Technical Aspects of Implementation

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eCTD Demonstrations

A shared commitment to adopt eCTD

- Health Authorities and industry share a joint goal of ensuring patients have access to safe and effective medicines
- ICH (M8) eCTD format introduced in 2003 and has been implemented by more than 30 national Health Authorities (HAs)
- eCTD, with careful introduction, brings us closer to operational excellence in support of the above
- Critical success factors
  - 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 eCTD groups – active since 2003 with high participation
      - Change Control process – ongoing, hundreds of changes implemented
      - Maximising the utility of the eCTD with a regulatory activity view.
      - Examples of collaboration include the support and co-development of the roadmap, gateways and automated dossier handling and validation criteria

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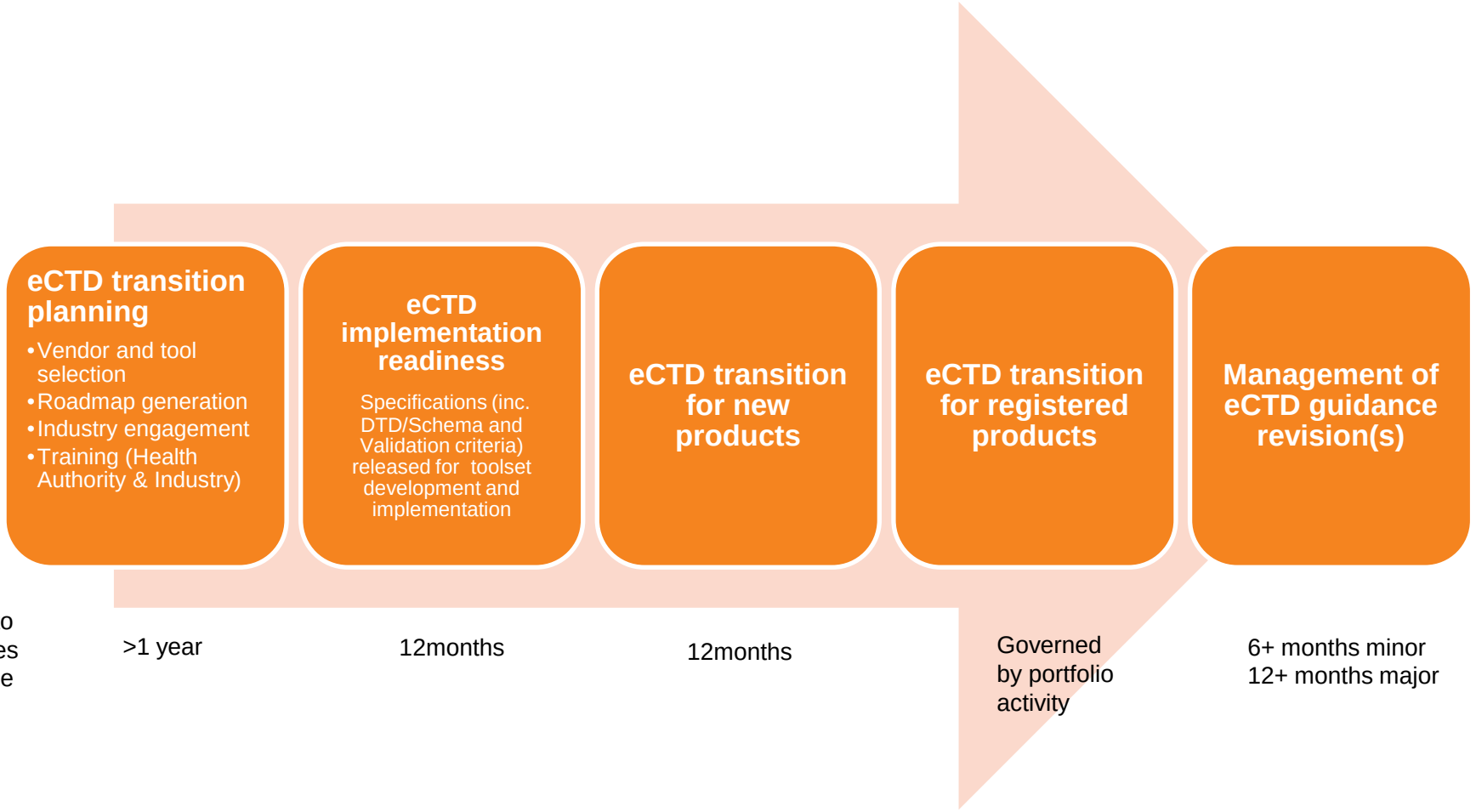
eCTD adoption timeline and considerations



Guide to timelines by stage	>1 year	12months	12months	Governed by portfolio activity	6+ months minor 12+ months major

eCTD transition planning – Vendor and tool selection

- Engage with established vendor(s) to develop 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

eCTD transition planning – roadmap

- Post the 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 gateway/portal for submission delivery enabling filings to be made from virtual support locations
  - Establishment of service desk in support of MAHs technical questions / issues

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eCTD transition planning – roadmap – a shared goal

- A careful and collaborative approach to implementation is beneficial to both the Health Authority and Industry
- It is encouraged to engage industry and health authorities from regions that have implemented eCTD as well as local experts.
- This includes education, pre-planning and industry engagement in tests/pilots.
- Benefits in the shared efforts include;
  - Reduces effort at both Health authority and industry
  - Leverages industry experience
  - Non CTD or electronic submission markets may benefit from the introduction of NeeS prior to eCTD adoption to increase familiarisation and experience in processing and reviewing electronic format CTD submissions

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eCTD transition planning – industry engagement

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eCTD transition planning – General Guidance

- Module 1 specifications are regionally driven and should be provided to accommodate regional requirements. M2-5 should follow ICH specifications.
- Best practice in formatting and validation guidance for markets that have adopted eCTD should be considered in the interest of consistency and harmonisation.
- Advantageous to minimise # of eCTDs for a product
  - Reduces time and effort on the Health Authority and industry
    - Less individual dossiers to build, validate, import and review
  - An eCTD application can cover all dosage forms and strengths of a product with one invented name
- Reuse of content. A physical document is supplied once and is referenced from multiple locations.
  - One eCTD submission can contain multiple ‘leafs’ each referencing (linking to) the same physical document
  - If application path is consistent, content can also be shared across different eCTDs
  - Content already supplied in a submission does not need to be provided again in future

eCTD transition planning – Validation

- eCTD sequences are validated before Applicant submission and after Health Authority receipt. This technical validation is a planned step, and an automated preparation for upload into a review tool. Technical problems can be expected and corrected prior to Health Authority content review.

- Pass/Fail and Best Practice as defined in the validation criteria
  - **Pass/Fail** – Failure to comply means the eCTD will not be uploaded into the HA review system. The submission is rejected due to technical failure and a replacement (with the same sequence number) is requested.

  - **Best Practice** – Failure to comply results in eCTD acceptance with advice intended to prevent future repetition. The applicant should make every effort to check and conform with Health Authority preferences prior to eCTD submittal. Importantly, such submissions may be rejected during subsequent content validation if ease of review is significantly affected

eCTD transition planning – recommendations

- Split technical validation versus validation criteria and content validation versus business rules for that particular submission type into two distinct processes each with defined timelines.
- Technical validation - criteria
  - **Pass/Fail** – ideally limited to factors critical for upload and review, such as valid XML or readable PDF files. Pass/fail checks on less critical aspects of eCTD, such as file naming, invalid links and bookmarks should be avoided as they could result in unnecessary rejection of dossiers.
  - **Best Practice** – should not be used to reject a submission at the initial validation stage, only later as assessment starts if the number of errors affects the review.

eCTD Transition Planning

eCTD transition for new products

- Experience shows that a phased and careful approach to eCTD adoption is the preferred option for both HA and industry – reducing time, wasted effort and achieving a smooth transition
  - Commencing with new product adoption in a staged manner allows for learnings across both HA and industry.

- Lead times typically introduced: Optional → Mandatory timeline encourages use while allowing phasing for
    - Pilots, learnings, Health Authority transition, Applicant preparation

eCTD for registered products

- eCTD format can be started with any regulatory activity
- A baseline can be used to resubmit existing approved content, however…
- Introducing eCTD baselines for registered products often carries many challenges
  - The difficulty often has a direct correlation with the age of the product.
  - Potential disruption to product
  - Implementation timelines to consider variability in registered product activity
  - Migration of existing products in ‘old’ format

Handling Different Strengths and Dosage Forms

Managing Strengths and Dosage Forms

Trade Name	Formulation	Strength	Licence number	
Mydrug	Powder for solution for infusion	1500mg	ABC/1234/01	eCTD 1
Mydrug	Powder for solution for infusion	500mg	ABC/1234/02	eCTD 2
Mydrug	Powder and solvent for solution for infusion	500mg	ABC/1234/03	eCTD 3
Mydrug	Powder and solvent for solution for infusion	1500mg	ABC/1234/04	eCTD 4

Each licence in its own eCTD application

Managing Strengths and Dosage Forms

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Mydrug	Powder for solution for infusion	500mg	ABC/1234/02	
Mydrug	Powder and solvent for solution for infusion	500mg	ABC/1234/03	eCTD 2
Mydrug	Powder and solvent for solution for infusion	1500mg	ABC/1234/04	

Each dosage form in its own eCTD application

Managing Strengths and Dosage Forms

Trade Name	Formulation	Strength	Licence number	
Mydrug	Powder for solution for infusion	1500mg	ABC/1234/01	eCTD 1
Mydrug	Powder for solution for infusion	500mg	ABC/1234/02	
Mydrug	Powder and solvent for solution for infusion	500mg	ABC/1234/03	
Mydrug	Powder and solvent for solution for infusion	1500mg	ABC/1234/04	

All dosage forms/strengths in its one eCTD application

Managing Strengths and Dosage Forms

One eCTD Application Per Strength Or Dosage Form

Advantages	Disadvantages
A new strength (line extension) could be handled in a new eCTD and would not affect existing lifecycle	All clinical and non-clinical reports are provided for each strength or dosage form (cannot cross reference across different eCTDs in many regions)
Each strength or dosage form is managed individually.	Any changes to the drug substance or changes that affect all strengths/dosage forms of the product (eg safety related changes to the labelling) would mean building and submitting multiple eCTD sequences, one within each eCTD application.
	Lifecycle is maintained separately, and would need to be managed across multiple potentially identical eCTD applications
	Common documents must be included in each eCTD application, (cannot cross reference from one eCTD to another in many regions)
	Difficult for the assessor to know what to read/what is unique. This needs therefore to be thoroughly described in each submission, which will typically consist of multiple identical sequences in different eCTD application lifecycles.

Managing Strengths and Dosage Forms

One Combined eCTD For Multiple Strengths And Dosage Forms

Advantages	Disadvantages
Documents that are common are presented only once and therefore read only once by the assessor	Some sequences would cover all products covered by the eCTD application, other sequences may affect only one strength or dosage form. Applicants need to use the submission description to describe what each sequence covers.
Any changes to drug substance, or safety related changes that affect the product, will require only one sequence	Adding a new strength (line extension) could involve replacing all 'common' documents with documents covering existing strengths plus the new strength, and also adding new additional strength specific documents
Common documents can be included only once (e.g., Pharmaceutical Development for multiple tablet strengths)	Lifecycle management becomes more complex in the following situations: • An applicant wants to transfer a certain marketing authorisation (certain strength) within one eCTD application to another MAH. • An applicant wishes to withdraw one strength • Variations may be only applicable for one specific strength, and result in the creation of strength specific documents. These would have to be added to the lifecycle and managed alongside the existing documentation, which, if originally 'common', would then only cover the existing (non-affected) strengths
All lifecycle is in one place	

Managing Strengths and Dosage Forms

Recommendations

- Merge strengths *and dosage forms* where possible to reduce workload in industry and regulators
- Be aware of product differences (stability, supply route, API etc)
- Industry: be clear about what decision has been made and be prepared to justify it
- Regulators – make use of eCTD metadata to understand what the eCTD application covers

Maintaining the eCTD

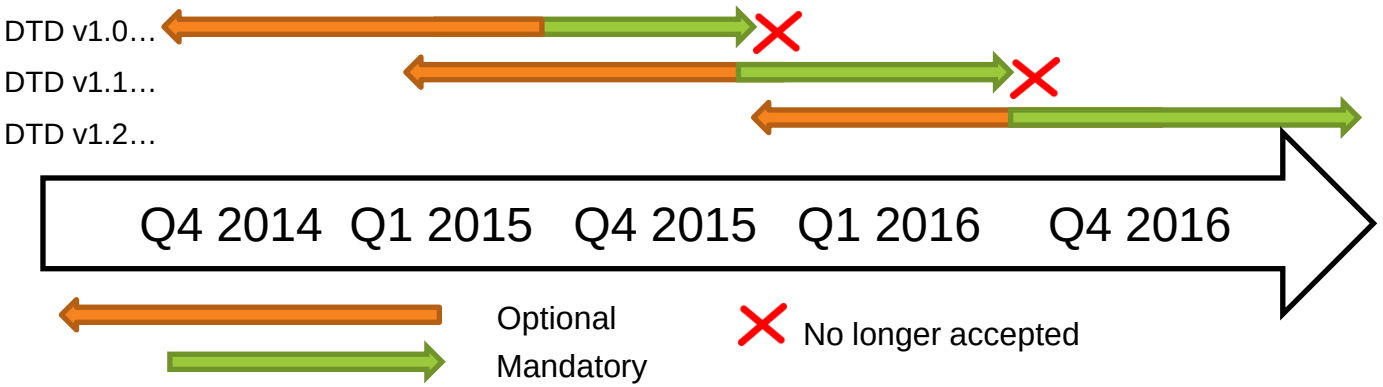
Management of eCTD guidance revision(s)

- Any change to the eCTD technical specification can involve:
  - Development and testing of the new specification and technical files (DTD, Schema, XSL)
  - 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:
  - 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.

Management of eCTD guidance revision(s) (example best practice)

	eCTD m1 Specification v1.4 with DTD v1.0	eCTD m1 Specification v1.5 with DTD v1.1	eCTD m1 Specification v1.6 with DTD v1.2
Release Notes	Link	Link	Link
Specification	Link	Link	Link
Annex	Link	Link	Link
DTD	Link	Link	Link
Examples	Link	Link	Link
Package	Link	Link	Link
Implementation Guide	Link	Link	Link



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Summaries and Comclusion

Maximising the benefits of electronic submissions

- Submission logistics – electronic gateways
  - Most eCTD implementations have started with submission of the eCTD dossier on a CD or DVD
  - Electronic gateways are a much more efficient way of sending and receiving eCTD dossiers
- Use of metadata
  - Metadata, unlike information in PDF documents, can be extracted directly into review and assessment systems
  - The eCTD has some metadata describing the submission in the m1 envelope
  - Further metadata can be provided in delivery files sent with the eCTD, or in the application form (in Europe, the eAF)
  - Introducing a fixed standard for the container folder for the eCTD (the folder above ‘0000, 0001 etc) allows cross reference from one application to another

Summary recommendation to adoption

Move to ICH eCTD standard is welcomed by industry and this proven approach achieves the shared objective with minimal rework for all:

- **New Products:**
  - *eCTD Submittal from [x date] optional and encouraged*
    - Opportunity to select industry participants for pilot
    - Providing training and guidance/Q&A for applicants
    - Encourage adoption by avoiding vigorous validation testing (e.g. rejecting because of broken hypertext links)
  - *eCTD Submittal after [y date] mandatory*
    - Gives notice, accommodates transition period for portfolio and technology

- **Currently Registered Products**
  - *eCTD Submittal from [x date] encouraged, optional & recommended baseline*
    - Any baseline provided will focus on Module 3.
  - *eCTD Submittal after [y date] mandatory, optional & recommended baseline.*
    - Over time, Variations will provide current registered CMC commitments to the HA system, with no additional cost, time or resources to HA or applicant
- Submittal in eCTD format to remove HA requirement for paper.

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Key Learnings from other Regions

- Need clear guidance, closely aligned to ICH
- Material readily available (e.g. on agency website)
- Advance notices of changes and plenty of time to comply
- Engagement with industry throughout process

Key Recomendation Summary

Bullet	Background
Foster the ICH community beyond US/EU/JP/CA/CH and encourage inclusion of Eurasian, Middle East, Asian, African and Pan-American/ Pacific Countries	EFPIA supports and encourages adoption of global standards. EFPIA continues to be engaged at all levels in ICH, HL7, CDISC etc. and will consider any new standard or change in existing standard in a global context.
Work on a worldwide roadmap for eSubmission	
Strive to reduce regional specialties in eCTD Modules 2 – 5 (keep it simple) and push regional specifics to Module 1 only	
Higher acceptance of regional needs (don‘t disregard standards like CDISC if provided in M2 –M5)	
Support harmonization of regional associations like 31 countries under EU procedure; expand to GCC and others where a common M1 spec is used	EFPIA also supports regional harmonisation where there is an opportunity to develop and share standards that compliment global standards, such as EU eSubmissions harmonisation, Eurasian adoption of eCTD, other….

Key Recomendation Summary (contd)

Bullet	Background
Collaborate across agencies and industry when setting up new local eCTD specifications (no re-invention of the wheel every time)	EFPIA has a long history of collaboration with SDOs and agencies to develop mutually beneficial standards and guidance, and to implement suitable change control and maintenance processes. For example, in Europe, EFPIA member companies worked with EU agencies from 2003 onwards in the development of all eSubmission capability in all EU countries, helping to drive harmonisation, but also providing technical resources and know how, and representing the view of the applicant to the regulator.
Allow sufficient time for transition periods (vendors!)	
Strive for re-use of documents globally by telematics tool support (Controlled Vocabulary, ISO-IDMP)	EFPIA also supports global initiatives such as IDMP, and other activities with respect to global harmonisation of requirements and technology. Such initiatives improve patient safety and access to medicines globally.
Openness to accept English language (reduce translations)	
Harmonize having one format (eCTD) for registrations, CTAs, Orphans, Paediatrics, Medical Devises, Veterinary rather than having specific formats	

Questions?

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