# 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

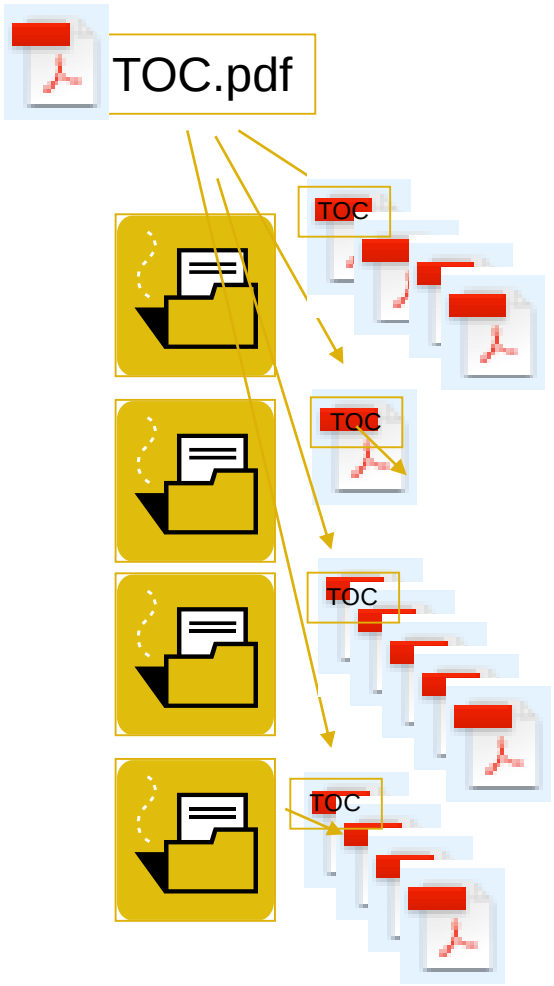
- Alastair Nixon
- Regulatory Submissions, GlaxoSmithKline
  - 20 years in electronic dossiers, global role
- Chair, EFPIA eCTD Focus Group
  - Implementation of electronic dossiers in Europe
  - Monitoring and understanding the global environment with respect to electronic standards for regulatory information

# Agenda

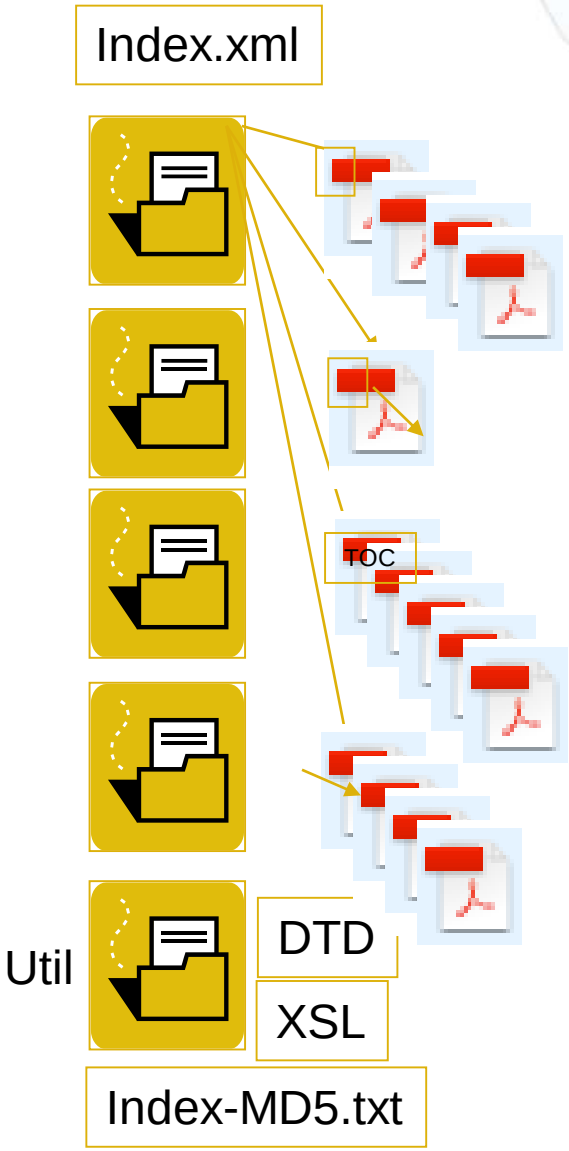
- eCTD introduction
- eCTD Lifecycle
- Global use of the ICH eCTD
- Modules 2-5
- Regional part – module 1
- eCTD Adoption
  - EFPIA experience
  - Timelines
  - Maintenance
- Overall EFPIA Recommendations

# ICH eCTD
# The Basics

# eSubmission vs eCTD

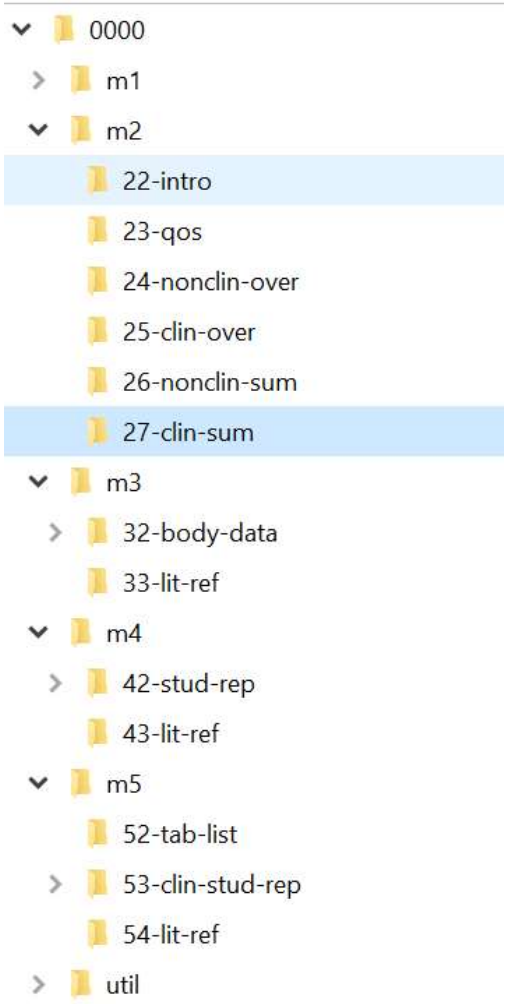



e-Submission




eCTD

# 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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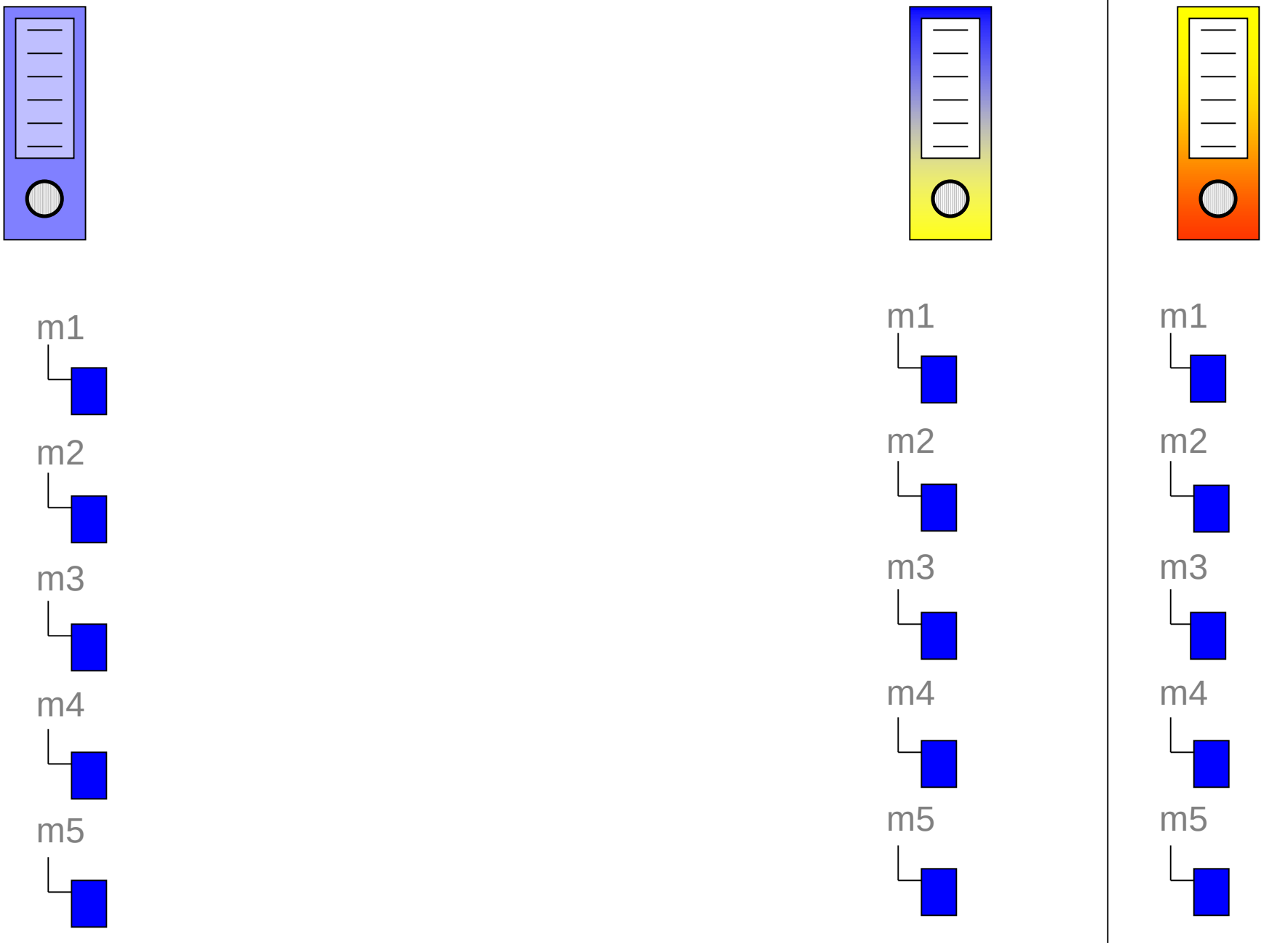
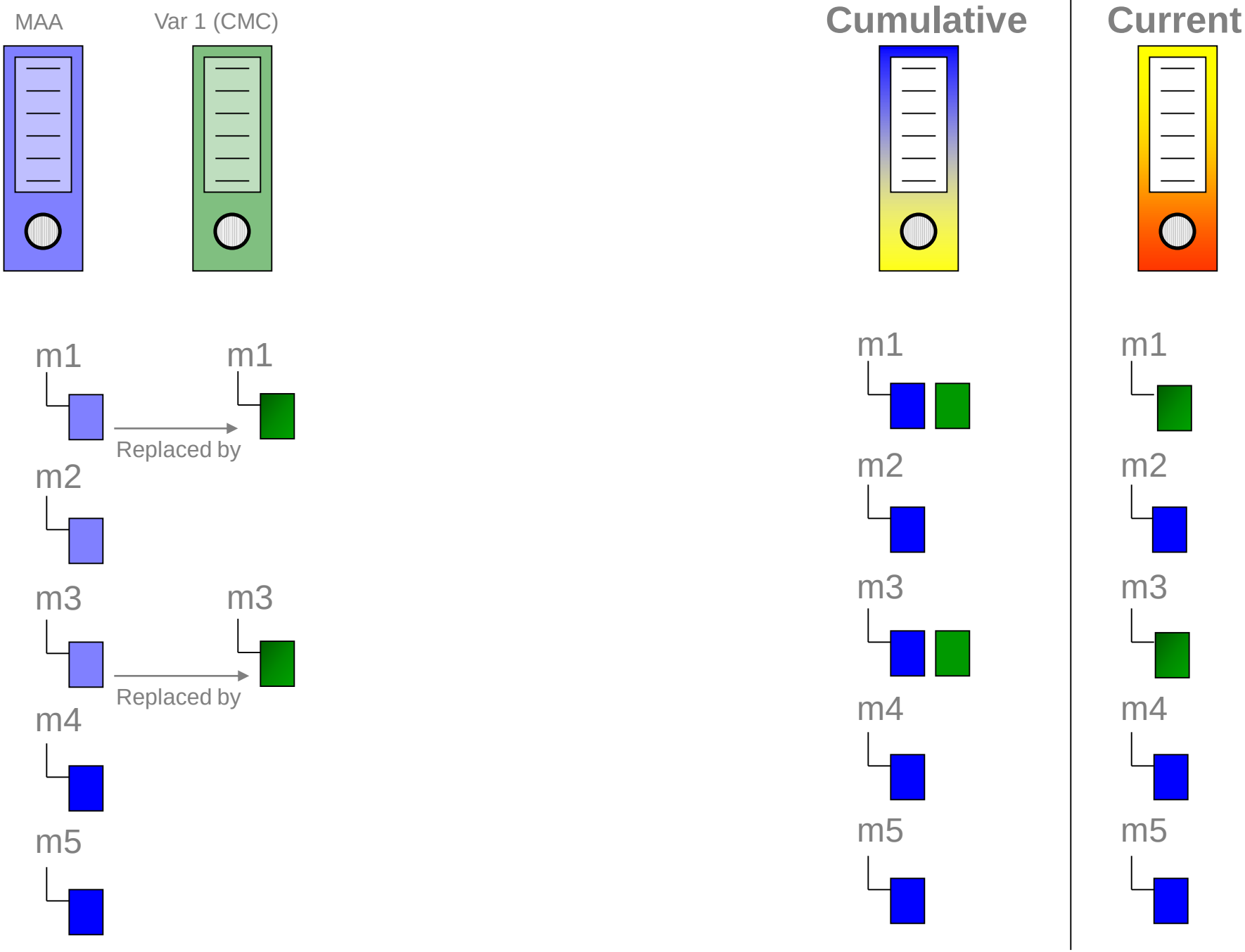
# eCTD Lifecycle Management

# 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
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m1
m2
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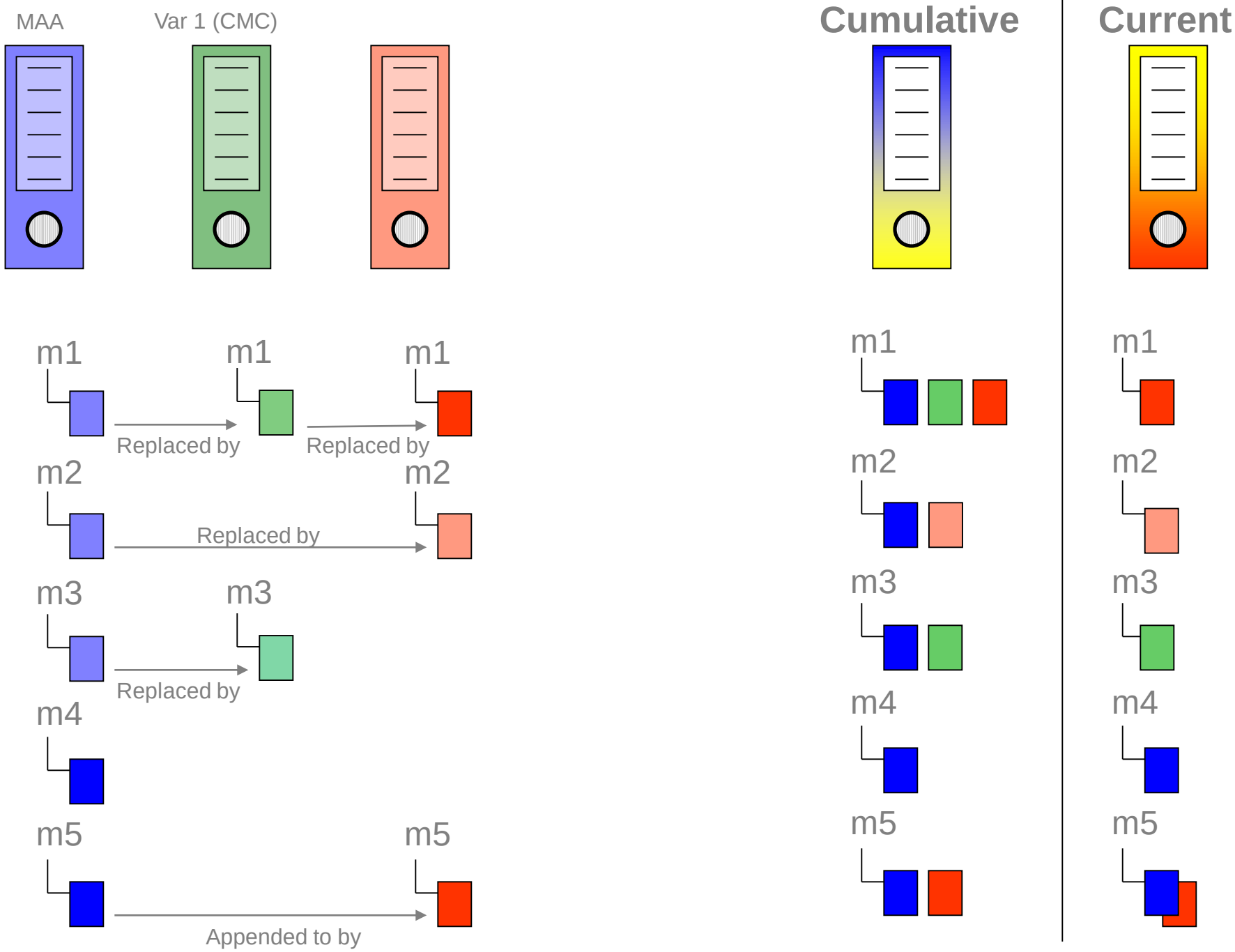
m4
m5


MAA
Var 1 (CMC)
Cumulative
Current
m1
m1
m1
Replaced by
Replaced by
m2
m2
Replaced by
m3
m3
Replaced by
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m5
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Appended to by
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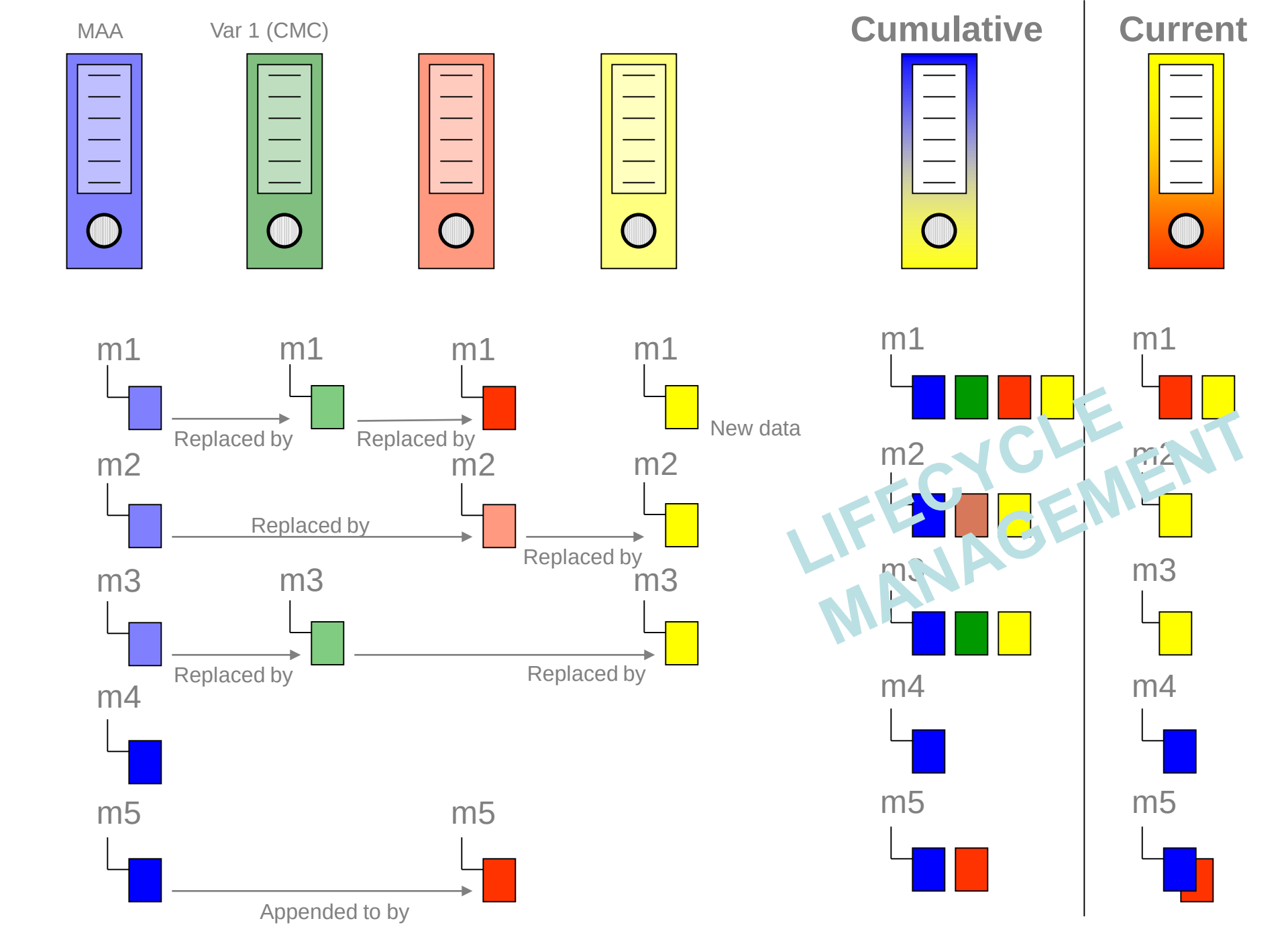
MAA
Var 1 (CMC)
Cumulative
Current
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m1
m1
Replaced by
Replaced by
New data
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m2
m2
Replaced by
Replaced by
m3
m3
m3
Replaced by
Replaced by
m4
m5
m5
Appended to by
m1
m2
m3
m4
m5
m1
m2
m3
m4
m5
LIFECYCLE 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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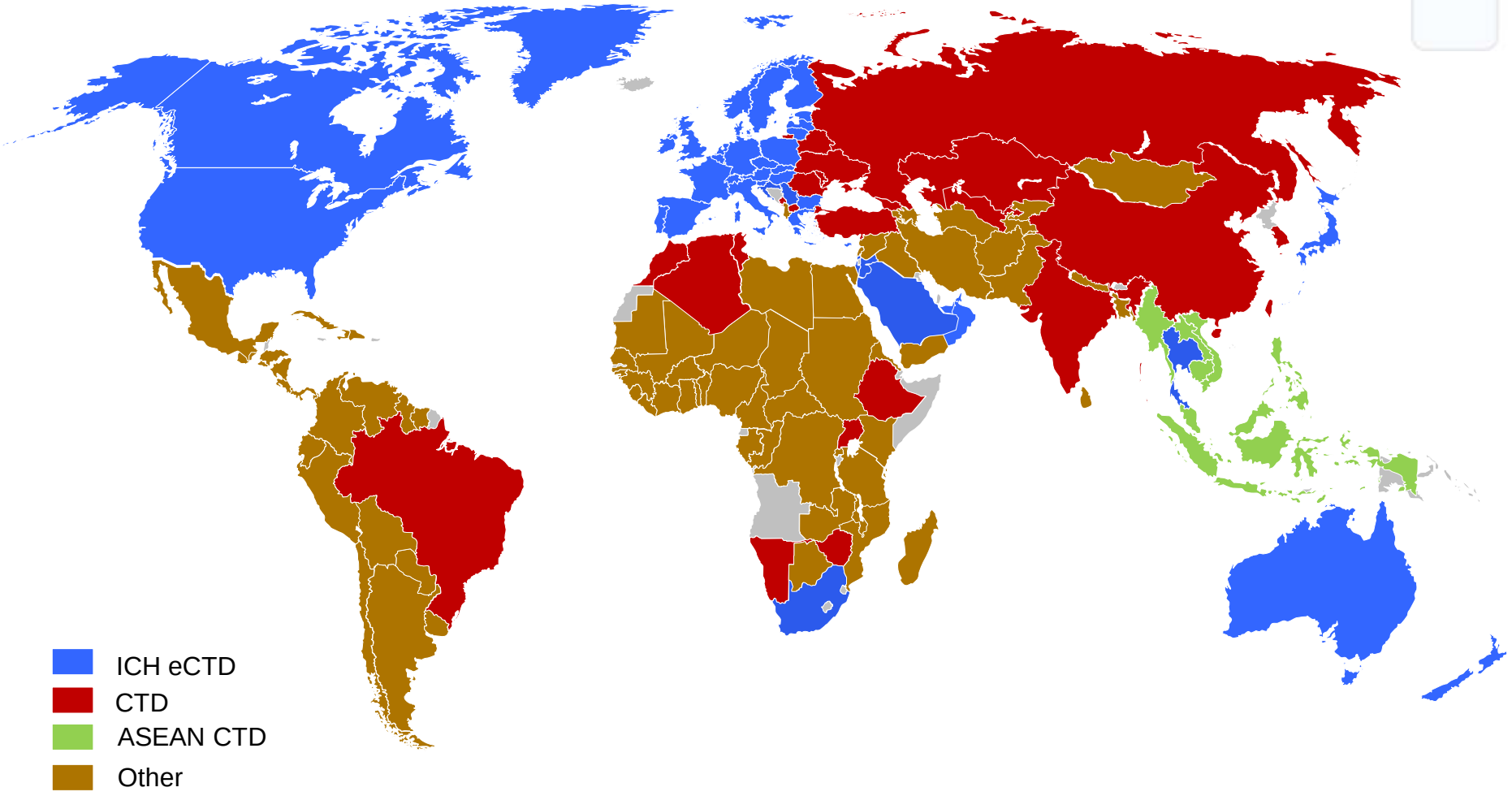
# ICH CTD and eCTD Scope October 2019

## 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

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# 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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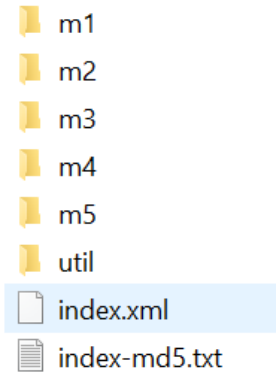
# Modules 2-5 in the ICH eCTD

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

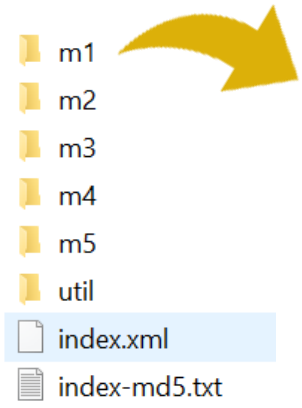
- m1-administrative-information-and-prescribing-information
  - eu-regional [new]
- m2-common-technical-document-summaries
  - m2-2-introduction
    - Introduction [new]
  - m2-3-quality-overall-summary
    - m2-3-introduction
      - Introduction [new]
    - m2-3-s-drug-substance [manufacturer: 3rd-Party] [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……

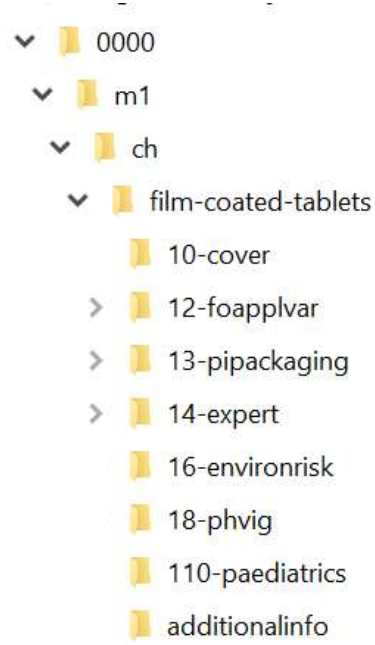
Link to the regional Table of Contents

The ICH CTD

# ICH eCTD Structure

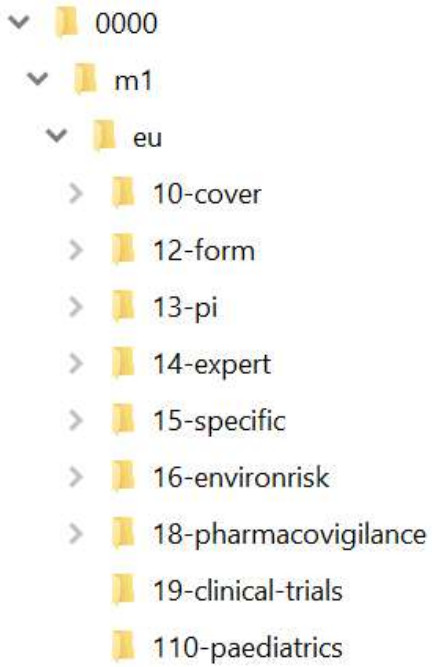



Switzerland

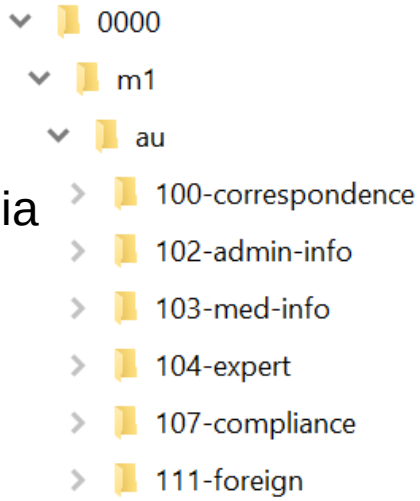



United Arab Emirates


European Union




Australia



# EU Module 1

DTD version 3.0.1

| **Envelope for EMA** | |
|---|---|
| Identifier: | badfccc2-cf51-4be7-b15f-24749a4929f1 |
| Submission: | Type: Marketing Authorisation<br>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**<br>Swissmedic Number: pending<br>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

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# Focus on what Adds value - to Regulator and Applicant

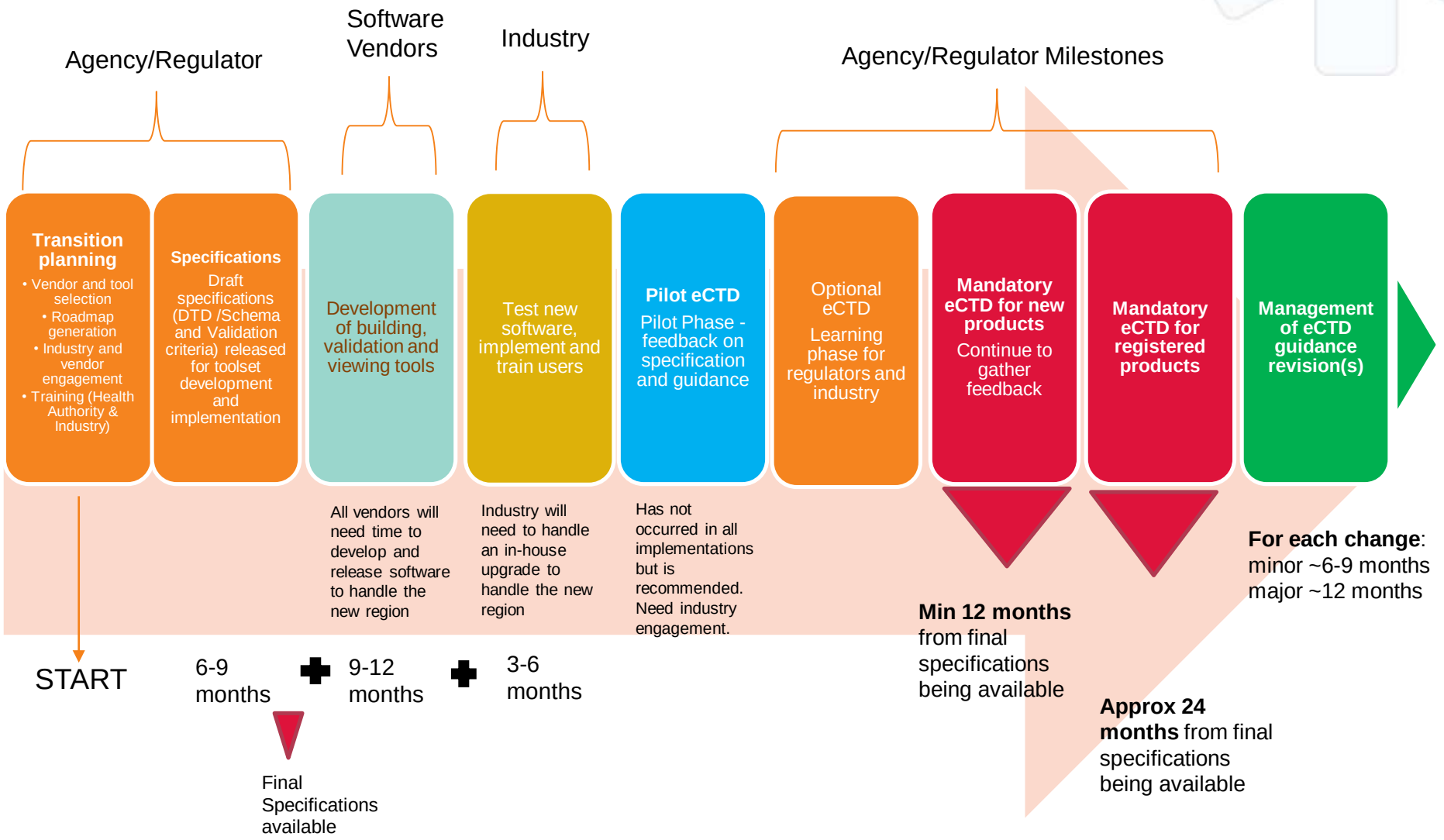
Regulator

- 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

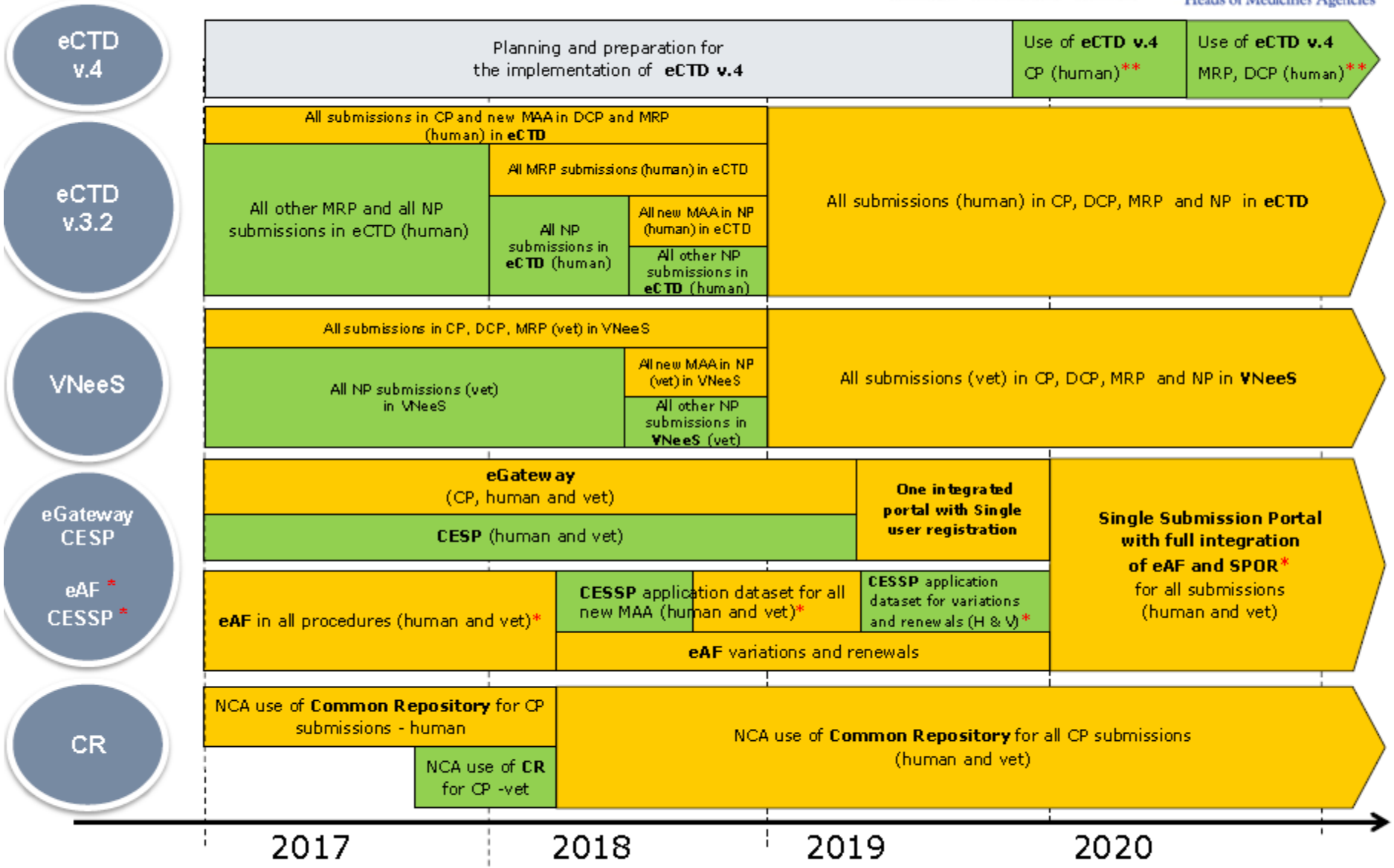
* Link to current EU roadmap, older version with eCTD timelines on next slide

# 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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