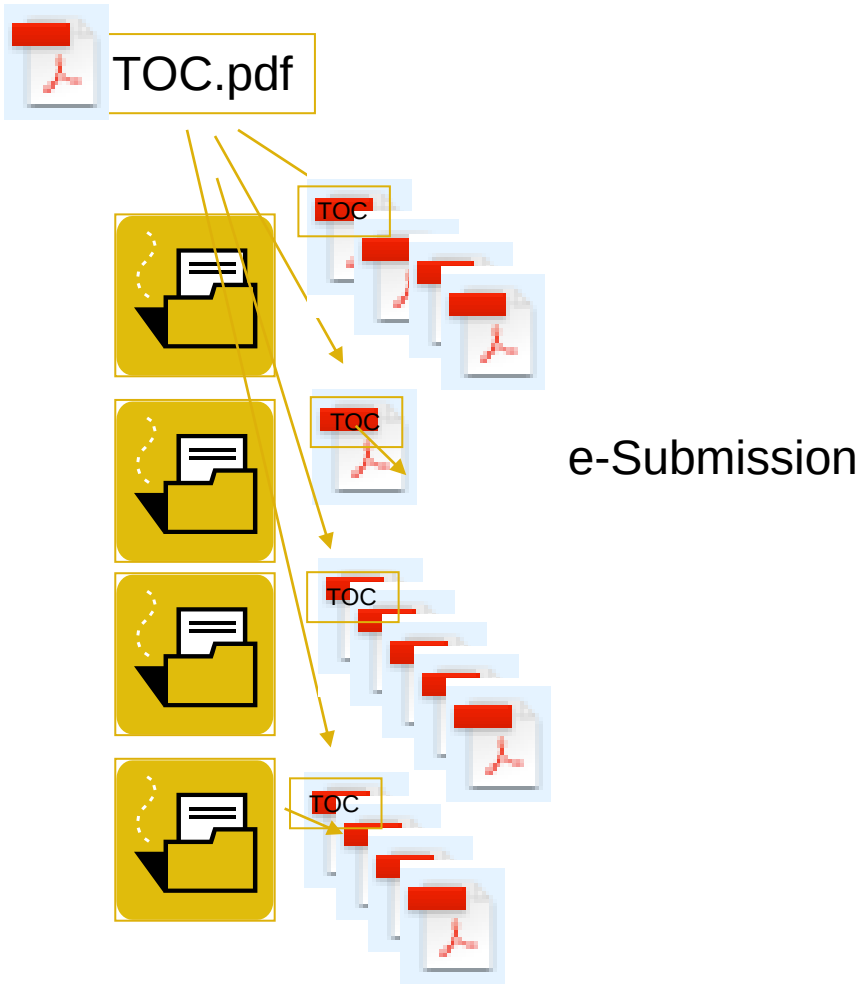
- Alastair Nixon
- Regulatory Submissions, GlaxoSmithKline
  - 20 years in electronic dossiers, global role
- Chair, EFPIA eCTD Focus Group
  - Implementation of electronic dossiers in Europe
  - Monitoring and understanding the global environment with respect to electronic standards for regulatory information

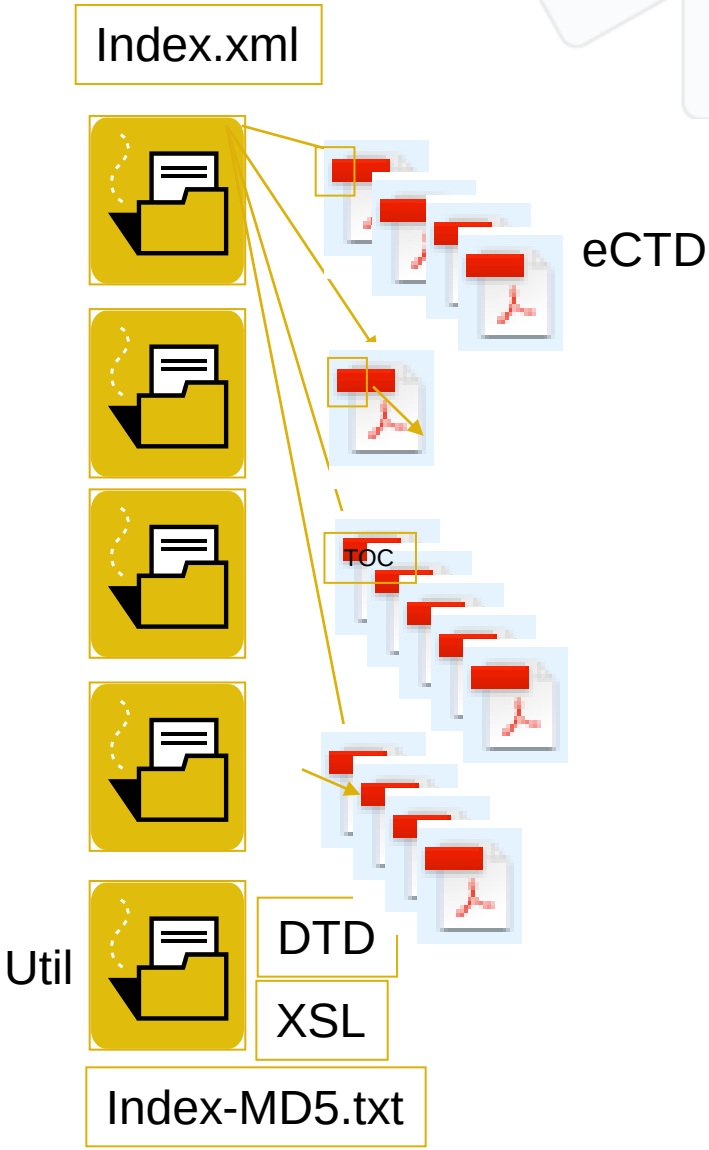
Agenda

- eCTD introduction
- eCTD Lifecycle
- Global use of the ICH eCTD
- Modules 2-5
- Regional part – module 1
- eCTD Adoption
  - EFPIA experience
  - Timelines
  - Maintenance
- Overall EFPIA Recommendations

ICH eCTD
The Basics

eSubmission vs eCTD





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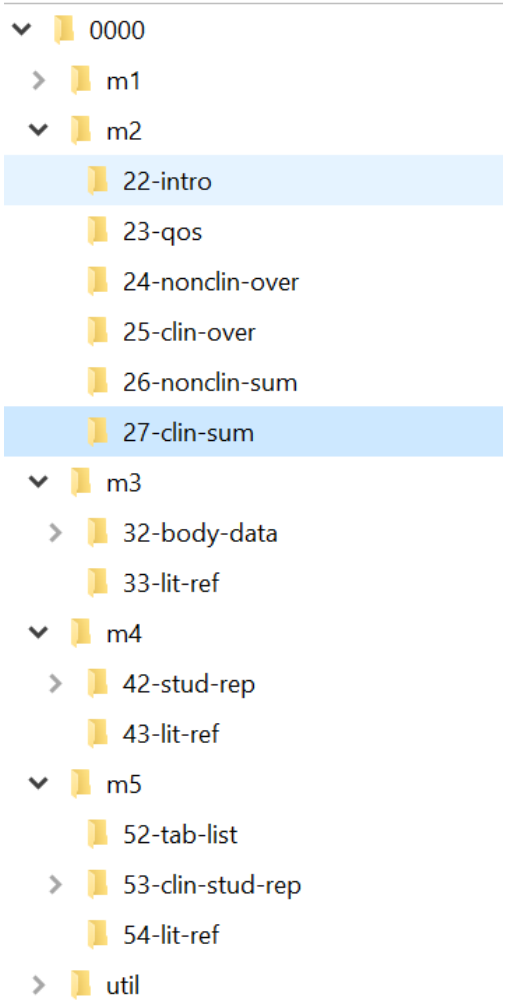
ICH eCTD – Organisation (M4) and Key concepts



- PDF file naming and location
  - But not critical with good navigation
- Navigation (see above)
- Controlled vocabularies (application types, submission types) – can be regional
- Context of use – this document relates to e.g. manufacturer, product
- Lifecycle – what is current (not yet deleted or replaced)?

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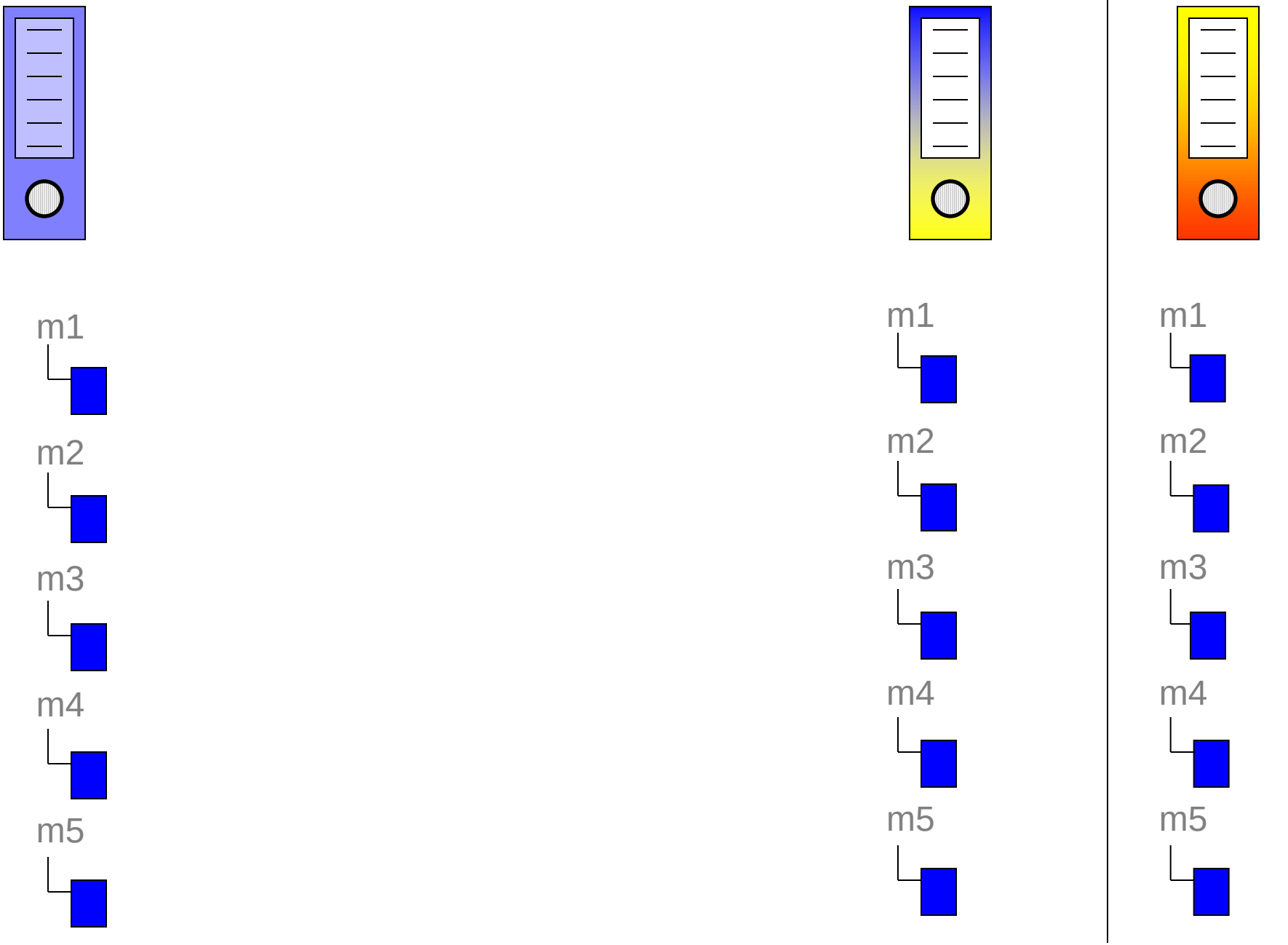
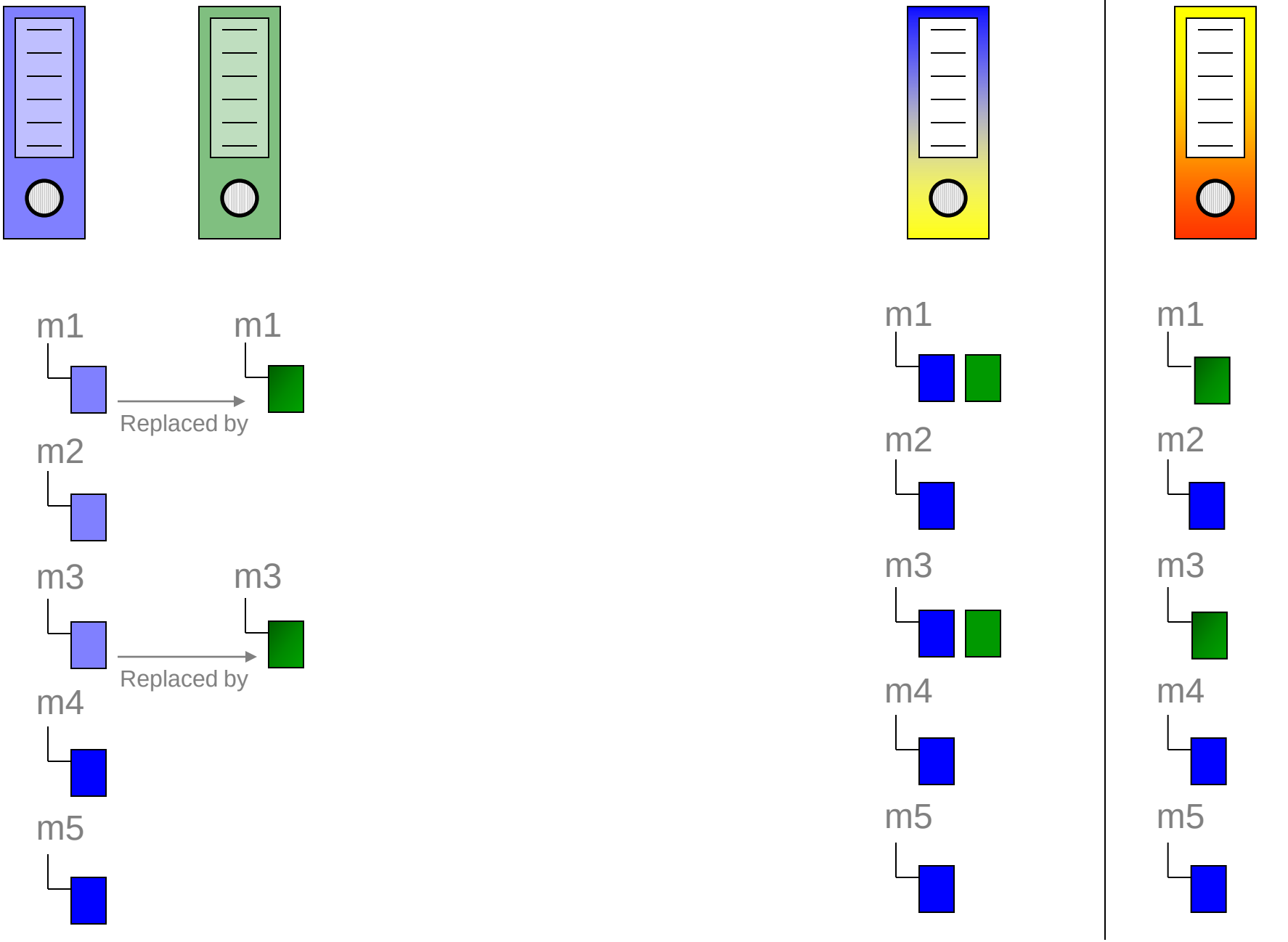
eCTD Lifecycle Management

eCTD Lifecycle Management

- Sequences
  - All eCTDs have a four digit sequence number
  - Start at 0000
  - Any change to eCTD content is submitted as the next sequence
  - You only submit what has changed – not the whole MAA!
- Operation Attribute
  - For each document submitted, the operation attribute describes its lifecycle status
    - New – first time this document has been seen in eCTD
    - Append – read in conjunction with a previously submitted eCTD document
    - Replace – use this instead of a previously submitted eCTD document
    - Delete – delete this document – no longer relevant


MAA
m1
m2
m3
m4
m5
Cumulative
m1
m2
m3
m4
m5
Current
m1
m2
m3
m4
m5


MAA
Var 1 (CMC)
Cumulative
Current
m1
m1
Replaced by
m2
m3
m3
Replaced by
m4
m5
m1
m2
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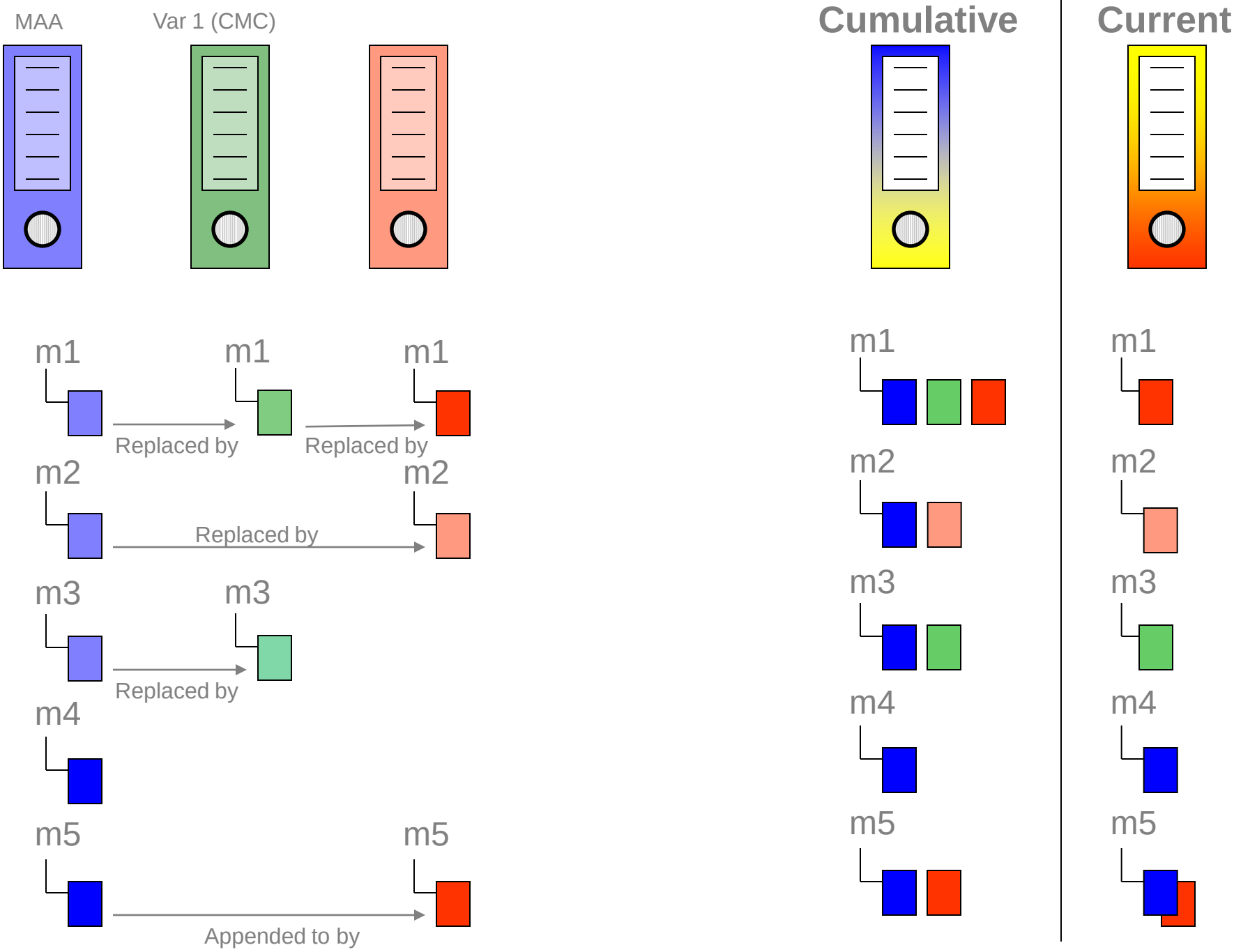
m4
m5
m1
m2
m3
m4
m5


MAA
Var 1 (CMC)
Cumulative
Current
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m1
m1
Replaced by
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Replaced by
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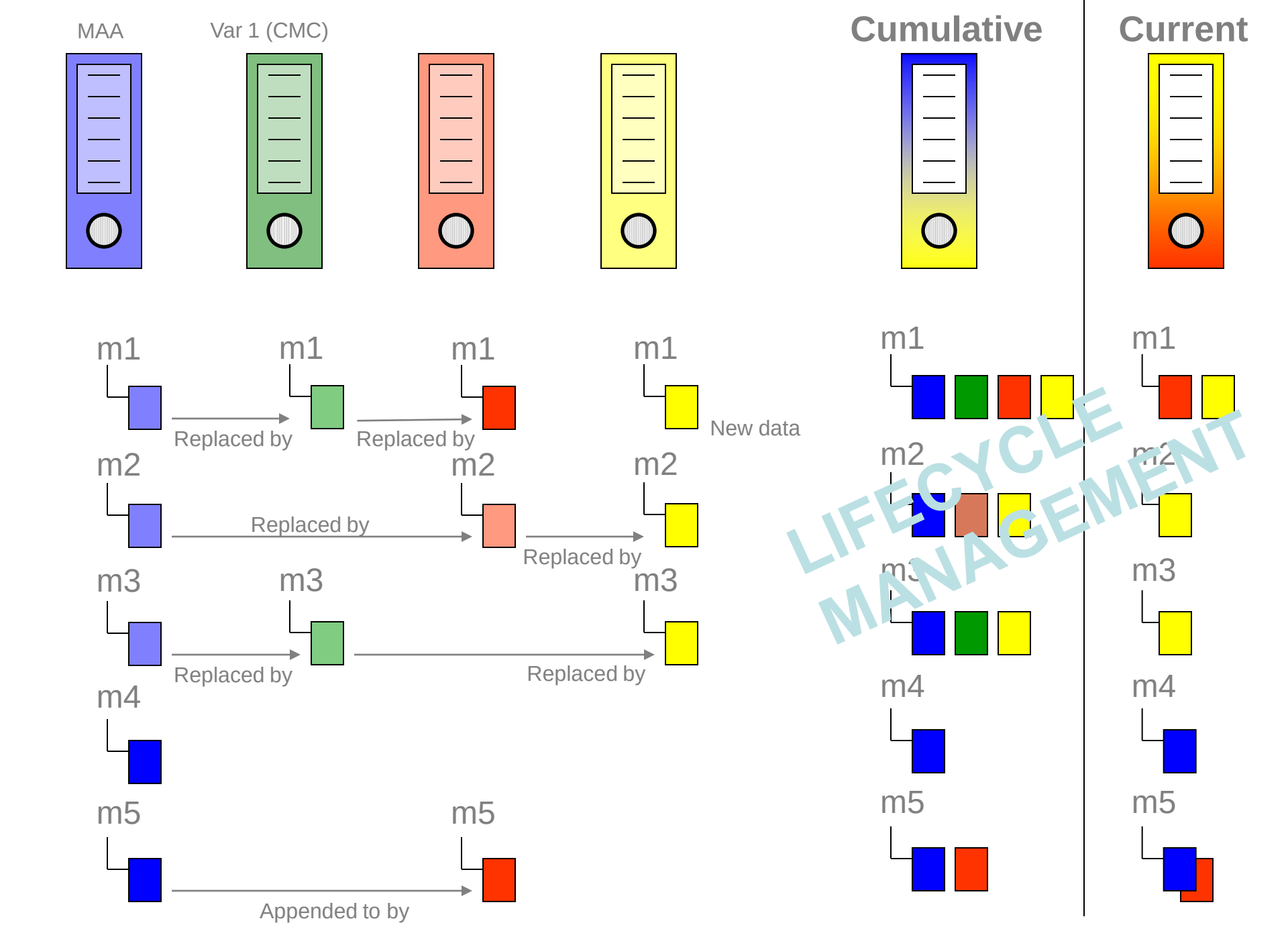
m5


MAA
Var 1 (CMC)
Cumulative
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Replaced by
Replaced by
New data
m2
m2
m2
Replaced by
Replaced by
m3
m3
m3
Replaced by
Replaced by
m4
m5
m5
Appended to by
m1
m2
m3
m4
m5
m1
m2
m3
m4
m5
LIFECYCLE MANAGEMENT

eCTD and Lifecycle Management

- Manual creation of Cumulative and Current dossiers would be a laborious and repetitive task
  - Manual updates following each submission
- eCTD specification allows viewing tools to derive them as Views
  - Sequence View i.e. separate conventional Dossiers
  - Cumulative View i.e. everything in one Dossier
  - Current View i.e. most recent in one Dossier

Global eCTD Adoption

An EFPIA view, October 2019

European Federation of Pharmaceutical Industries and Associations

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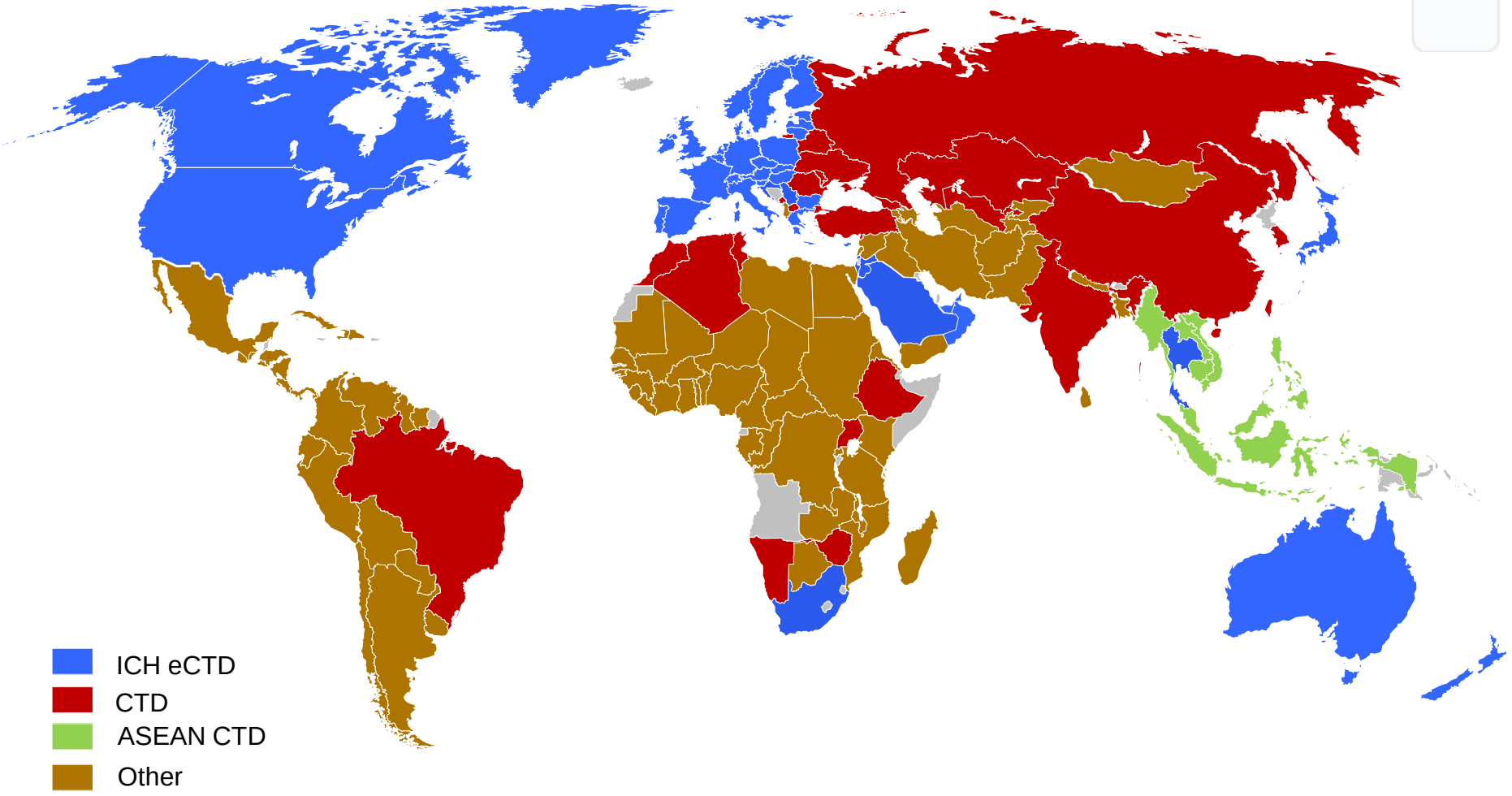
ICH CTD and eCTD Scope October 2019

One Company's View



Established eCTD Regulators

- US FDA, Health Canada, Japan PMDA – >10-15 years experience, eCTD mandated
- EU – eCTD Mandated for Centralised procedure from 2009, MR/DCP from 2018, all others from 2019
- Switzerland – eCTD since 2010 but still accept electronic alternative (eDOK)
- Gulf Cooperation Council – GCC Specifications and guidance from 2011, mandatory Saudi Arabia, UAE, Oman, Bahrain - eCTD since 2014, baselines mandatory (only region globally)
- Thailand – eCTD since 2015, new chemical entities

Timeline, Newly Adopting Countries

	Q2 2019	Q3 2019	Q4 2019	Q1 2020	Q2 2020	Q3 2020
EAEU	* XML Submission Mandatory					
Jordan	* eCTD Mandatory for new		* eCTD Mandatory for All?			
Qatar	← eCTD for Renewal (with baseline) →				* eCTD Mandatory for All?	
China	← * eCTD Pilots →					
Turkey			* Planned EFPIA Meeting with TITCK			* *Timelines for eCTD Mandatory not clear*
Brazil	<--Tender---> * Contract to vendor					
Australia				* eCTD Mandatory for ext?		* eCTD Mandatory for All?
Taiwan	← eCTD Specification Development →			← Build system →		Live '21 →

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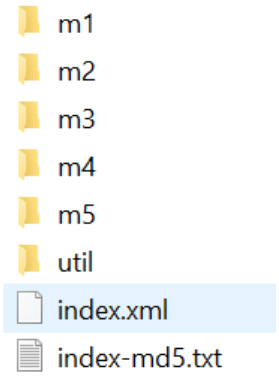
Modules 2-5 in the ICH eCTD

Regional Specifications

Modules 2-5 ICH eCTD



- m2 - 2-7-3-summary-of-clinical efficacy
  - Indication
- m3 – 3.2.S Drug Substance
  - Substance
  - Manufacturer
- m3 – 3.2.P Drug Product
  - Product
  - Manufacturer
  - Dosage form
- m5-3-5-reports-of-efficacy-and-safety-studies
  - Indication

Module 1 in the ICH eCTD

Regional Specifications

eCTD DTD version 3.2

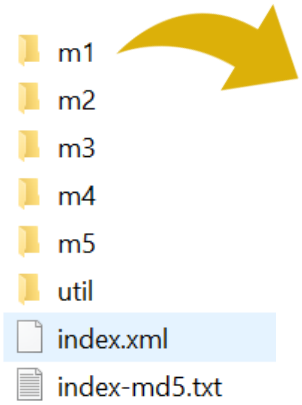
- m1-administrative-information-and-prescribing-information
  - eu-regional [new]
- m2-common-technical-document-summaries
  - m2-2-introduction
    - Introduction [new]
  - m2-3-quality-overall-summary
    - m2-3-introduction
      - Introduction [new]
    - m2-3-s-drug-substance [manufacturer: 3rd-Party] [substa
      - Drug Substance [new]
    - m2-3-p-drug-product [manufacturer: gsk] [product name Gel]
      - Drug Product [new]
    - m2-3-a-appendices
      - Appendices [new]
    - m2-3-r-regional-information
      - Regional Information [new]
  - m2-4-nonclinical-overview
    - Nonclinical Overview [new]
  - m2-5-clinical-overview
    - Clinical Overview [new]
  - m2-6-nonclinical-written-and-tabulated-summaries
    - m2-6-1-introduction
      - Introduction [new]
    - m2-6-2-pharmacology-written-summary
      - Pharmacology Written Summary [new]
    - m2-6-3-pharmacology-tabulated-summary
      - Pharmacology Tabulated Summary [new]
    - m2-6-4-pharmacokinetics-written-summary
      - Pharmacokinetics Written Summary [new]
    - m2-6-5-pharmacokinetics-tabulated-summary

etc etc……

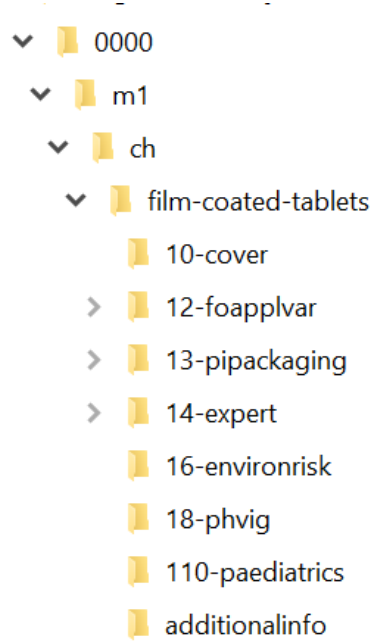
Link to the regional Table of Contents

The ICH CTD

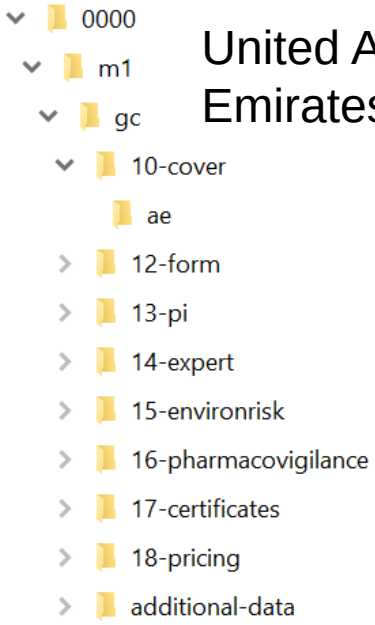
ICH eCTD Structure



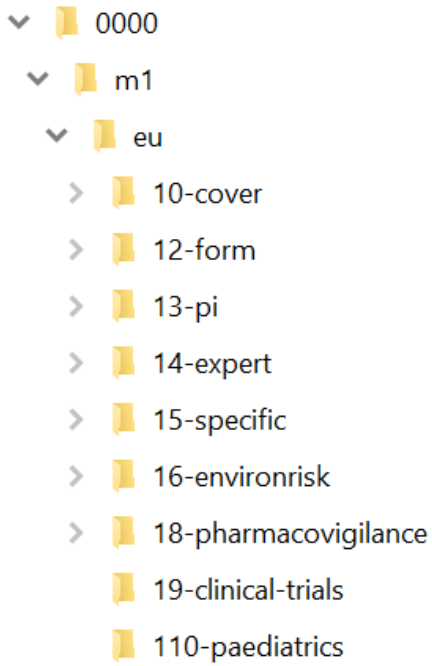
Switzerland



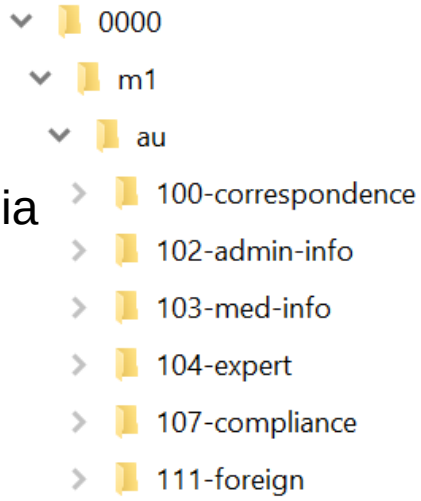
United Arab Emirates



European Union



Australia



EU Module 1

DTD version 3.0.1

Envelope for EMA	
Identifier:	badfccc2-cf51-4be7-b15f-24749a4929f1
Submission:	Type: Marketing Authorisation Number: H0004102
Procedure Tracking Number(s):	H0004102
Submission Unit:	Type: Initial submission to start any regulatory activity
Applicant:	GlaxoSmithKline
Agency:	EMA - European Medicines Agency (EU-EMA)
Procedure:	Centralised
Invented Name:	Dectova
INN:	zanamivir
Sequence:	0000
Related Sequence:	0000
Submission Description:	Marketing Authorisation Appliation for Dectova

Module 1 EU

1.0 Cover Letter

For EMA:

- Cover Letter (new)
- Notes to Reviewer (new)
- Notes of EMA Pre-submission Meeting (new)
- Notes of NoMA Pre-submission Meeting (new)
- Notes of MHRA Pre-submission Meeting (new)
- FDA Scientific Advice (new)
- Investigators Table - NAI114373 (new)

GCC Module 1

DTD version 1.1

Envelope for BH	
Application Reference Number:	n/a
Applicant:	GlaxoSmithKline
Agency:	BAHRAIN - Ministry of Health (BH-MOH)
ATC:	PO2CA03
Submission:	None
Submission unit:	Reformatting of an existing submission application from any format to eCTD
Procedure:	National Procedure
Invented Name:	Zentel
INN:	Albendazole
Sequence:	0000
Related Sequence:	
Submission Description:	Baseline

Module 1

1.0 Cover Letter

For BH:

- Cover Letter (new)

1.2 Application Form

For BH:

- Application Form (new)

AU Module 1

Schema version 3.0
Style sheet version 3.0

eSubmission Id:	e000026
Applicant:	ViiV Healthcare Pty Ltd
AAN:	dolutegravir
Product Name:	Tivicay
ARTG Number:	205212
Sequence Type:	J - PI Change requiring evaluation
Regulatory Activity Lead :	Prescription
Sequence:	0000
Related Sequence:	0000
Sequence Description:	Initial

Module 1 AU

1.0 Correspondence

1.0.1 Cover letter

- Cover Letter (new)
- Media statement (new)

1.0.2 Lifecycle management tracking table

- Lifecycle management tracking table (new)

1.0.3 Response to request for information

1.2 Administrative Information

CH MODULE 1

DTD VERSION 1.1

Envelope for CH

Application Number:	pending
Submission Description:	Initial Marketing Authorisation
Invented Name:	Eperzan
Galenic Form:	**Powder and solvent for solution for injection in pre-filled pen** Swissmedic Number: pending Galenic Name: German: Pulver und Lösungsmittel zur Herstellung einer Injektionslösung in einem Fertigpen
DMF Number:	n/a
PMF Number:	n/a
INN:	Albiglutide
Applicant:	GlaxoSmithKline
DMF Holder:	n/a
PMF Holder:	n/a
Agency:	Swissmedic
Submission:	New Application: New Active Substance(na-nas)
Paragraph 13 TPA:	no
eCTD Sequence:	0000
Related eCTD Sequence:	none

Module 1

Powder and solvent for solution for injection in pre-filled pen

1.0 Cover Letter
ch cover (new)

1.2 Application for Marketing Authorisation and Variation

1.2.1 Form Application for Marketing Authorisation and Variation
ch foapplvar (new)

Regional Module in ICH eCTD – Common Aspects

- Envelope – information about the dossier
- Leaf elements (like m2-m5):

```
<m1-0-cover>
    <specific country="ema">
        <leaf>
            operation="new"
            xlink:href="10-cover/emea/emea-cover.pdf"
            xlink:type="simple"
            checksum-type="md5"
            ID="isi22836"
            application-version="PDF 1.4"
            checksum="19bbe4263c71b02b4064c72abd48e2ab">
            <title>1.0 Cover Letter</title>
        </leaf>
</m1-0-cover>
```

Lifecycle

Link to file

Security

File ID

Title when viewed as Contents Page

What a Regional Specification Consists of

- Written specification – guidance to applicants
- XML template (DTD or XSD) defining envelope, pick lists, module 1 sections
- Style sheet – to display module 1 in an internet browser
- Validation criteria – to determine if a submitted eCTD is correct valid, readable, assessable or not
  - Not for content checks, this is done at a secondary stage

eCTD Adoption

eCTD Adoption – EFPIA Company Experience

- ‘Electronic submission’ vs ICH eCTD
- Electronic instead of paper vs metadata, structure, standard
- Need good software to maximise value – vendors critical
- Ideally one global vendor – for the whole company
  - More on next slide

eCTD transition planning – Vendor and tool selection

- Engage with vendor(s) or developers to establish timelines and infrastructure needs in order to implement software solutions
- Health Authority and Applicants use vendor supplied technologies (tools) to ❶ Build ❷ Validate ❸ View & Review eCTD submissions
- Common standards and criteria for ❶ ❷ ❸ = success
  - Validation tools differ, all aim to follow identical criteria per market – ensures choice of technology vendor, same validation results
  - When interpretation differs between vendors, there needs to be a mechanism to work with the agencies
  - EU solution is change request process. Vendor webinars for new releases have also helped applicants.
- As with Validation tools, Health Authority and Applicants do not always buy the same vendor viewing/reviewing tool
  - eCTD vendors provide different ways to provide the same standard views: Individual Sequence; Cumulative; Current View

Focus on what Adds value - to Regulator and Applicant

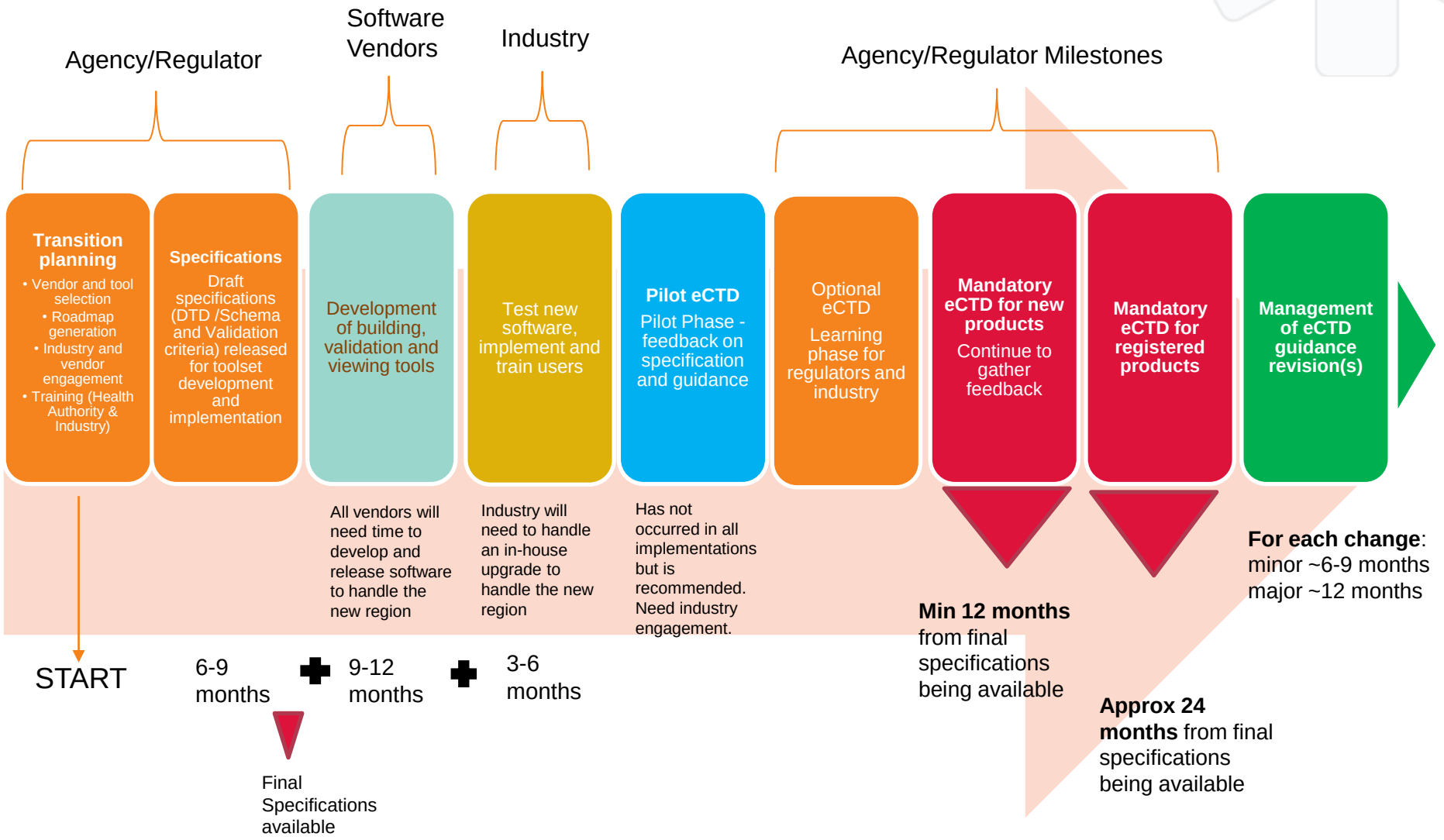
Regulator

- Receipt and handling
- Categorisation
- Assessment
- Searching
- Links, bookmarks
- Creation of assessment report
- Archiving
- Working with other regulators
- Pharmacovigiliance

Applicant

- Building process
- Submission process
- Records maintenance
- Sharing across the company
- Cloning for other regions

Suggested EFPIA eCTD adoption timelines



eCTD transition planning – roadmap guide

- After any vendor selection activities it is usual that the Health Authority will build a roadmap * that outlines the path towards full eCTD adoption.

- This usually takes into consideration
  - Tool selection and testing
  - Training for Health Authority reviewers and technical processing teams; industry authors, submission groups
  - Staged New Product implementation
    - Optional -> Mandatory timelines
  - Registered Product implementation
    - Optional -> Mandatory timelines
  - Management of eCTD guidance revision(s)
  - Consideration of benefits associated with the establishment of a secure and stable gateway/portal for submission delivery enabling large sized (>1GB) filings to be made from virtual support locations
  - Establishment of service desk in support of MAHs technical questions / issues

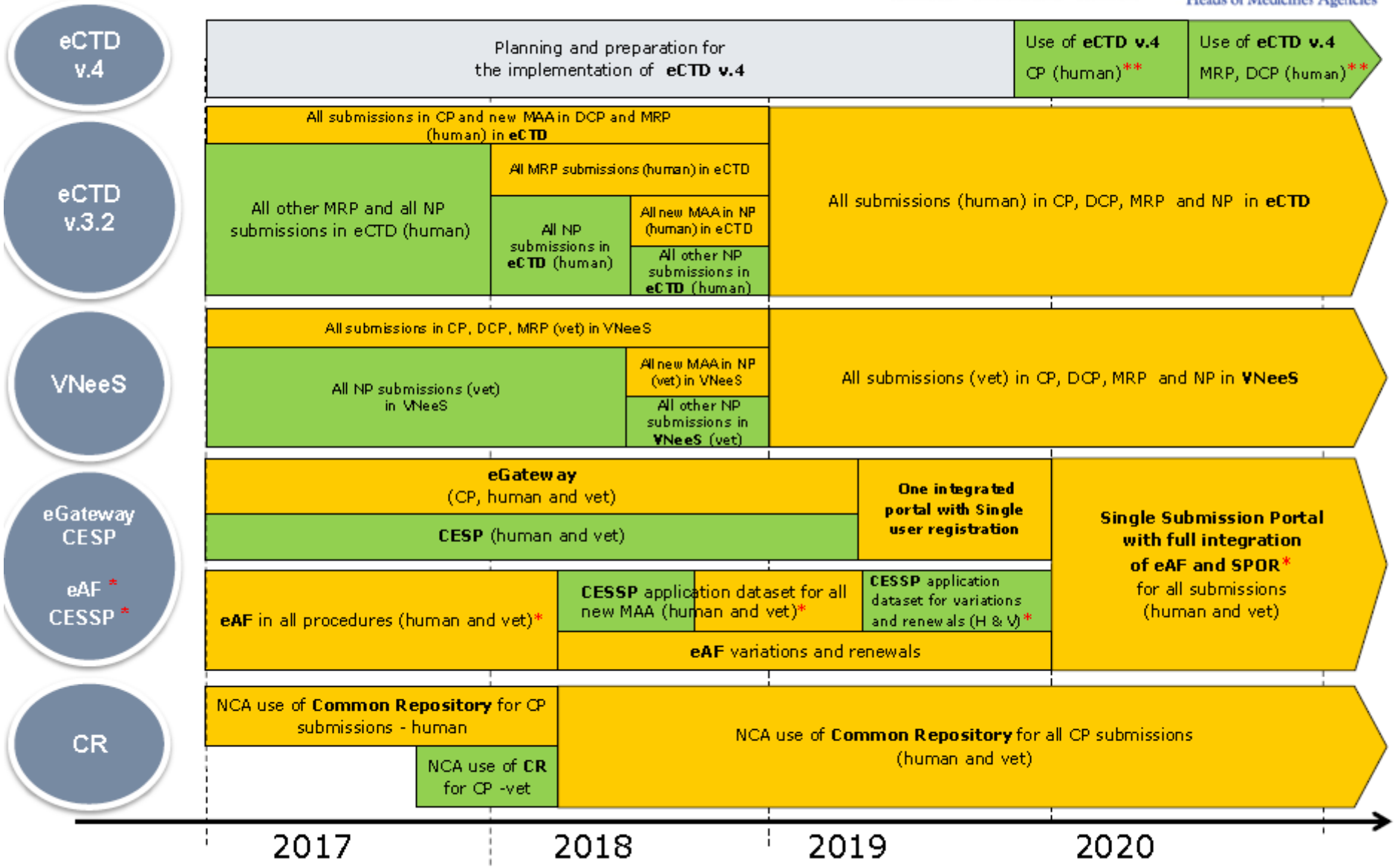
* Link to current EU roadmap, older version with eCTD timelines on next slide

eSubmission Roadmap - timelines

(reflecting final adopted version 2.0 dated 24-02-17)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies



Ongoing or optional

Mandatory

*) The SPOR project will stepwise (see specific Roadmap) deliver master data services (RMS, OMS, SMS, PMS) to be integrated with the eAF and CESSP during the roadmap period.

**) Timelines subject to planning

Critical success factors (1)

- Timelines (consider sufficient time for each stage of the adoption)
- Roadmap (carefully planned and aligned with industry)
- Vendor engagement
- Alignment and learning from other health authorities
- Gateway and eCTD logistics – ideally electronic transfer from applicant to regulator

Critical success factors (2)

- Partnership between regulators and industry leveraging experience
  - Advice, testing, pilots and discussion
  - Example - EU wide collaboration on eCTD & e-submission topics:

  Joint HA and Industry e-forum– active since 2003 with high participation

  Change Control process – ongoing, hundreds of changes implemented

  Examples of collaboration include the support and co-development of the roadmap, gateways and automated dossier handling and validation criteria

Maintaining the eCTD

Management of eCTD guidance revision(s)

- Any change to the eCTD technical specification can involve:
  - Development and testing of the new specification and technical files (DTD, XSL, MOD, Schema)
  - Vendors develop and release updated eCTD solutions for the updated specification
  - Health Authorities and industry then verify, test and implement new or updated solutions into production environments
  - Transition into full production and withdrawal of previous guidance
- Health Authorities therefore need to allow sufficient lead time for technical implementation before mandating or changing Guidance or Standards

- Industry recommendations:
  - Follow ICH guideline for Module 2 to Module 5.
  - Updates to eCTD specifications are managed carefully to minimise the number and frequency of changes.
  - Upon issue of new or revised eCTD Guidance a period of transition where clear optional and mandatory timelines are provided, with a minimum of 12 months between availability of the new standard and mandatory use.

Overall EFPIA Recommendations

EFPIA Recommendations

- EFPIA fully supports the adoption of ICH eCTD and recognises the many benefits, including:
  - Global regulatory harmonisation
  - 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
  - Maximise use of technology – electronic gateways and automated upload, use of metadata.

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