Comparison of eCTD and CTD & Preparing your company for electronic submission – required business process changes

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DIA

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About the Presenter

- Karl-Heinz Loebel
  Director, Principle Consultant Regulatory Operations,
  Industry/Agency Liaisons
  PHARMALEX GmbH
- 14 years in Regulatory Affairs/ Regulatory Operations (= eSubmissions)
- eSubmissions, NeeS, eCTD, XEVMPD, IDMP
- Software Configuration & Implementation

- PHARMALEX
- consultancy in Regulatory Affairs and Pharmacovigilance
- Headquarters in Germany, subsidiaries in US, Brazil, ES, UK, FR, IT, DK, BG, LT, Georgia, India, …
- global headcount ca. 800
- client portfolio: all types and sizes of pharmaceutical industries

Topics

- What is eCTD?
- CTD *versus* eCTD
- eCTD impact on industry and agencies
- all the things that can go wrong

Topics

- **What is eCTD?**
- CTD *versus* eCTD
- eCTD impact on industry and agencies
- all the things that can go wrong

What is eCTD? (I)

What people have in mind, when they talk about ‘eCTD’
‘an interface for industry to agency transfer of regulatory information […]’*
any assortment of PDF files for submission to Regulatory Agencies
the rules about how to structure applications to Regulatory Agencies
What I see on my screen/with my reviewing software when doing assessments

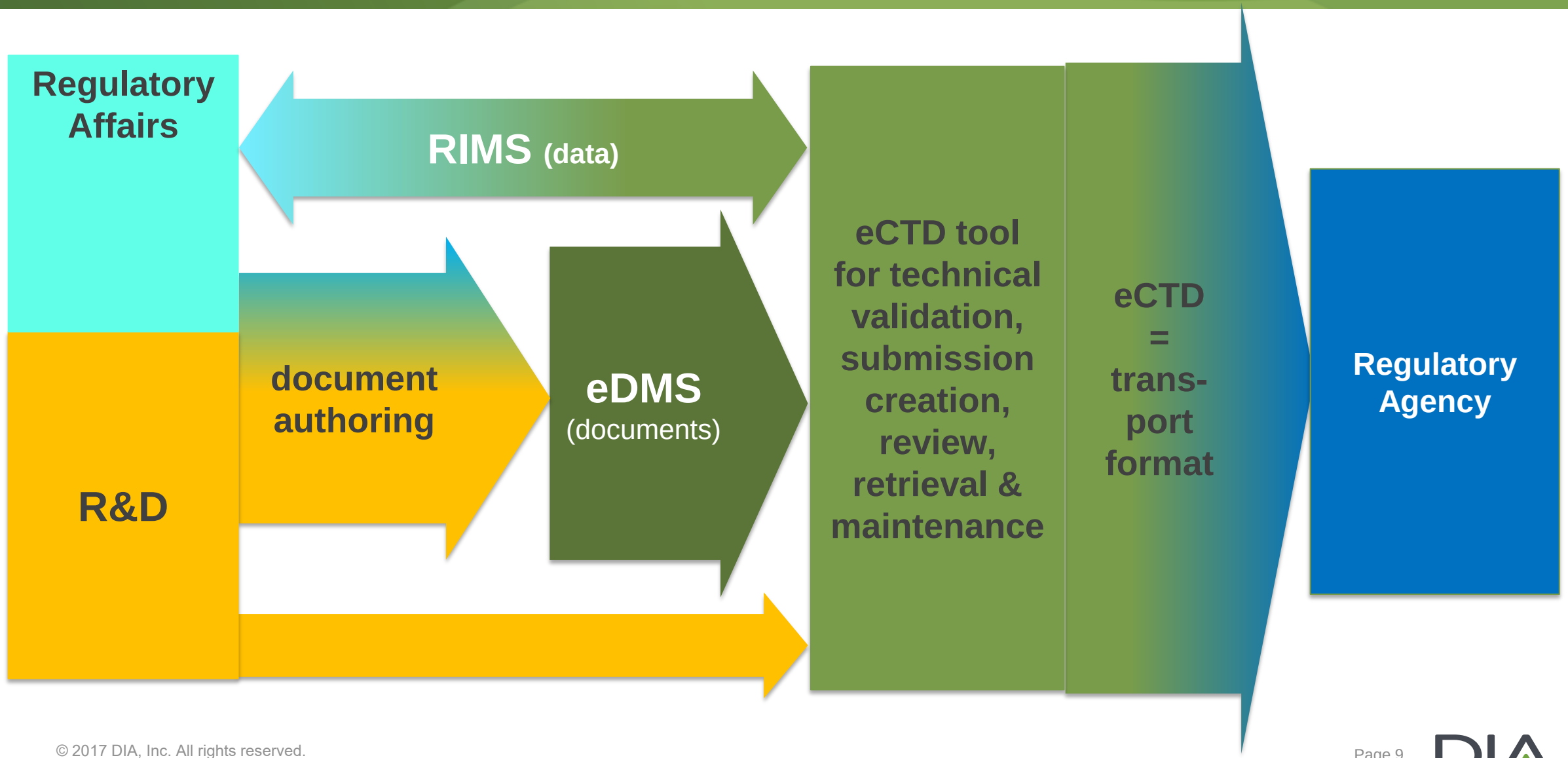
* ICH eCTD Specification V 3.2.2, 2008

What is eCTD? (II)

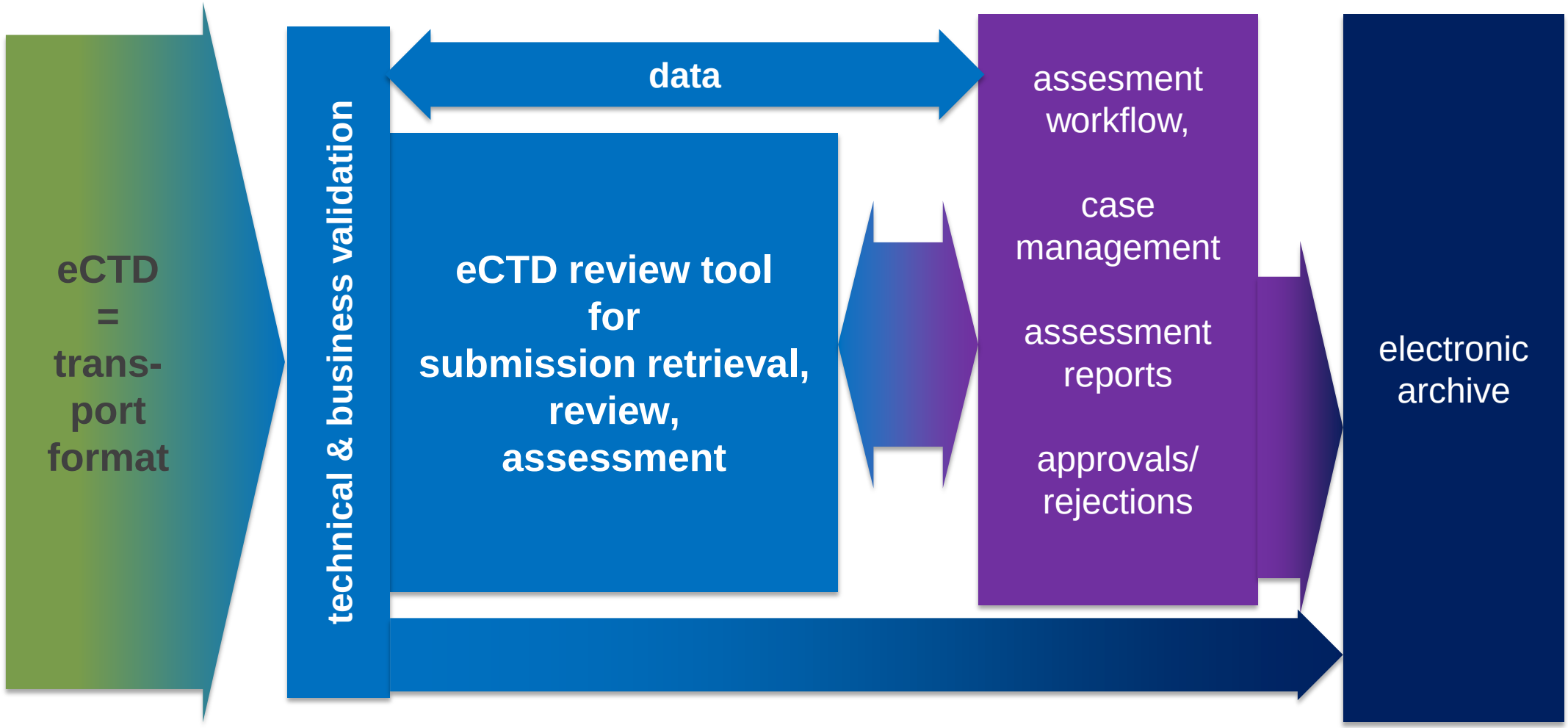
What people have in mind, when they talk about ‘eCTD’
a kind of electronic document management system
submitting data instead of documents
all the SOPs and work Instructions in my company on eCTD
creating hyperlinks in a submission
…

* ICH eCTD Specification V 3.2.2, 2008

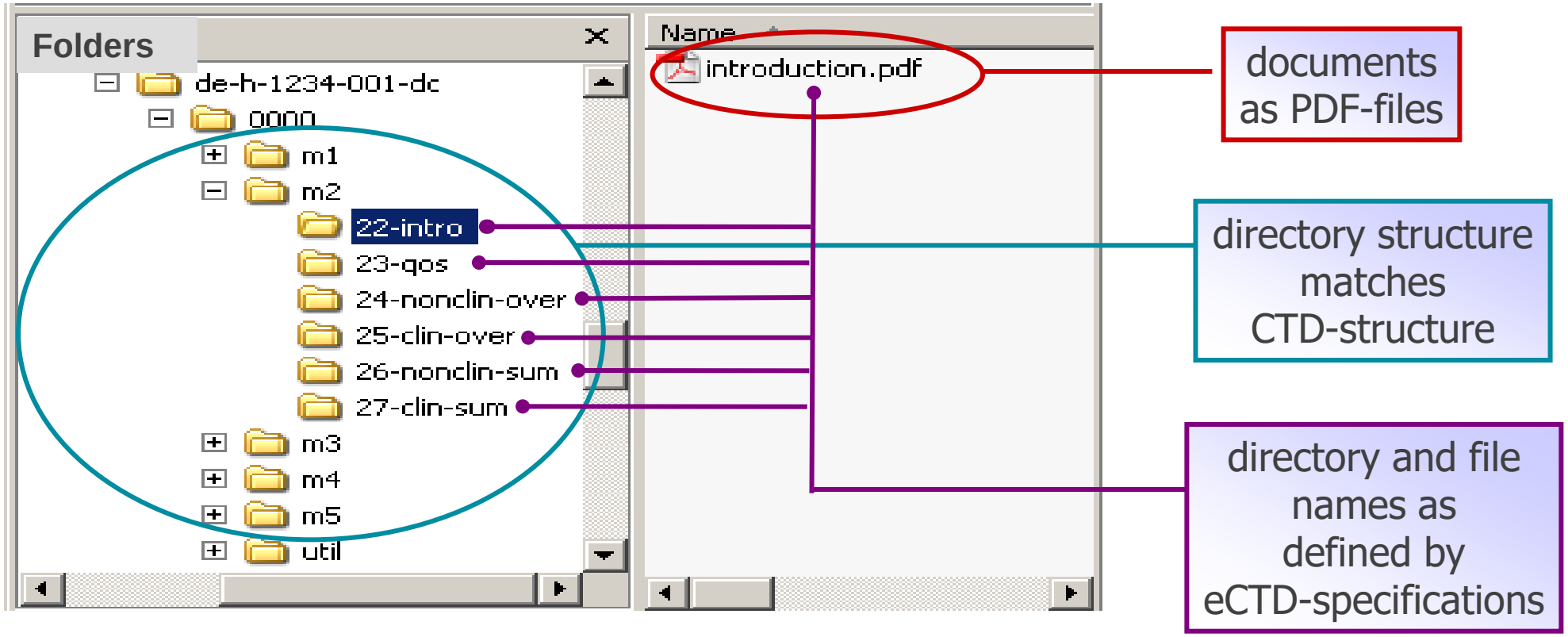
What is eCTD? (IV) – **industry** point of view



What is eCTD? (V) – **agency** point of view



What is eCTD? (VI) – ICH files & folder structure



See ICH eCTD Specification V 3.2.2

What is eCTD? (VII) – granularity of documents/files

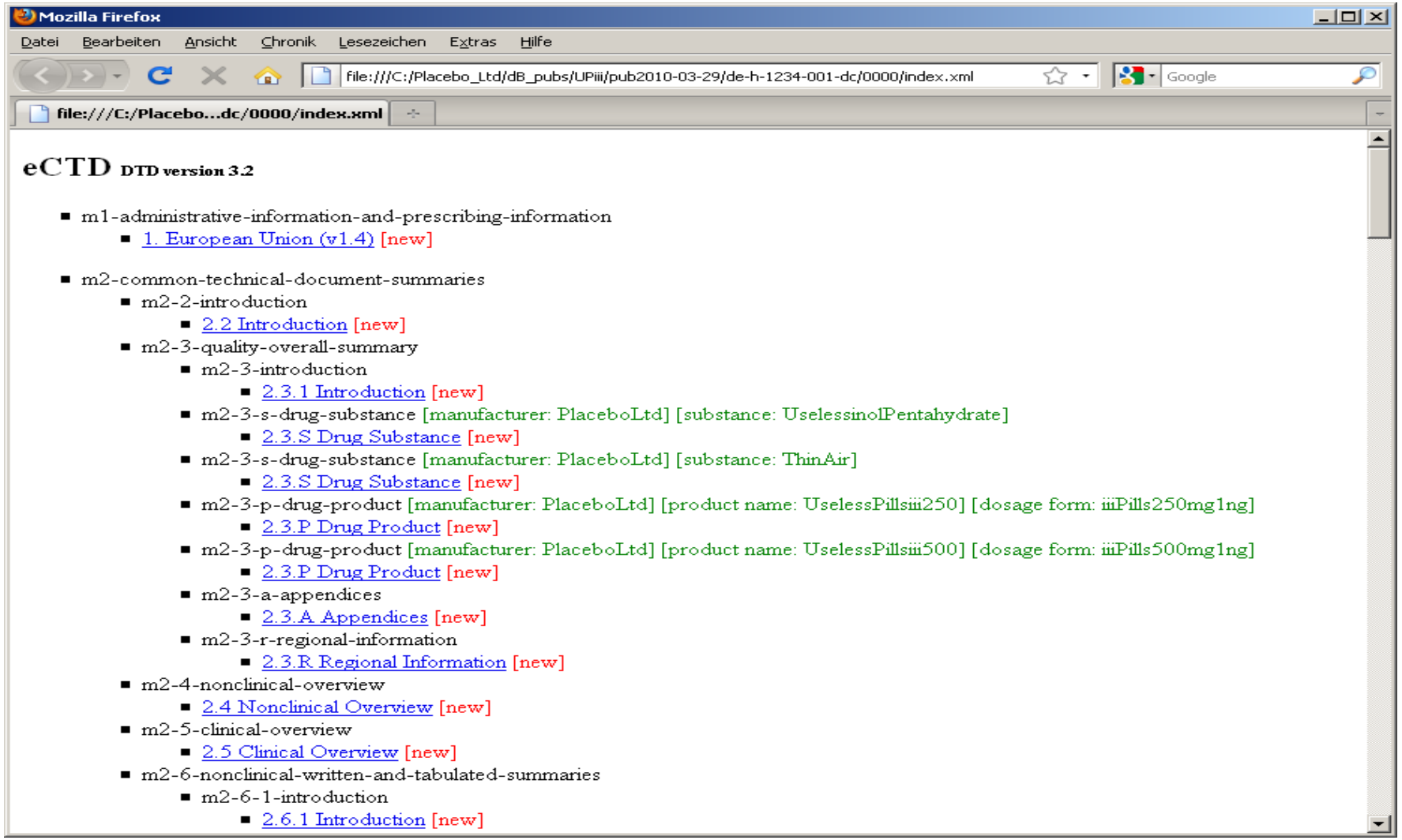
Module 4	4.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD			
	4.2	4.2.1	4.2.1.1	Studies Note 1	
			4.2.1.2	Studies Note 1	
			4.2.1.3	Studies Note 1	
			4.2.1.4	Studies Note 1	
		4.2.2	4.2.2.1	Studies Note 1	
			4.2.2.2	Studies Note 1	
			4.2.2.3	Studies Note 1	
			4.2.2.4	Studies Note 1	
			4.2.2.5	Studies Note 1	
			4.2.2.6	Studies Note 1	
			4.2.2.7	Studies Note 1	
		4.2.3	4.2.3.1	Studies Note 1	
			4.2.3.2	Studies Note 1	
			4.2.3.3	4.2.3.3.1	Studies Note 1
				4.2.3.3.2	Studies Note 1
			4.2.3.4	4.2.3.4.1	Studies Note 1
				4.2.3.4.2	Studies Note 1
				4.2.3.4.3	Studies Note 1
			4.2.3.5	4.2.3.5.1	Studies Note 1
				4.2.3.5.2	Studies Note 1
				4.2.3.5.3	Studies Note 1
				4.2.3.5.4	Studies Note 1
			4.2.3.6	Studies Note 1	
			4.2.3.7	4.2.3.7.1	Studies Note 1

http://www.ich.org/LOB/media/MEDIA554.pdf

- **32p5-contr-drug-prod**
  - **32p51-spec**
    - specifications-var.pdf
  - **32p52-analyt-proc**
    - analytical-procedure.pdf
  - **32p53-val-analyt-proc**
    - validation-analytical-procedures.pdf
  - **32p54-batch-analys**
    - batch-analyses-var.pdf
  - **32p55-charac-imp**
    - characterisation-impurities-var.pdf
  - **32p56-justif-spec**
    - justification-of-specifications-var.pdf
- **32p6-ref-stand**
  - reference-standards-var.pdf
- **32p7-cont-closure-sys**
  - container-closure-system-var.pdf
- **32p8-stab**
  - stability-summary-var.pdf
  - postapproval-stability-var.pdf
  - stability-data-var.pdf

http://esubmission.ema.europa.eu/tiges/docs/eCTD%20EU%20Validation%20Criteria%20v7.1_Feb-2018.xlsx

What is eCTD? (IX) – ICH xml backbone



Linked submission
Table of Content
for Modules 2 – 5

&

Module 3 meta data on
active substance(s)' name(s),
product(s)' name(s)

manufacturers,
dosage form(s)

&

Module 5 meta data on
Indications

&

life cycle operators
(new, replace, delete, append)

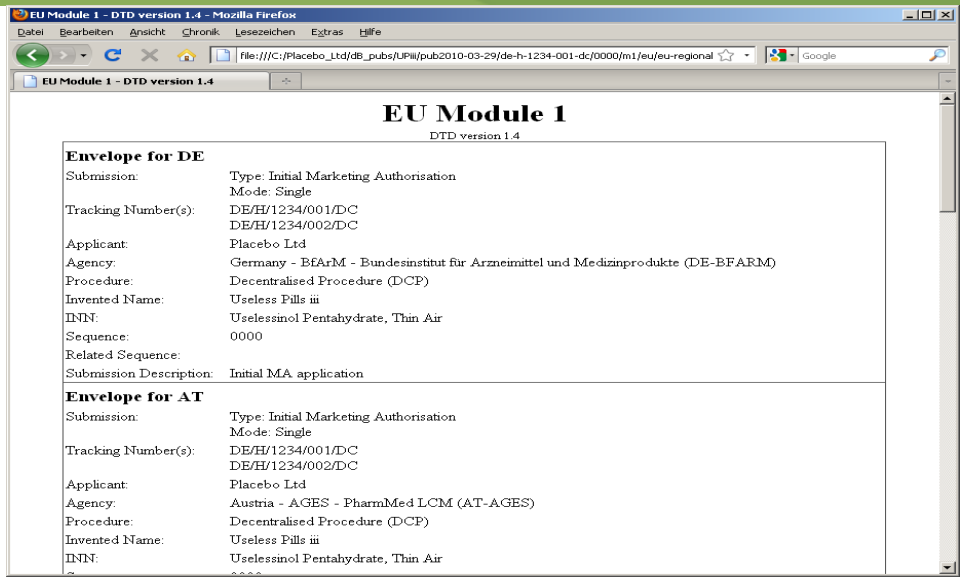
See ICH eCTD Specification V 3.2.2

What is eCTD? (X) – ICH PDF file properties

- PDF version (1.4 … 1.7)
- certain PDF properties (fast web view, file display settings, no password protection, …)
- PDF file size restrictions
- File name characters
- bookmarks & hyperlinks
- page size & orientation
- handling of scanned pages
- embedded fonts
- …

See **Specification for Submission Formats for eCTD v. 1.2**

What is eCTD? (XI) – Module 1



- different in all regions, but content is similar:

  cover letter, product information/labelling in local language, (application) forms, administrative documents,

  previous communication with agency, …, anything that doesn't fit into M2 – M5
- eCTD 'envelope' with coded data ('structured data') about the submission.
- in some regions more detailed coded data ('structured data') within electronic forms (e.g. EU electronic Application Form)

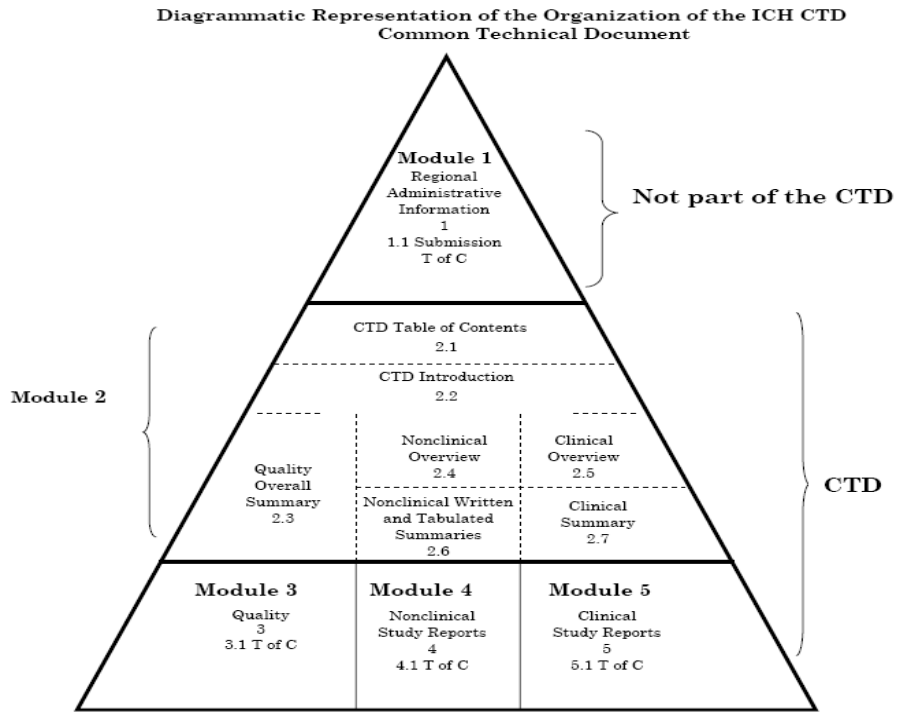
Topics

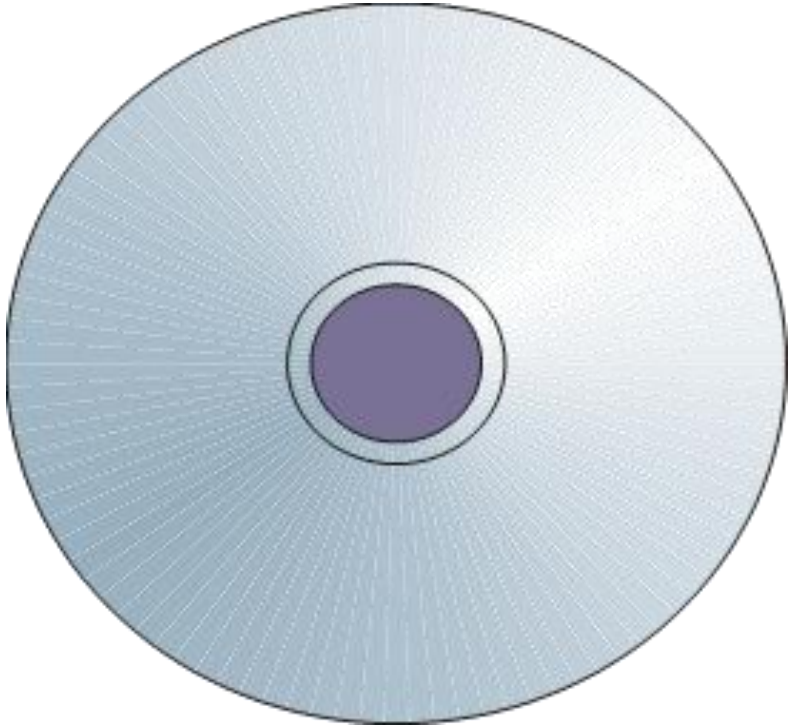
- What is eCTD?
- **CTD *versus* eCTD**
- eCTD impact on industry and agencies
- all the things that can go wrong

CTD *versus* eCTD (I)

- Both a brainchild of **ICH**
- **CTD** – the structure of documentation for submission of marketing authorisation/registration applications
- **eCTD** – technical requirements to submit CTD structured documentation electronically
- **CTD/eCTD** cover '**scientific**' part of documentation (Modules 2- 5) and **general technical requirements**, additional **REGIONAL** guidance covers '**administrative**' and **specific national** documentation
- Content of individual documents based on **ICH Quality**, **Safety** and **Efficacy** guidance

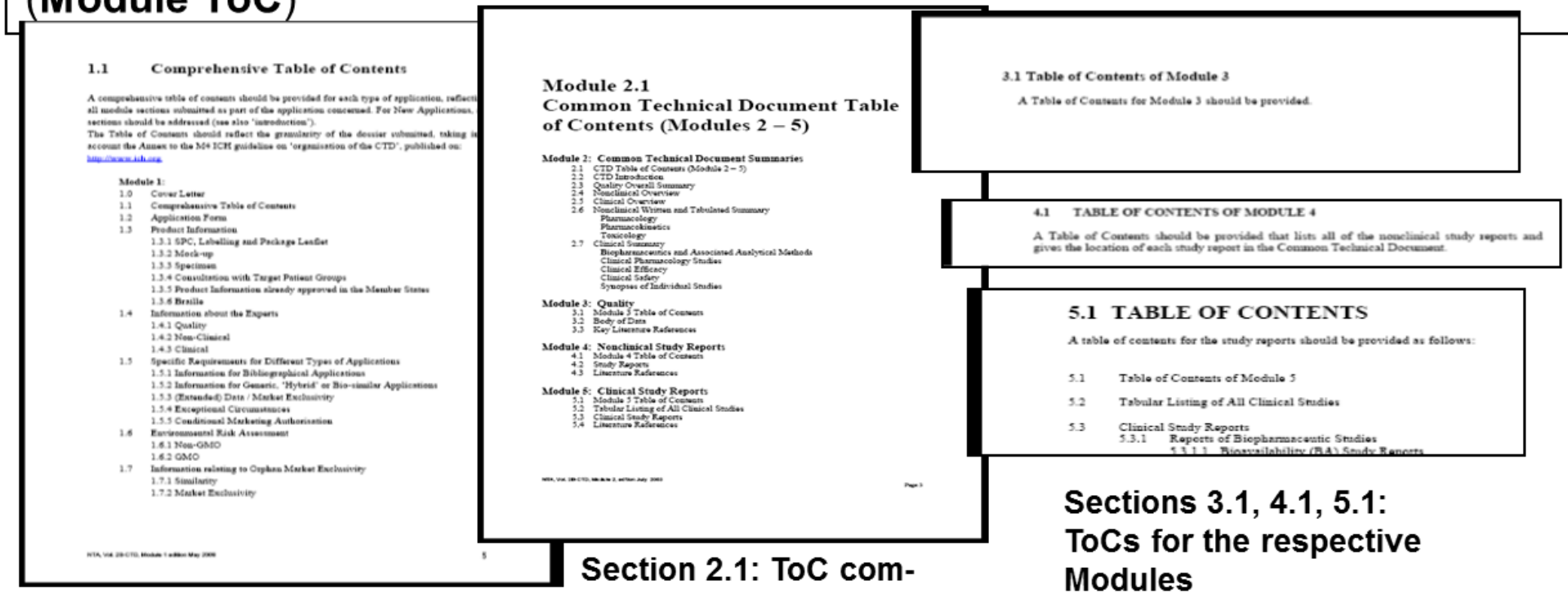
CTD *versus* eCTD (II)





CTD *versus* eCTD (III) – **CTD**: Modules' ToC

Each CTD Module includes a Module- or even submission-wide Table of Contents (**Module ToC**)



1.1 Comprehensive Table of Contents

A comprehensive table of contents should be provided for each type of application, reflecting all module sections submitted as part of the application concerned. For New Applications, all sections should be addressed (see also 'introduction').
The Table of Contents should reflect the granularity of the dossier submitted, taking into account the Annex to the M4 ICH guideline on 'organisation of the CTD', published on:
http://www.ich.org

Module 1:
1.0 Cover Letter
1.1 Comprehensive Table of Contents
1.2 Application Form
1.3 Product Information
1.3.1 SPC, Labelling and Package Leaflet
1.3.2 Mock-up
1.3.3 Specimen
1.3.4 Consultation with Target Patient Groups
1.3.5 Product Information already approved in the Member States
1.3.6 Braille
1.4 Information about the Experts
1.4.1 Quality
1.4.2 Non-Clinical
1.4.3 Clinical
1.5 Specific Requirements for Different Types of Applications
1.5.1 Information for Bibliographical Applications
1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications
1.5.3 (Extended) Data / Market Exclusivity
1.5.4 Exceptional Circumstances
1.5.5 Conditional Marketing Authorisation
1.6 Environmental Risk Assessment
1.6.1 Non-GMO
1.6.2 GMO
1.7 Information relating to Orphan Market Exclusivity
1.7.1 Similarity
1.7.2 Market Exclusivity

Module 2.1
Common Technical Document Table of Contents (Modules 2 – 5)

Module 2: Common Technical Document Summaries
2.1 CTD Table of Contents (Module 2 – 5)
2.2 CTD Introduction
2.3 Quality Overall Summary
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summary
Pharmacology
Pharmacokinetics
Toxicology
2.7 Clinical Summary
Biopharmaceutics and Associated Analytical Methods
Clinical Pharmacology Studies
Clinical Efficacy
Clinical Safety
Synopses of Individual Studies

Module 3: Quality
3.1 Module 3 Table of Contents
3.2 Body of Data
3.3 Key Literature References

Module 4: Nonclinical Study Reports
4.1 Module 4 Table of Contents
4.2 Study Reports
4.3 Literature References

Module 5: Clinical Study Reports
5.1 Module 5 Table of Contents
5.2 Tabular Listing of All Clinical Studies
5.3 Clinical Study Reports
5.4 Literature References

3.1 Table of Contents of Module 3

A Table of Contents for Module 3 should be provided.

4.1 TABLE OF CONTENTS OF MODULE 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the Common Technical Document.

5.1 TABLE OF CONTENTS

A table of contents for the study reports should be provided as follows:

5.1 Table of Contents of Module 5
5.2 Tabular Listing of All Clinical Studies
5.3 Clinical Study Reports
5.3.1 Reports of Biopharmaceutic Studies

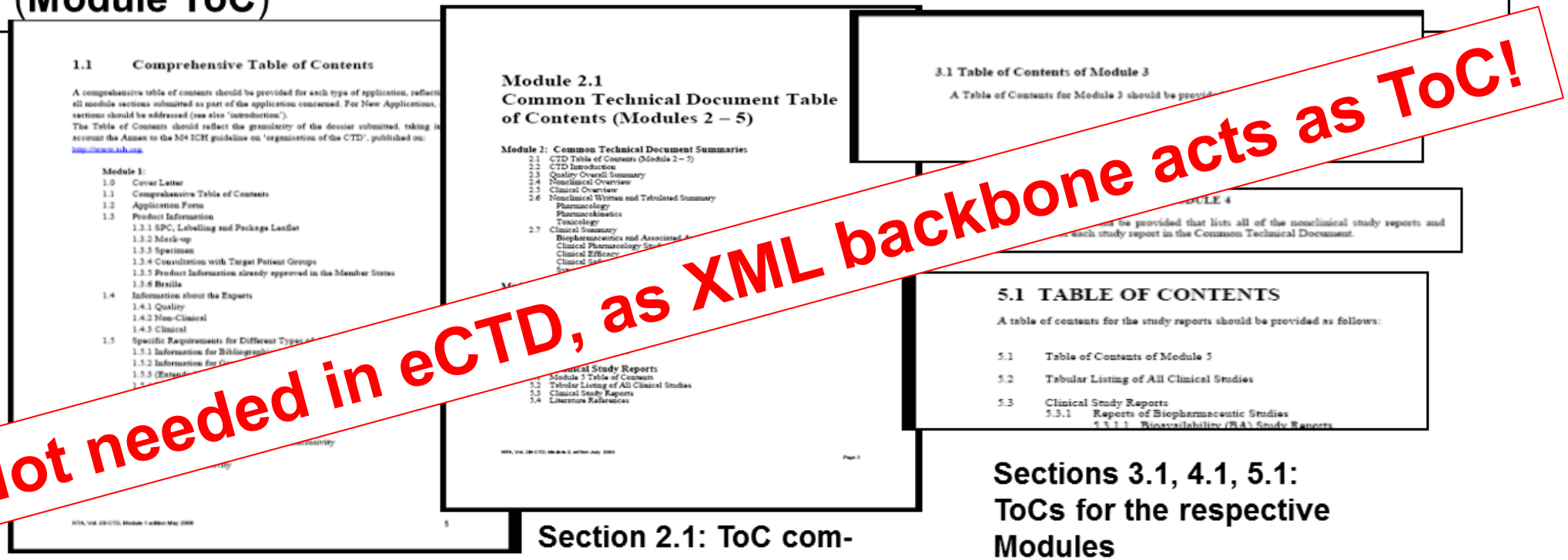
Section 1.1: comprehensive (submission wide) ToC

Section 2.1: ToC comprising Modules 2 - 5.

Sections 3.1, 4.1, 5.1: ToCs for the respective Modules

CTD *versus* eCTD (III) – **CTD**: Modules' ToC

Each CTD Module includes a Module- or even submission-wide Table of Contents (**Module ToC**)

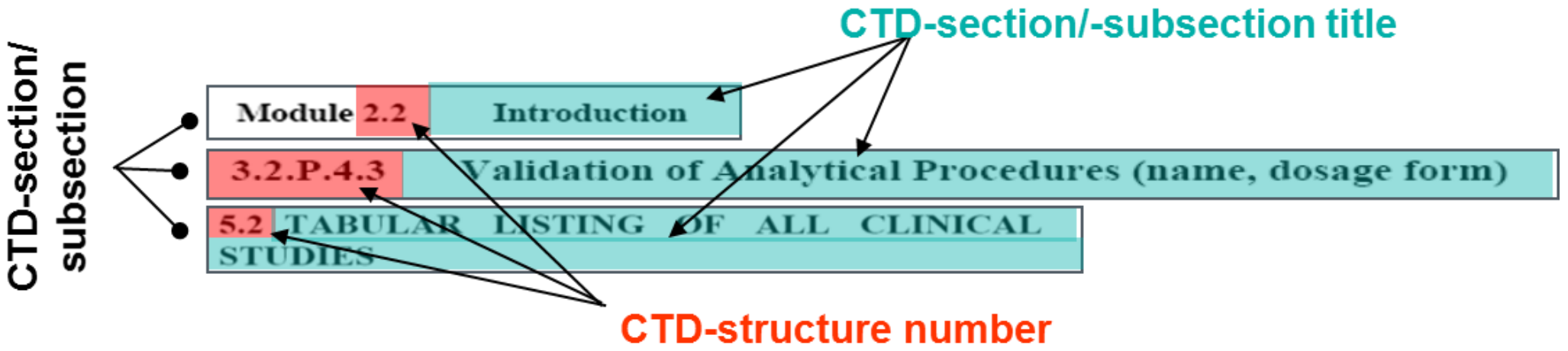


Section 1.1: comprehensive (submission wide) ToC

Section 2.1: ToC comprising Modules 2 - 5.

Sections 3.1, 4.1, 5.1: ToCs for the respective Modules

CTD *versus* eCTD (IV) – section numbers and headings

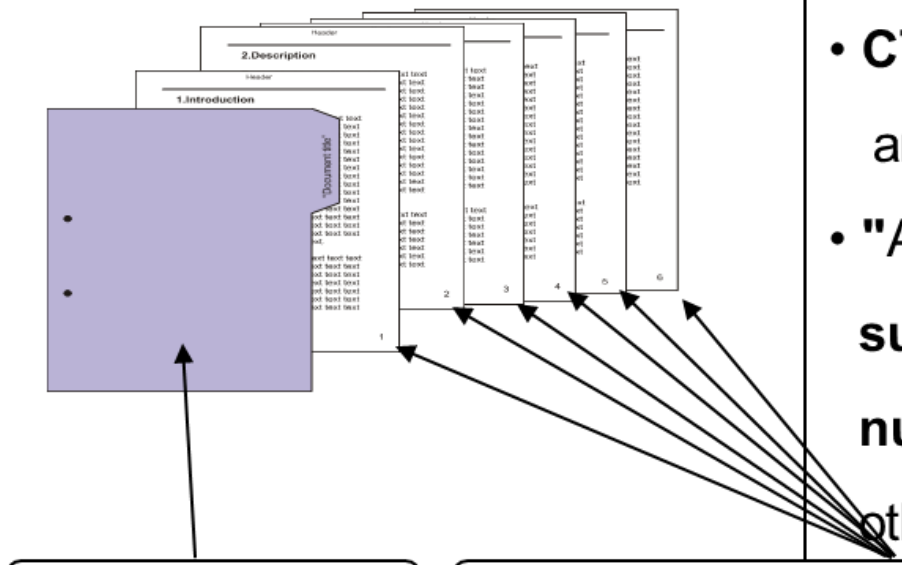


- section numbers & headings same in CTD and eCTD

but

- new eCTD era: headings in other languages than English (in line with ICH eCTD specifications)

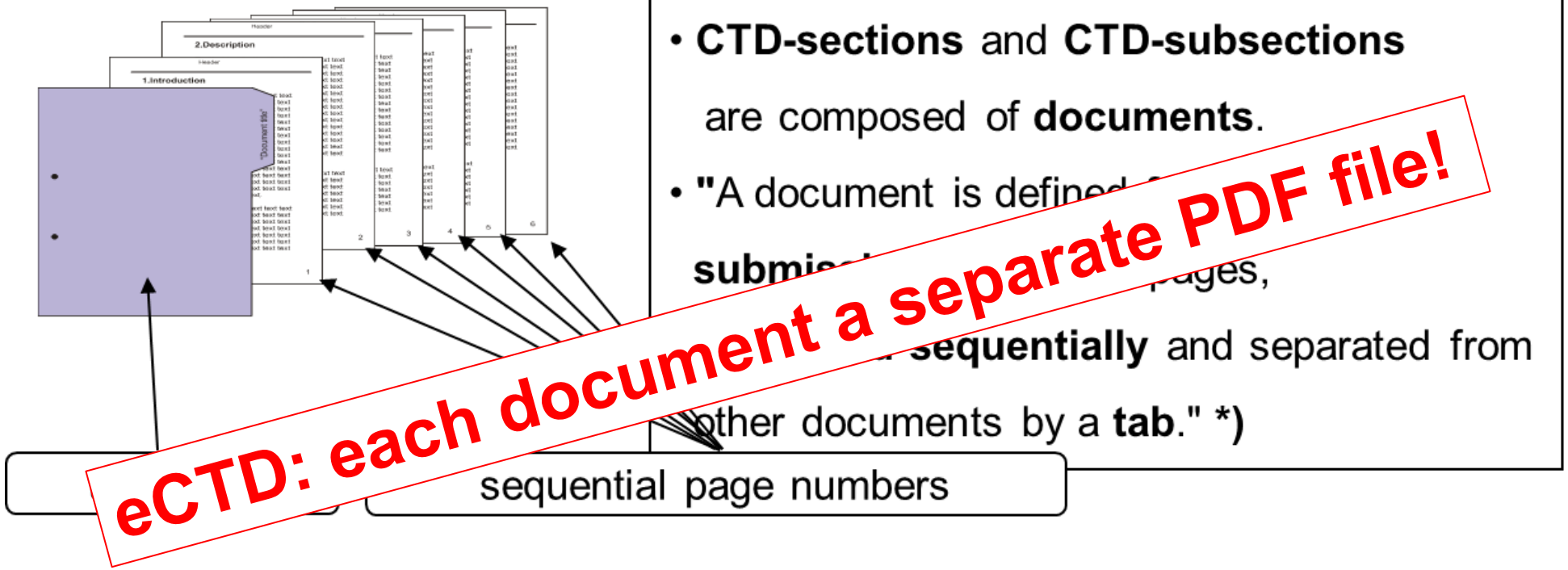
CTD *versus* eCTD (V) – **CTD** document definition



- **CTD-sections** and **CTD-subsections** are composed of **documents**.
- **"**A document is defined **for a paper submission** as a set of pages, **numbered sequentially** and separated from other documents by a **tab**." ***)**

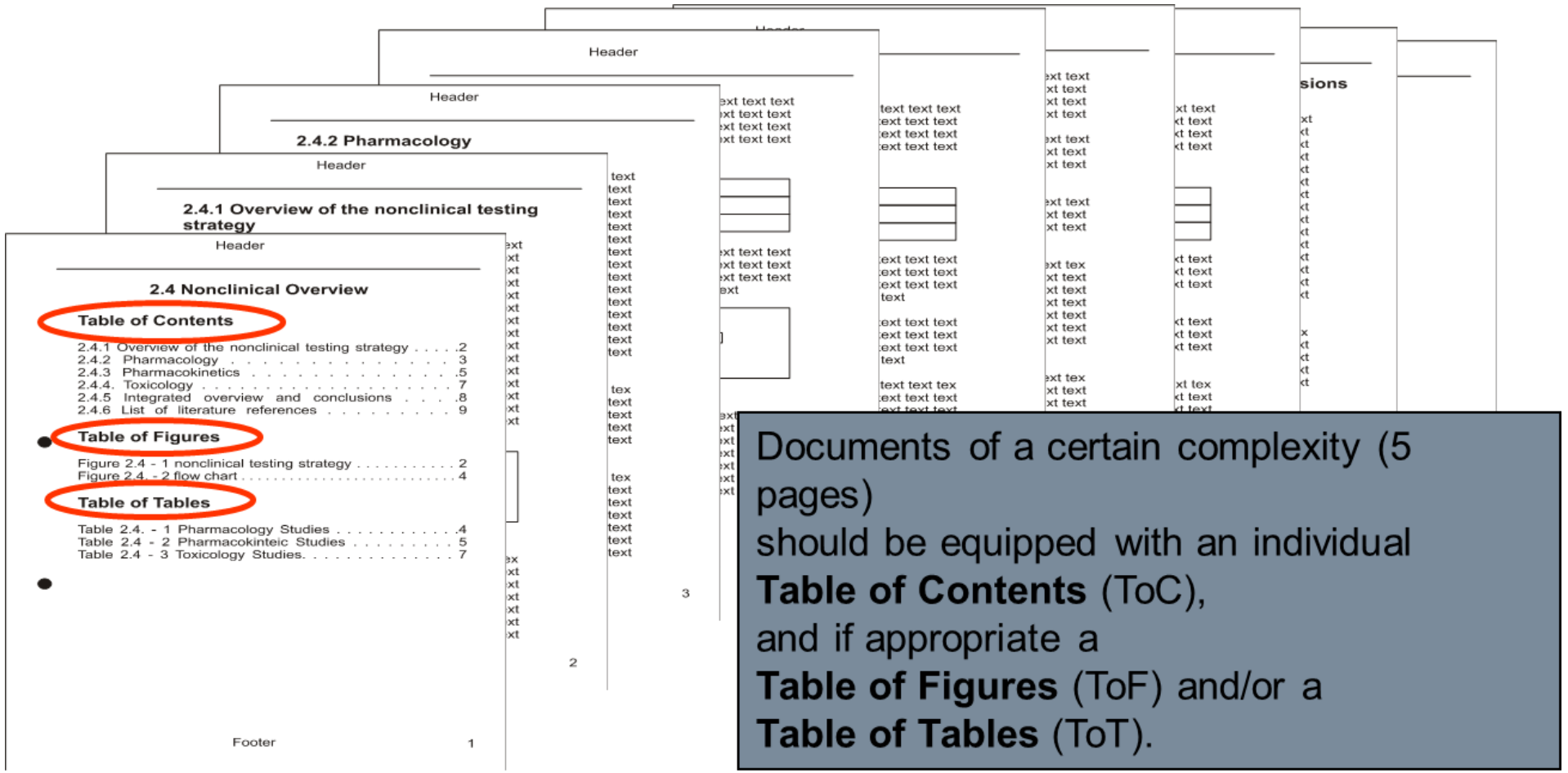
***)** cited from "ICH HARMONISED TRIPARTITE GUIDELINE ORGANISATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE M4.

CTD *versus* eCTD (V) – **CTD** document definition



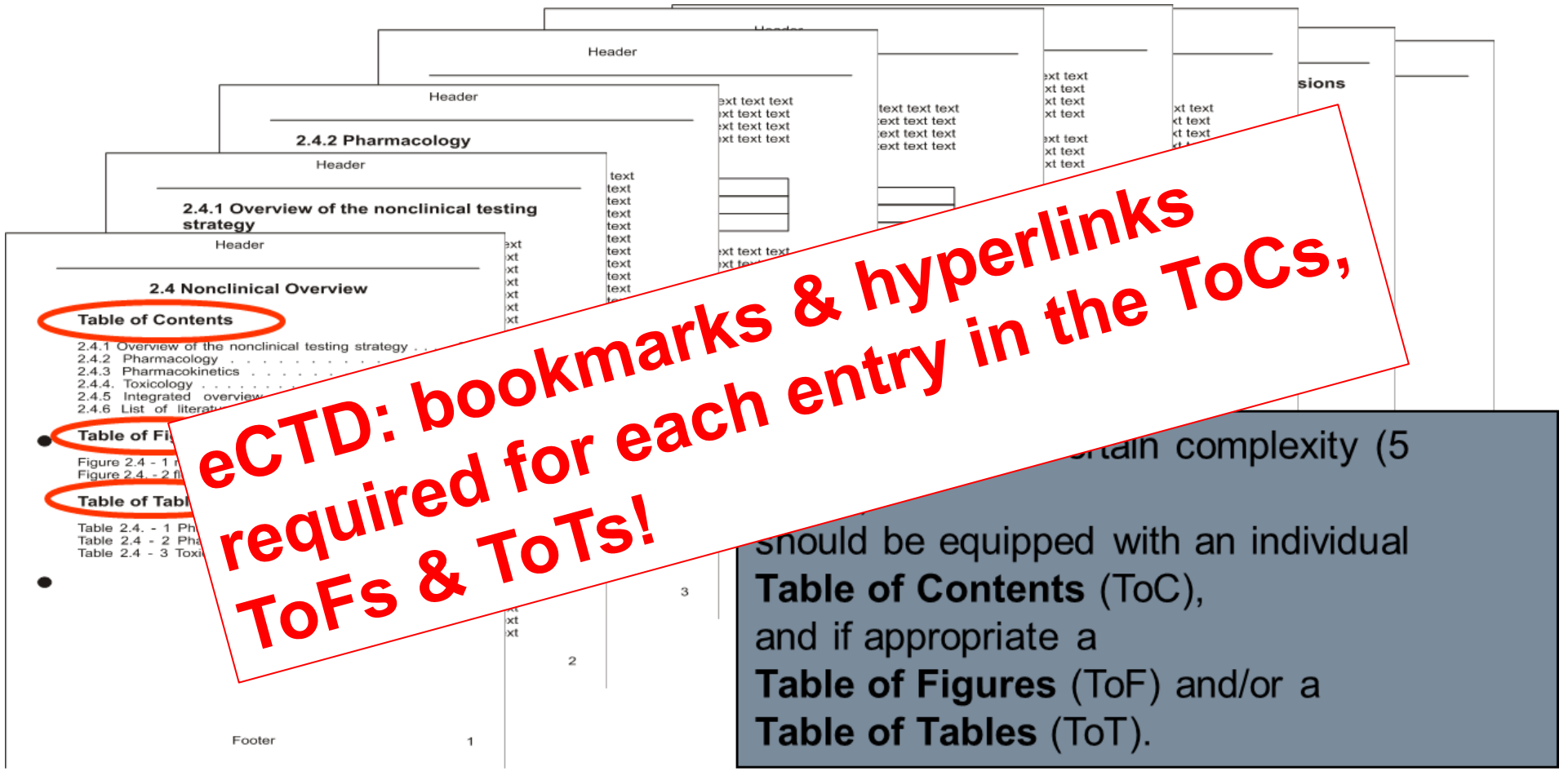
*) cited from "ICH HARMONISED TRIPARTITE GUIDELINE ORGANISATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE M4.

CTD *versus* eCTD (VI) – **CTD** document structure



Documents of a certain complexity (5 pages)
should be equipped with an individual **Table of Contents** (ToC),
and if appropriate a
Table of Figures (ToF) and/or a
Table of Tables (ToT).

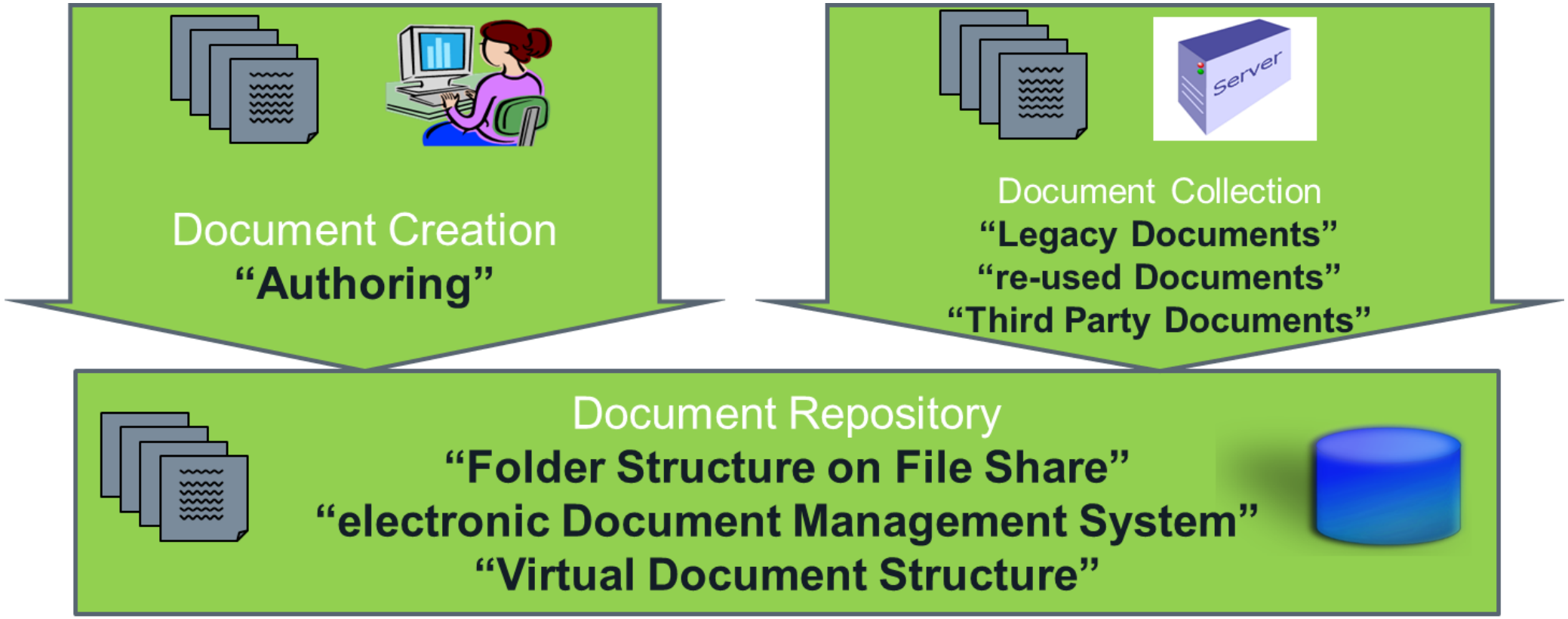
CTD *versus* eCTD (VI) – **CTD** document structure



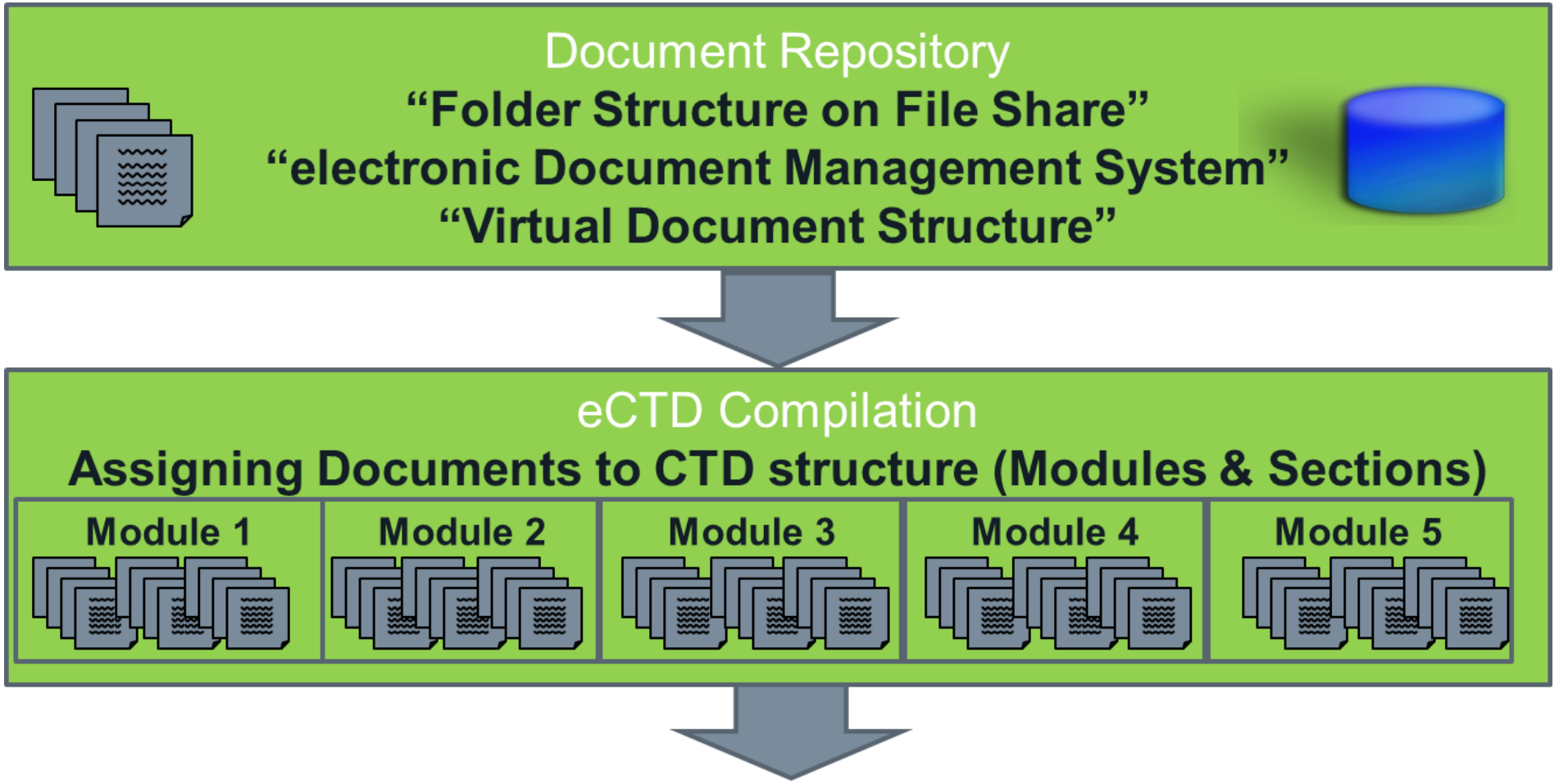
CTD *versus* eCTD (VII) – **eCTD** documents in general

- MS Word document templates to ensure correct granularity and provide cross references for bookmarks and hyperlinks
- authors to be trained to use MS Word features properly
- software settings to make sure PDF renditions from Word are correct
- document review to include Word **and** PDF rendition

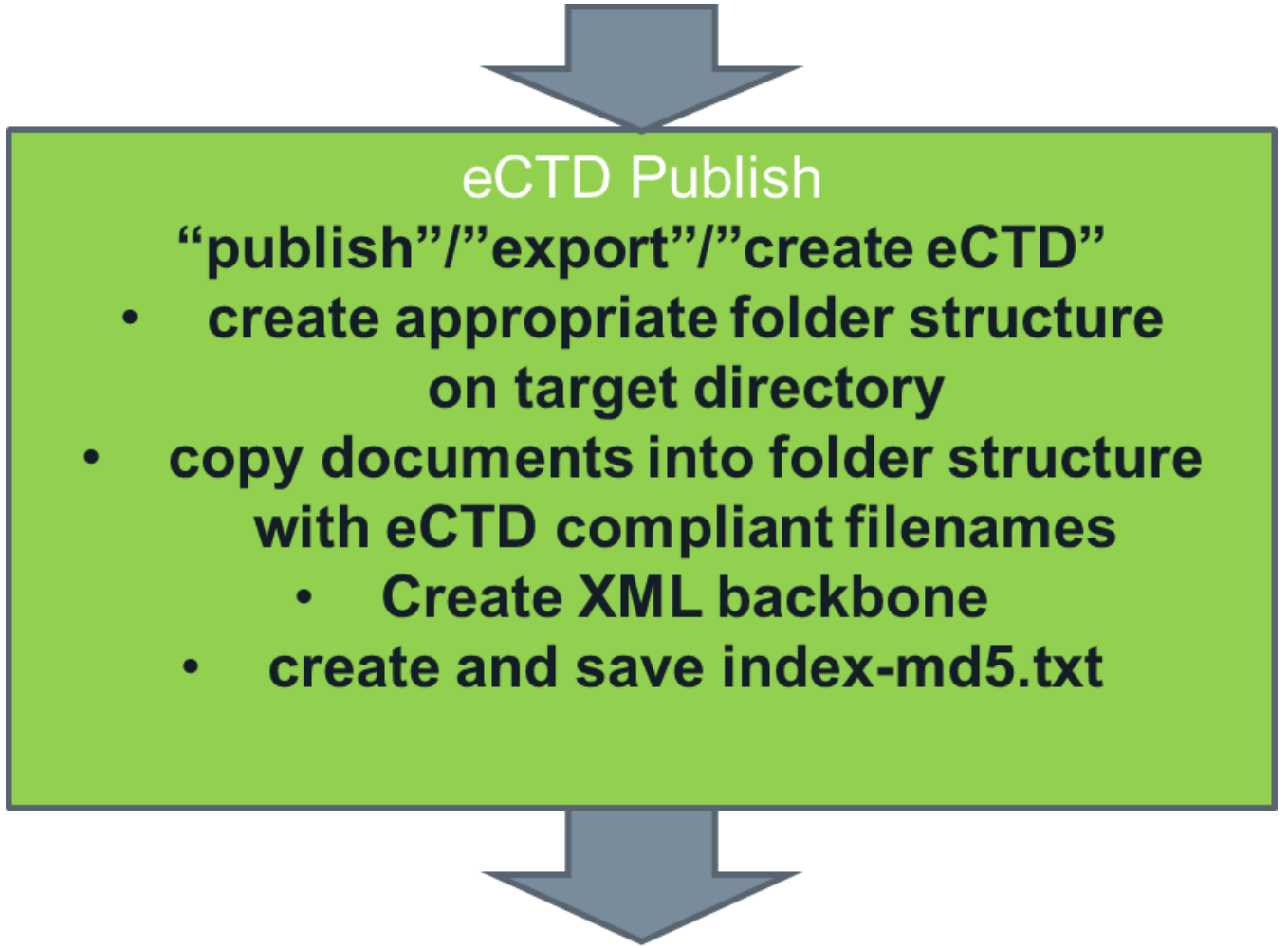
CTD *versus* eCTD (VIII) – eCTD compilation & submission process (I)



CTD *versus* eCTD (VIII) – eCTD compilation & submission process (II)



CTD *versus* eCTD (VIII) – eCTD compilation & submission process (III)



CTD *versus* eCTD (VIII) – eCTD compilation & submission process (IV)

eCTD Technical Validation

- **perform Technical Validation using Validation Tool and appropriate validation rules ("eValidator", "GlobalValidator", "GlobalSubmit Validator", …)**
- **correct and re-publish if necessary**

CTD *versus* eCTD (VIII) – eCTD compilation & submission process (V)

eCTD Dispatch

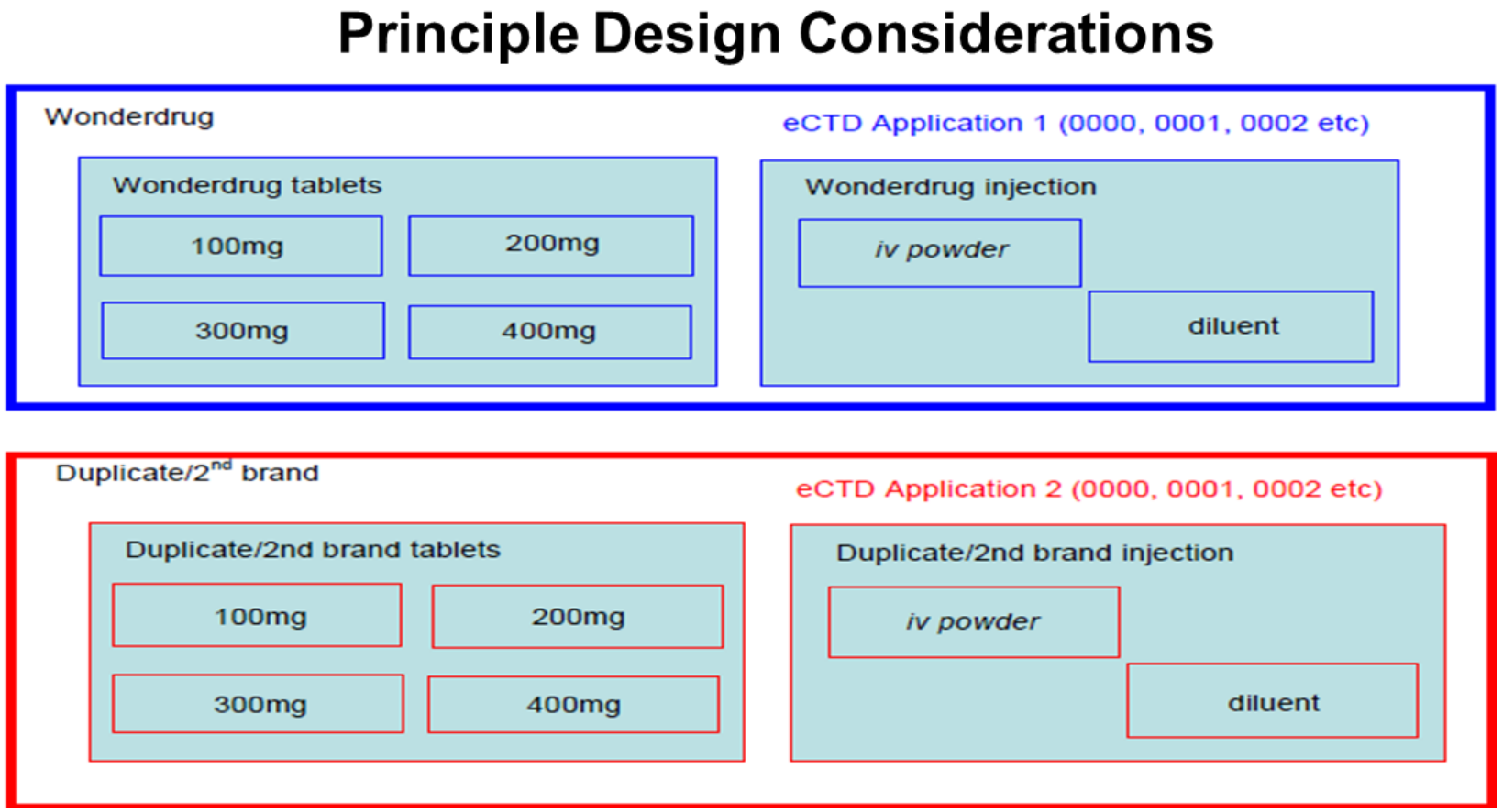
- **copy submission to disc**
- **(redo technical validation on disc)**
- **ship to agency**

or

- **compress eCTD to ZIP container**
- **upload to Agency via web portal (if applicable)**

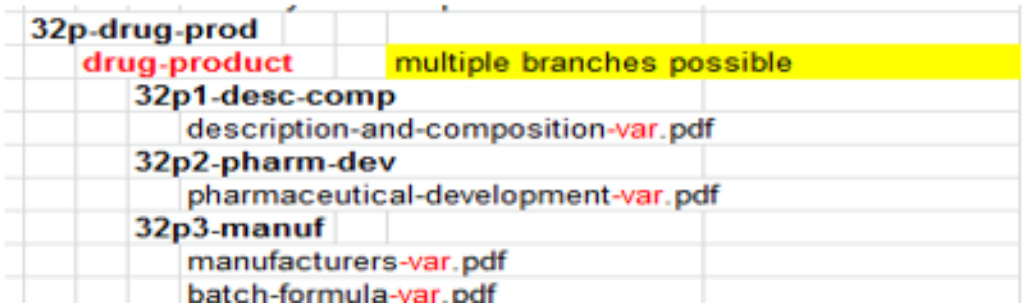
wait for agency approval mail

CTD *versus* eCTD (IX) – multiple 'registrations' in one eCTD (I)



Source: TIGeS Best Practice Guide eCTD

CTD *versus* eCTD (IX) – multiple ‘registrations’ in one eCTD (II)



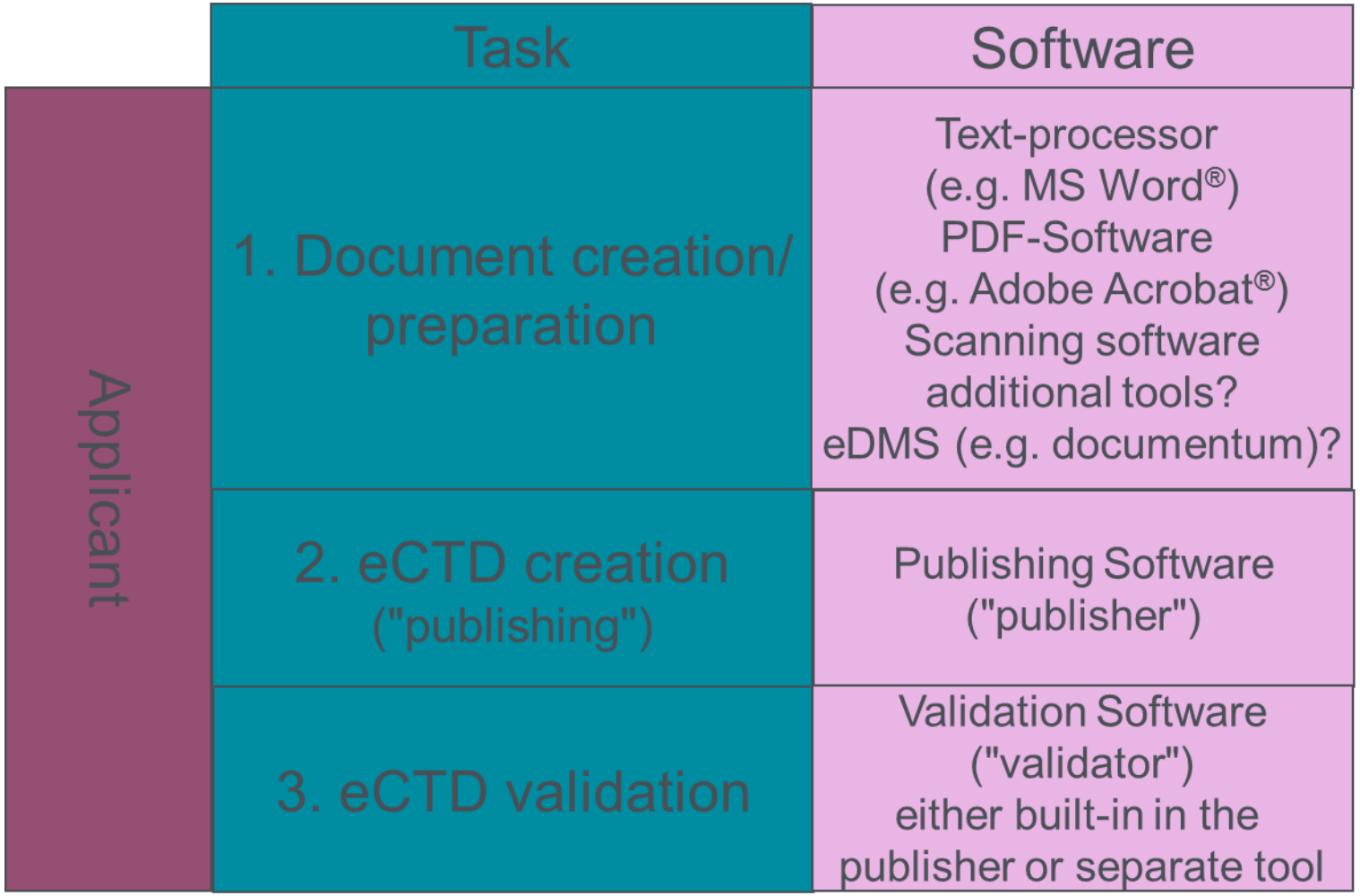
multiple **substructures** possible if
- combination product
- multiple strengths
- multiple pharmaceutical forms

and if it makes sense!

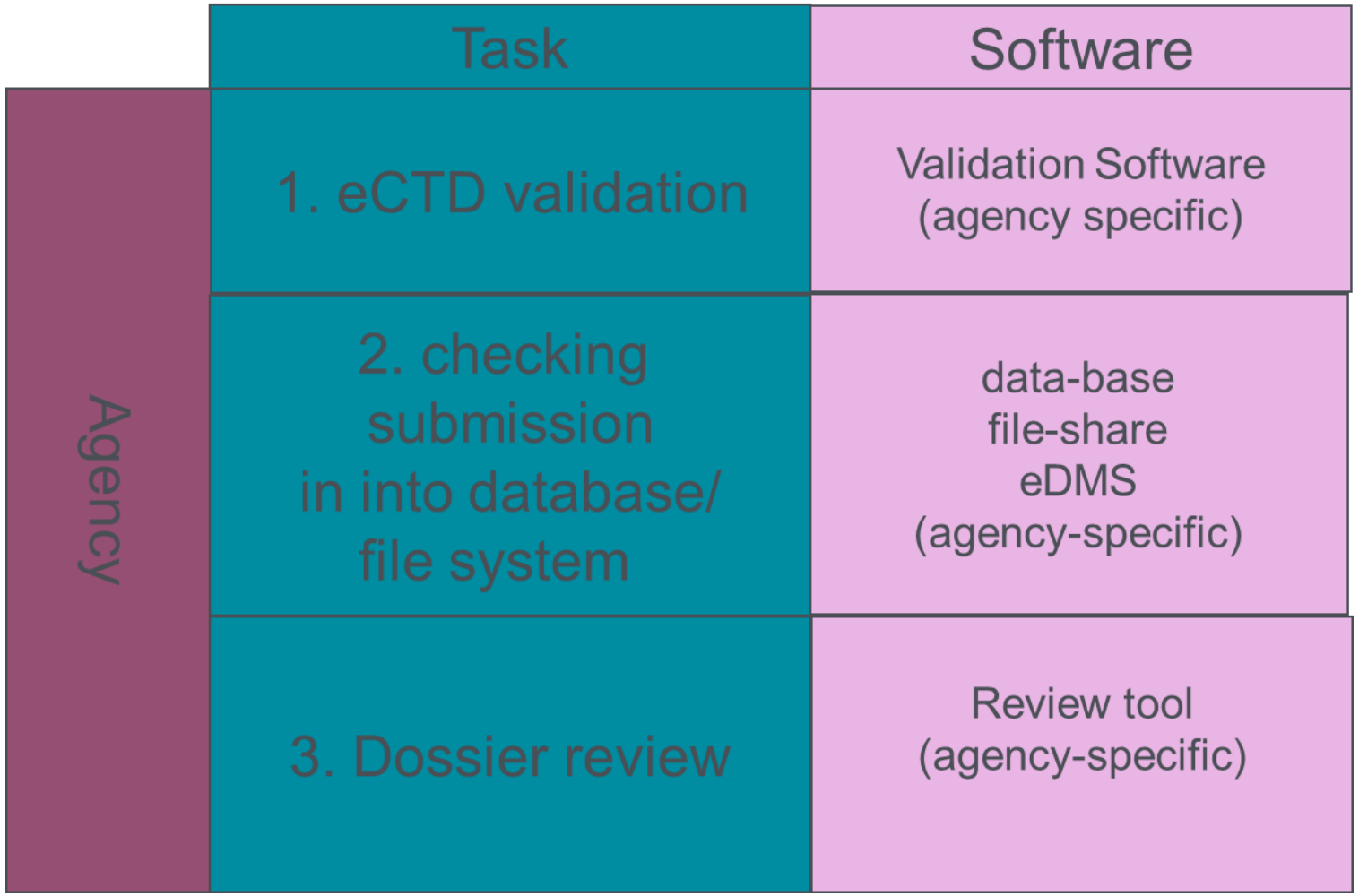
- The principle design of an eCTD is defined with the initial sequence and cannot be changed easily during life cycle (follow up sequences)

Source: TIGeS Best Practice Guide eCTD

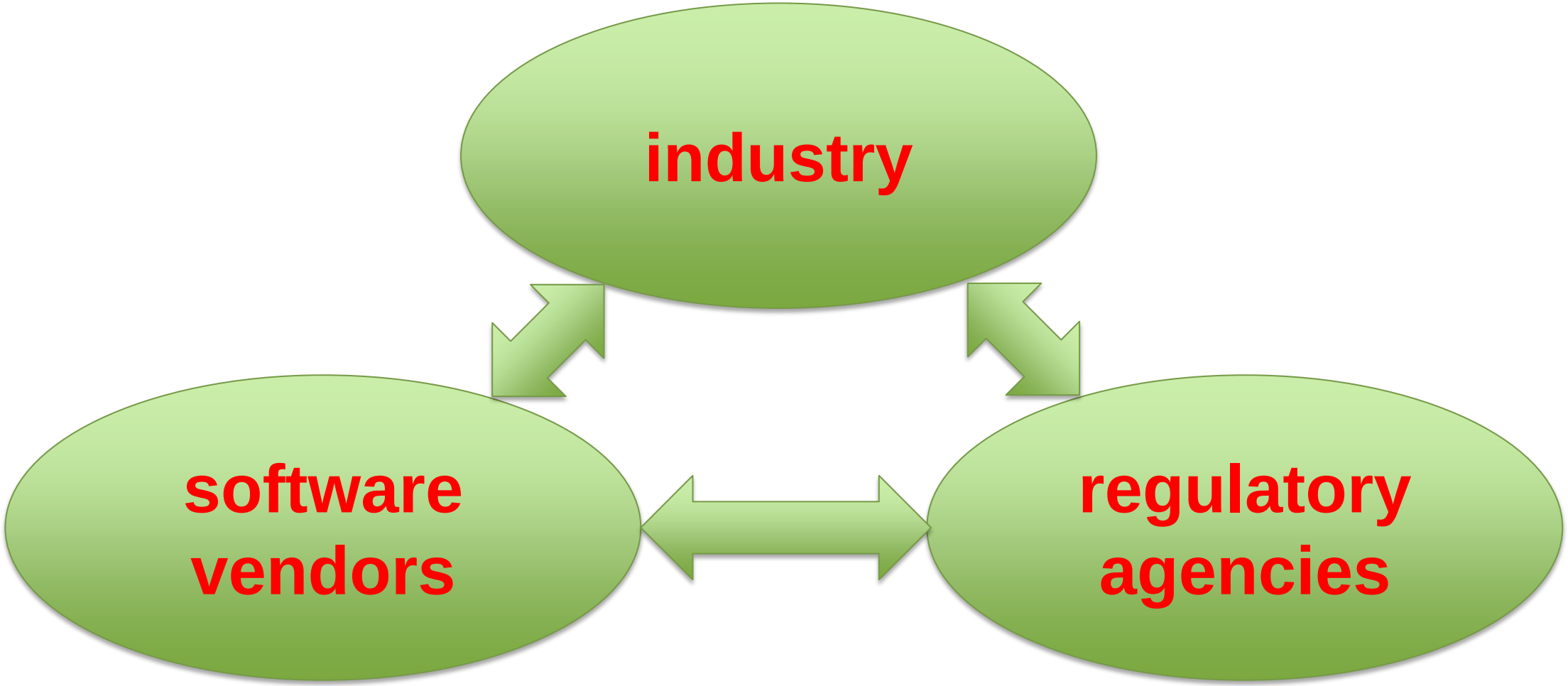
CTD *versus* eCTD (X) – technical validation (I)



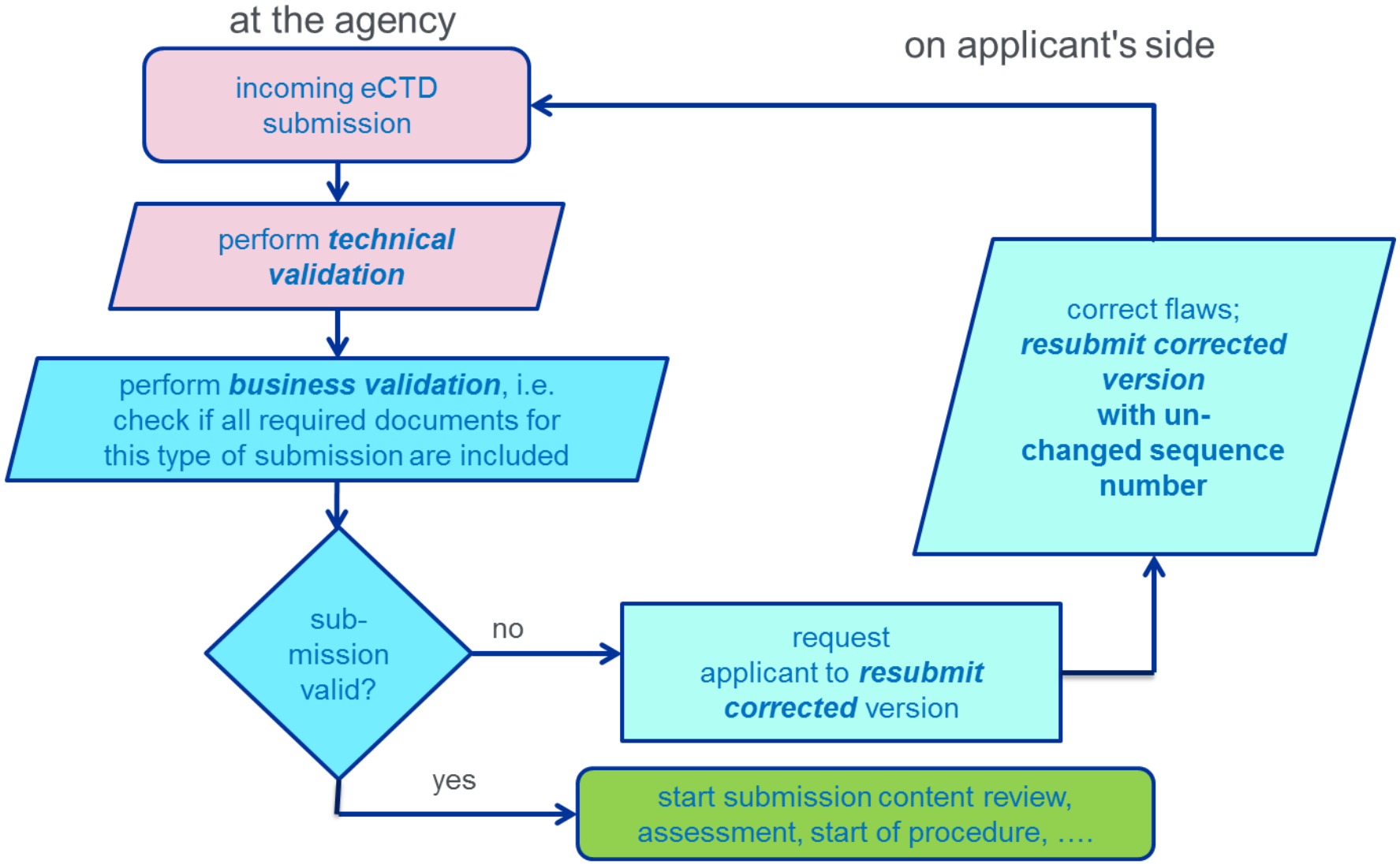
CTD *versus* eCTD (X) – technical validation (II)



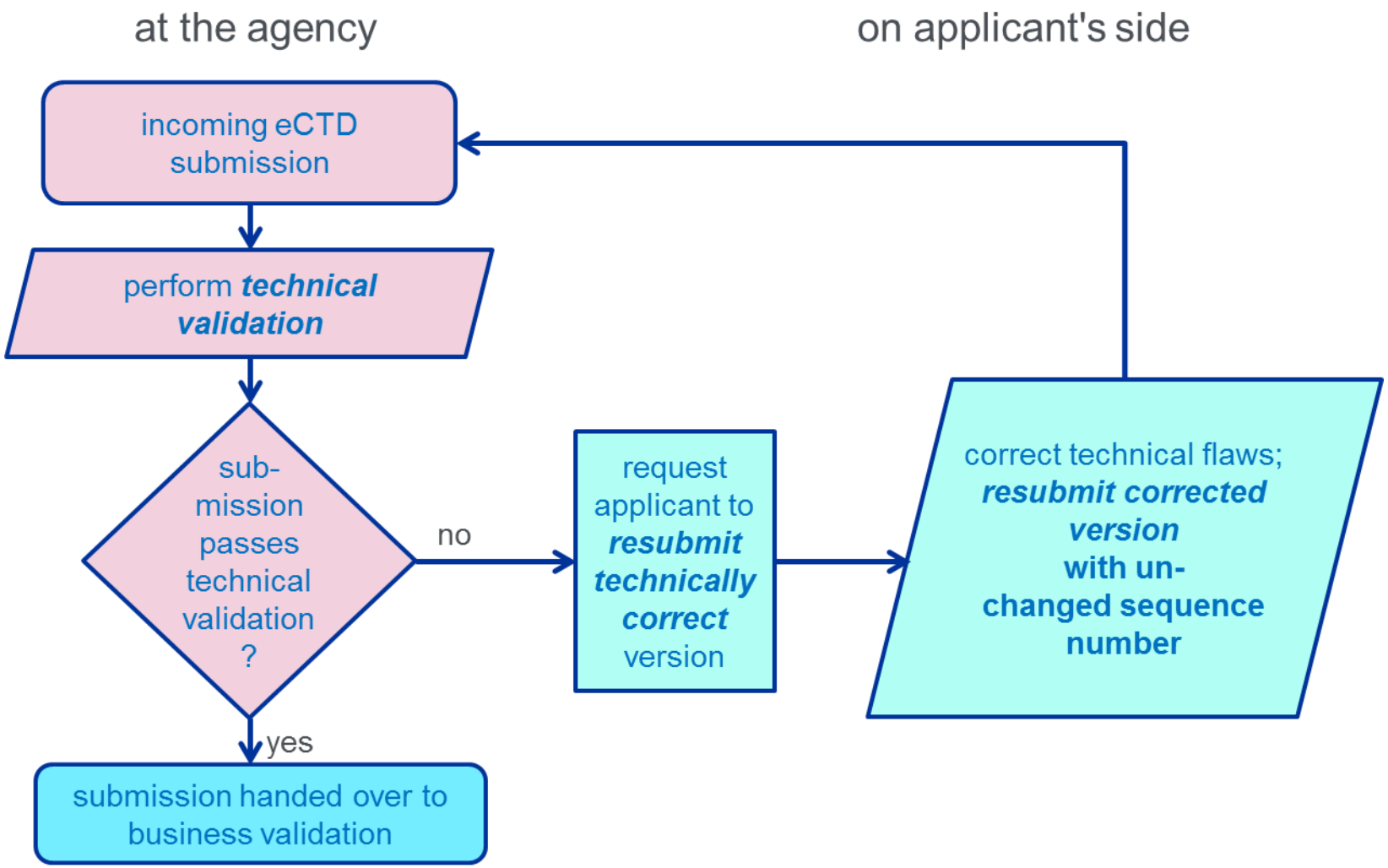
CTD *versus* eCTD (X) – technical validation (III)



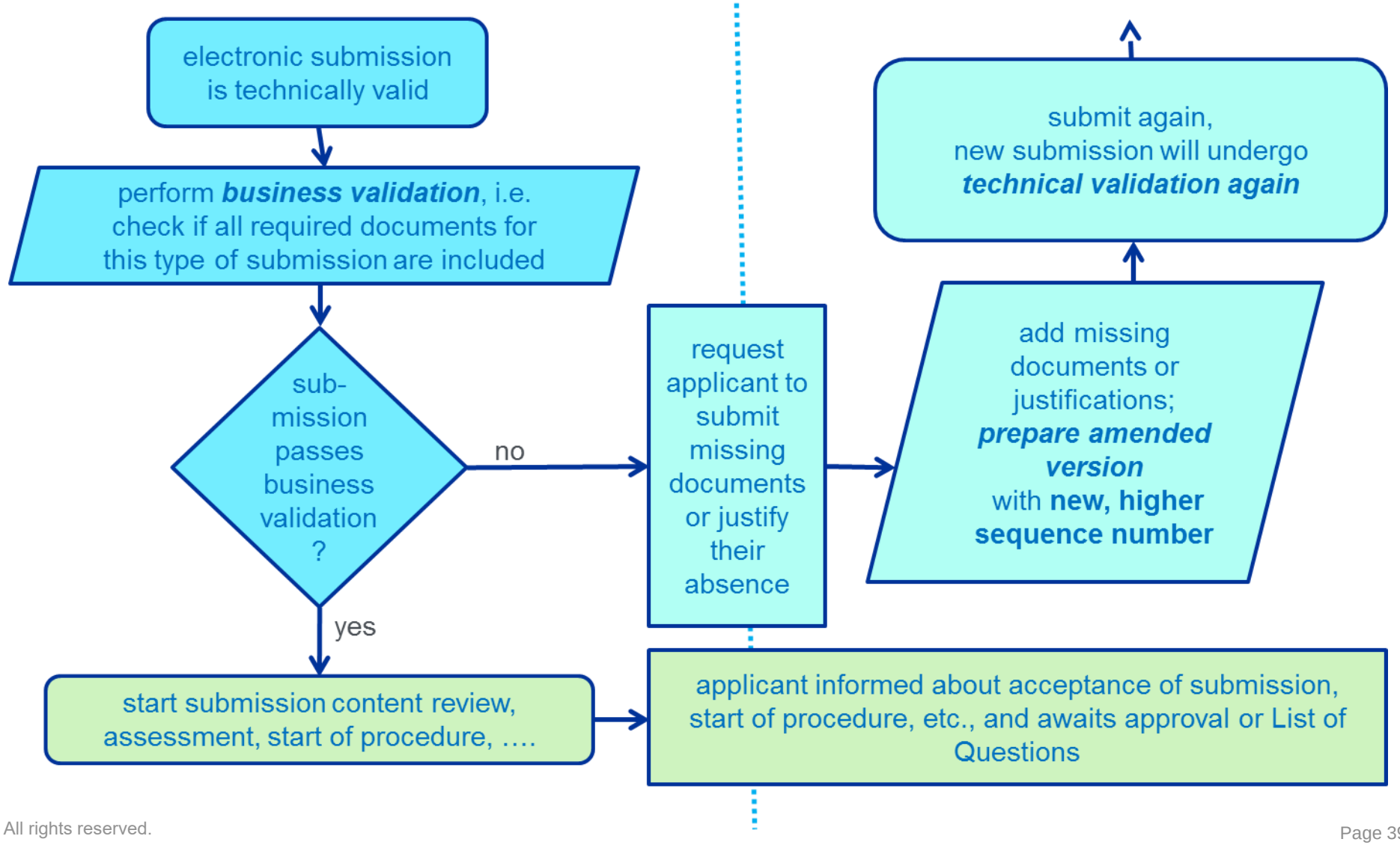
CTD *versus* eCTD (X) – technical validation (IV) submission to one single agency!



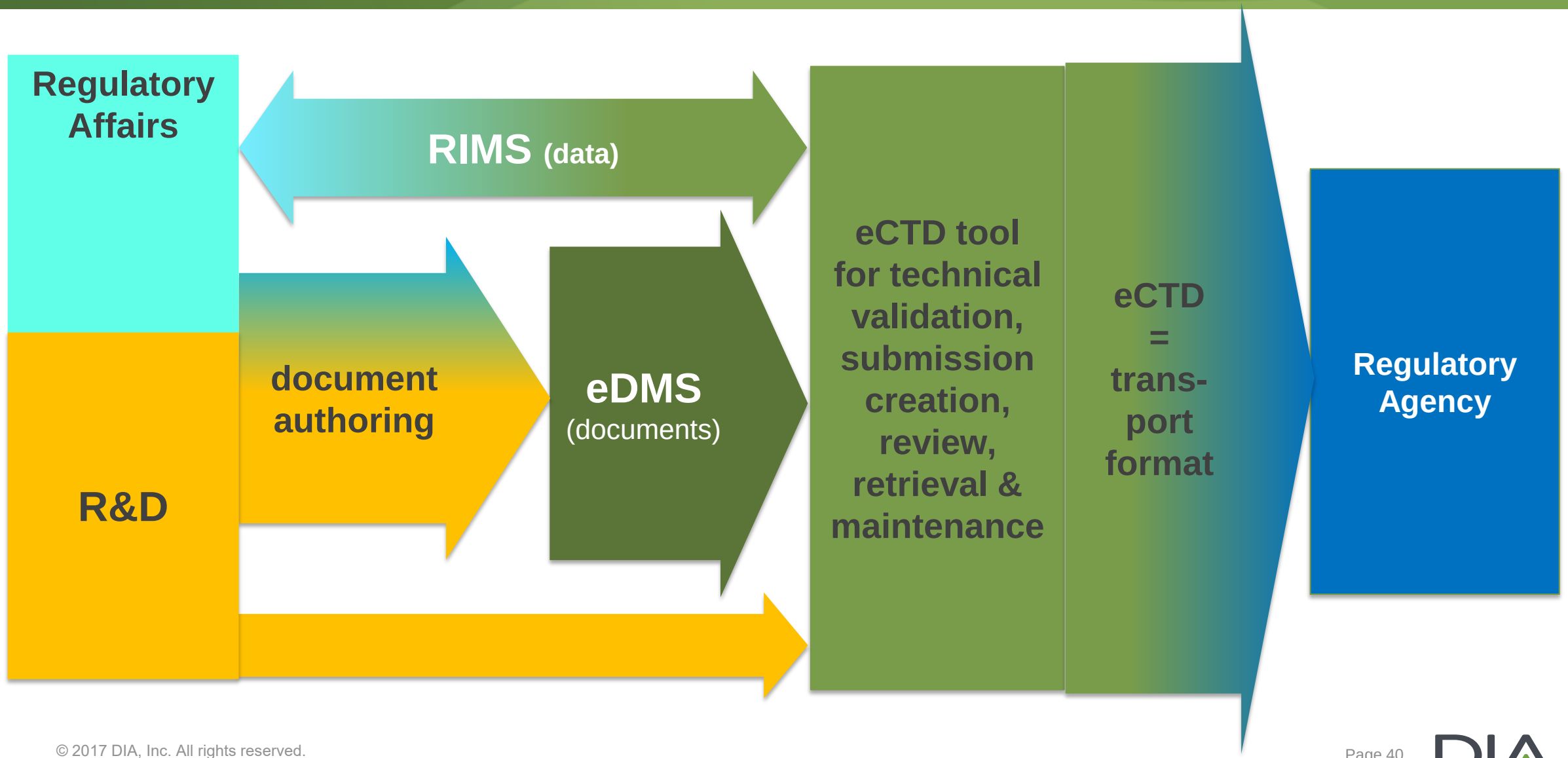
CTD *versus* eCTD (X) – technical validation (V) submission to multiple agencies in parallel!



CTD *versus* eCTD (X) – technical validation (VI) submission to multiple agencies in parallel!



CTD *versus* eCTD (XI) – software (I)

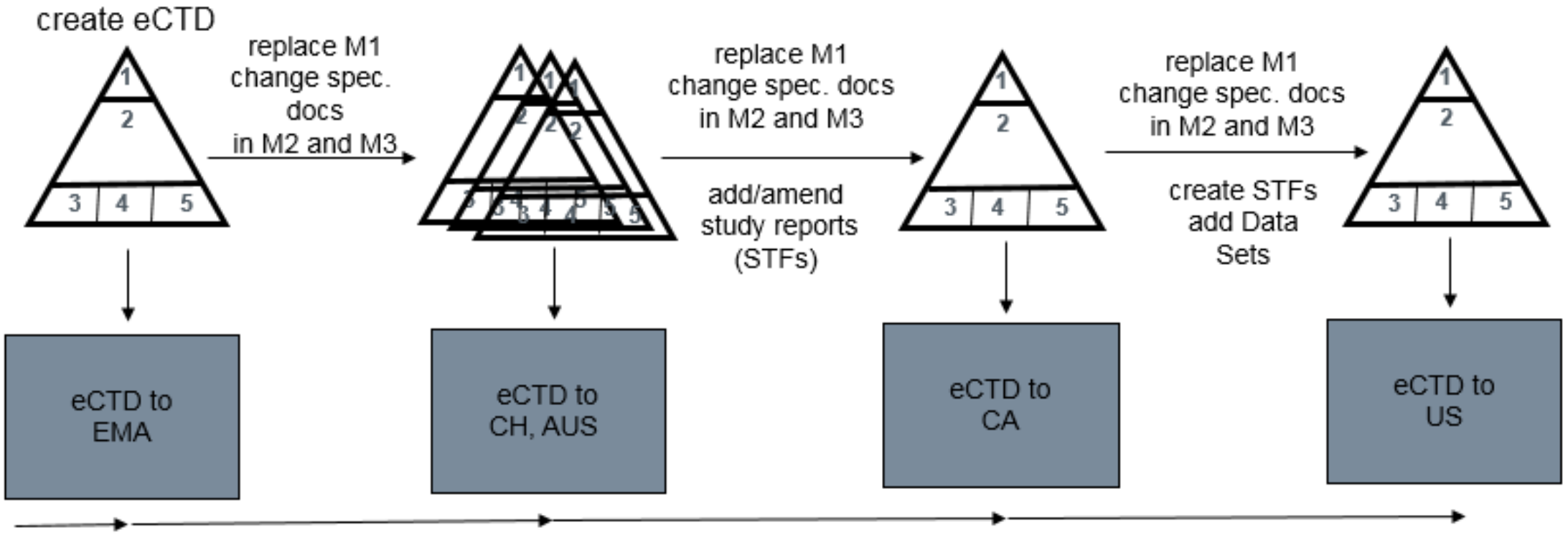


CTD *versus* eCTD (XI) – software (II)

- **core eCTD software (eCTD):** initial investment, validation, dedicated human resources, user training, frequent updates (re-validation)
- **integration with other systems:** interfaces, alignment, replacements, process changes
- **user awareness and acceptance:** training and re-training
- **workflow changes:** switch from local to headquarter responsibility, integrated local + central submission generation process

Don’t expect submission efficiency gains with your very first eCTD!
The benefit will arise during eCTD life cycle.

CTD *versus* eCTD (XI) – re-usability



Topics

- What is eCTD?
- CTD *versus* eCTD
- **eCTD impact on industry and agencies**
- all the things that can go wrong

eCTD impact on industry and agencies (I)

- process change: electronic compilation, review, approval & submission
- integration with other electronic workflows
- re-usability of large parts of an eCTD for different regions, as long as local eCTD specifications AND processes do not deviate too much from ICH standards

eCTD impact on industry and agencies

- a regulatory activity may consist of multiple sequences
- An application may consist of documents in the currently submitted set PLUS documents already submitted earlier!
- Multiple strengths and forms may be covered by one eCTD

Topics

- What is eCTD?
- CTD *versus* eCTD
- eCTD impact on industry and agencies
- **all the things that can go wrong**

Murphy’s Law / **Закон Мёрфи**

- Murphy's Law is commonly known as: ***"Whatever can go wrong, will go wrong.“***
- Murphy's precise wording was: **"If there's more than one possible outcome of a job or task, and one of those outcomes will result in disaster or an undesirable consequence, then somebody will do it that way.“**
- Murphy's Law is an **universal law**, and therefore **applies to "traditional" ways of Regulatory submissions as well as to electronic submissions** …
  - … **but electronic submissions provide many more possible outcomes! …**

*) Named after **Edward Aloysius Murphy, Jr.** (January 11, 1918 – July 17, 1990) , an American aerospace engineer who worked for US Air Force in 1948 and tested the influence of the forces acting on human bodies when accelerated/decelerated at the speed of rockets. (See Wikipedia for more detailed information)

Typical Validation Issues (Ia)

LORENZ eValidator

Application name	fr-h-[redacted]
Full path of application	\\docubridge01\db_data\publishingpooltmx\fr-h-0133-001
Sequence	0002
Preceding sequences found in application path	0000,0001
Other sequences referenced	0001
Missing referenced sequences	n/a
Profile	EU eCTD Validation Criteria 7.1
Profile Path	C:\ProgramData\LORENZ Life Sciences\eValidator\Profiles\
Profile status	Profile is protected (signed). - v1.0

Typical Validation Issues (Ib)

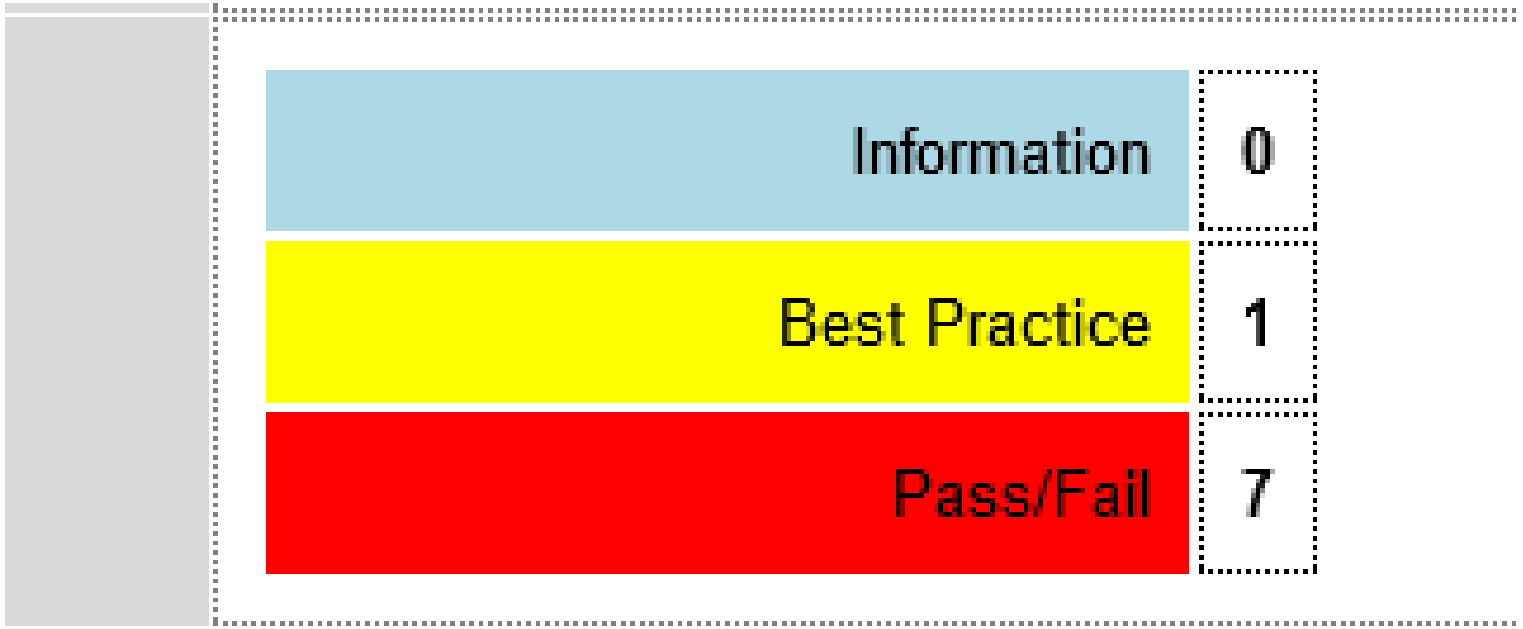
LORENZ eValidator

User name	dob_server
License information	Pharmalex GmbH / Corporate License
Date/time of execution (UTC)	2/28/2019 6:22:48 PM
Date/time of execution (local time)	2/28/2019 7:22:48 PM
Runtime (hh:mm:ss)	00:00:07
Total files	29
Total folders	18
Total size (MB)	9.38
Total PDF documents	20
Total PDF pages	31

DIA

Typical Validation Issues (Ic)

LORENZ eValidator



DIA

Typical Validation Issues (Id)

LORENZ eValidator

14.6	Pass/Fail(7)	If the submission unit type is 'initial' or 'reformat' then the related-sequence attribute must have a value equal to the current sequence.

\0002\m1\eu\eu-regional.xml

- [01] Invalid value for related-sequence (should be identical to current sequence): 0000. See envelope for 'be'
- [02] Invalid value for related-sequence (should be identical to current sequence): 0000. See envelope for 'de'
- [03] Invalid value for related-sequence (should be identical to current sequence): 0000. See envelope for 'fi'
- [04] Invalid value for related-sequence (should be identical to current sequence): 0000. See envelope for 'fr'
- [05] Invalid value for related-sequence (should be identical to current sequence): 0000. See envelope for 'it'
- [06] Invalid value for related-sequence (should be identical to current sequence): 0000. See envelope for 'lu'
- [07] Invalid value for related-sequence (should be identical to current sequence): 0000. See envelope for 'pt'

DIA

Typical Validation Issues (Ie)

LORENZ eValidator

16.BP2	Best Practice(1)	Hyperlinks and bookmarks within documents, or between documents within the same sequence, have a valid target.

active Bookmarks

Document	Page number or bookmark title	Destination
docubridge01\db_data\publishingpooltmx\fr-h[redacted]0002\m1\eu\12-form\it\it-form-annex-x51it0002.pdf	Diapositiva 2	

-> in this file a bookmark existed without a defined target page (structural bookmark)

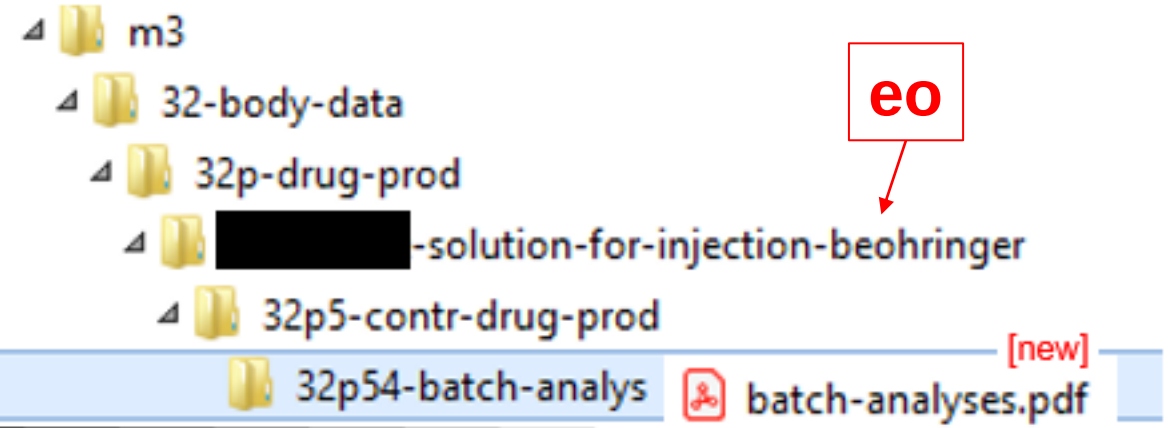
DIA

Typical Validation Issues (IIa)

- Applicant replaces a document (leaf) of a previous sequence with a new document at a different position of the CTD structure.
  - Likelihood depends on eCTD tool
- Possible reasons:
  - Applicant renamed leaf/node during lifecycle.
  - Applicant renamed M3 metadata (manufacturer, name, dosage form) during lifecycle.
  - Previous sequences were imported incorrectly into different tool.
- Correction can be difficult/impossible if the issue only turns up after several sequences.

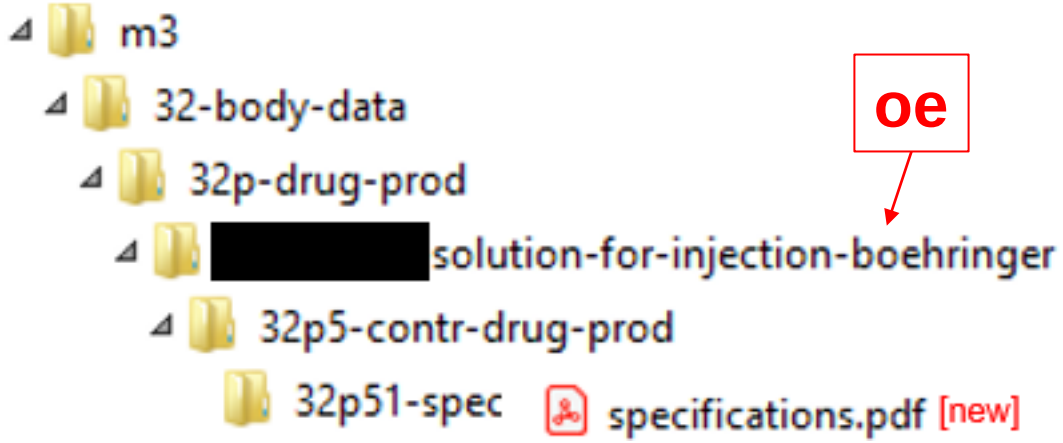
Typical Validation Issues (IIb)

0003:

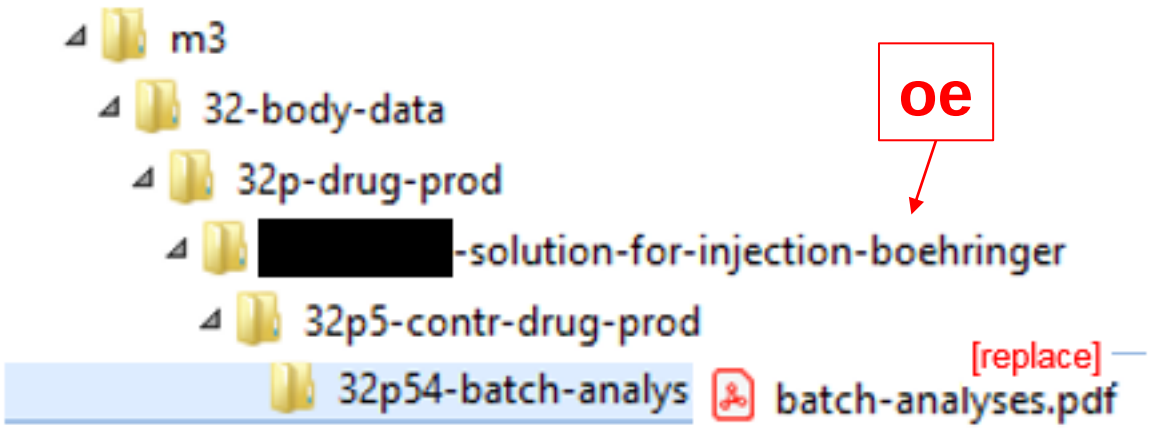


… 0004, 0005, 0006, 0007 … (all without Module 3)

0008:



0009:



-> 0009 is invalid!

Criteria: 11.10, Criteria Type: P/F

“For all leaves […] with an operation attribute value of replace […], the modified file must be present in the same CTD section of the dossier. […].”

Typical Validation Issues (IIIa)

- MD5 checksum of a file does not match the checksum stored in the xml file.
- Possible reasons:
  - Applicant has modified (or simply opened and saved) the file in the publish output.
- The submission needs to be re-published.

Typical Validation Issues (IIIb)

Name	Date modified	Date created
Oman ectd workshop agenda March 2019.pdf	18.02.2019 15:27	04.03.2019 05:11

MD5 checksum: c5b4bd07c911eed0d2c7f268bdd6d98c

-> open, -> close

Oman ectd workshop agenda March 2019.pdf	18.02.2019 15:27	04.03.2019 05:11

MD5 checksum: c5b4bd07c911eed0d2c7f268bdd6d98c

-> open, -> save

Oman ectd workshop agenda March 2019.pdf	04.03.2019 05:22	04.03.2019 05:11

MD5 checksum: 2c019378d0fd3747caf8702099999102

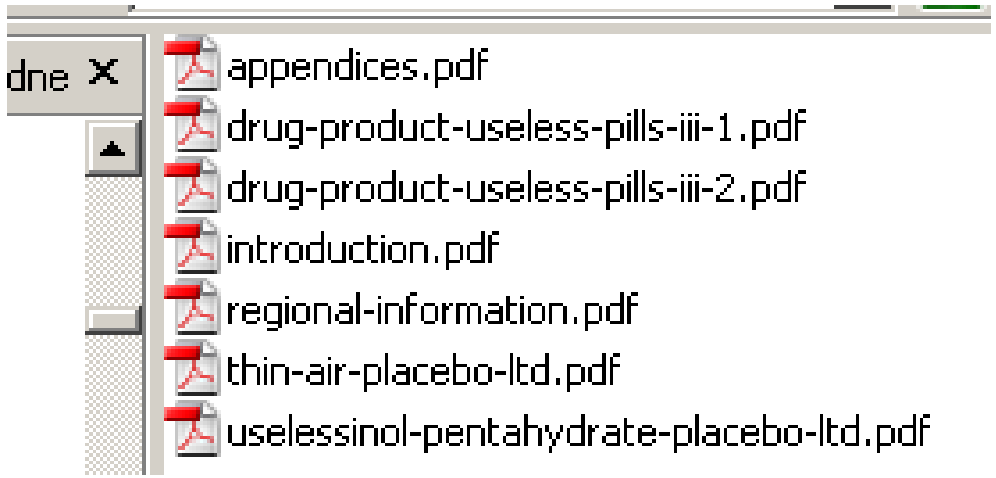
Typical Validation Issues (IVa)

- There are files in the eCTD folder structure that are not referenced in the XML backbone
- Possible reasons:
  - Someone has copied an additional file into the structure (sometimes Word files in addition to the PDFs, which should be provided in a separate folder *xxxx*-workingdocuments).
  - A PDF file inside the eCTD structure has been opened (for review or QC of the submission) on a computer with an older Windows operation system version. The operating system then creates a (hidden) preview file named ‘thumbs.db’.
- Make sure that all hidden / system files are visible in the File Explorer. Then delete all ‘thumbs.db’ files within the structure

Typical Validation Issues (IVb)

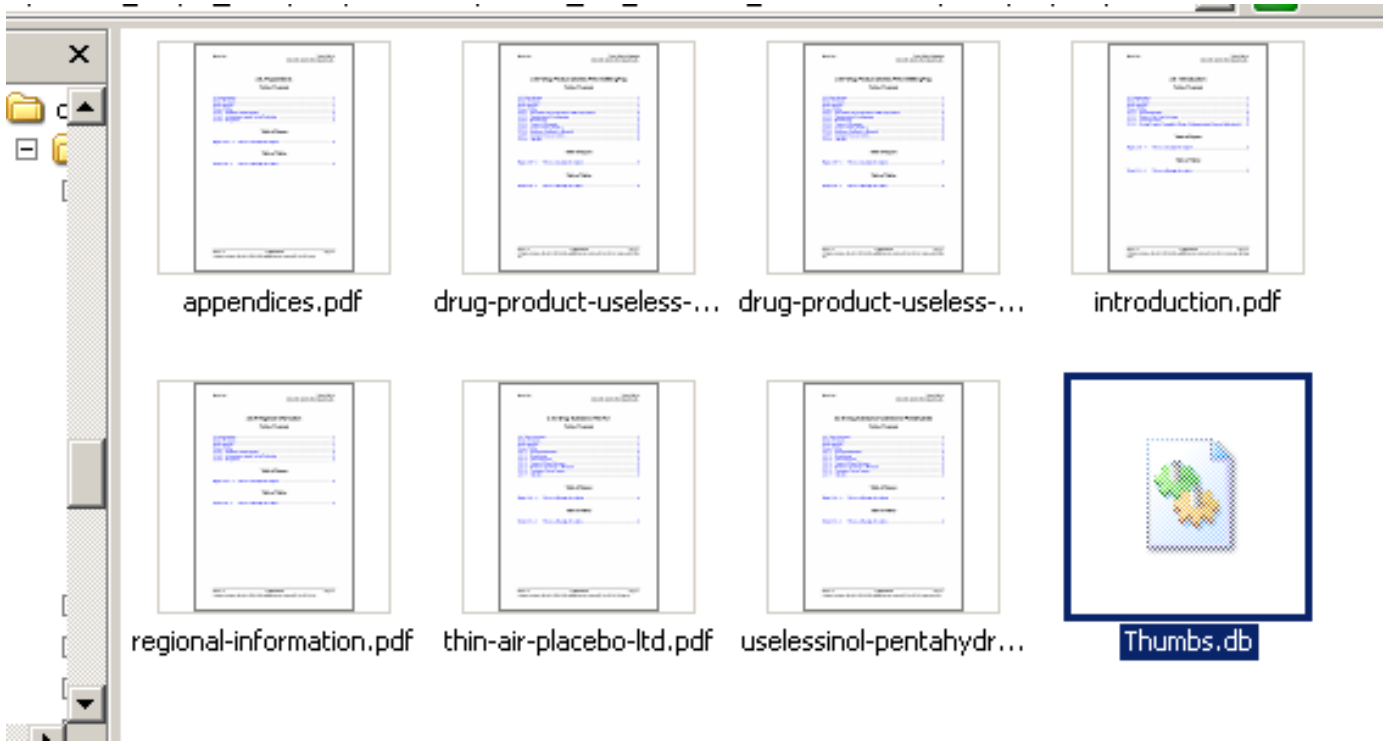
Obviously, a file named "Thumbs.db" has miraculously been inserted into the eCTD – but how?

If you check the contents of your eCTD directories on a local drive or file share using the Windows File Explorer and choosing the "list" or "details" view, it'll look like this:



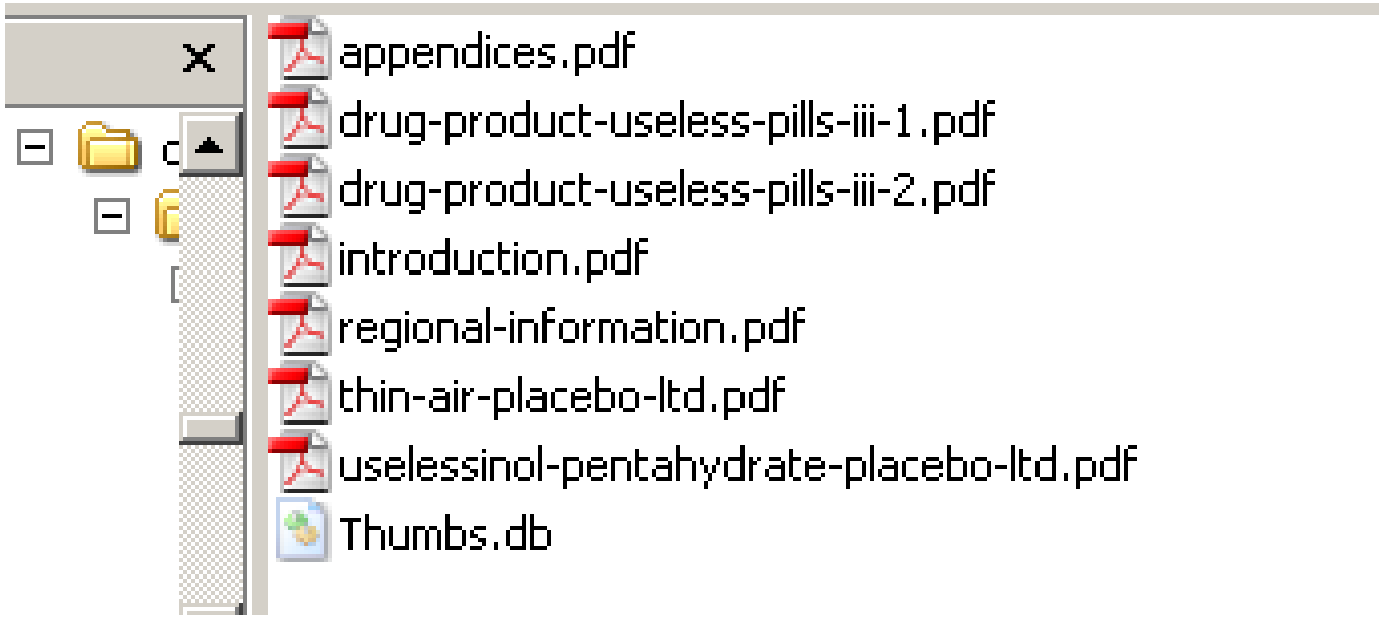
Typical Validation Issues (IVc)

but as soon as you change to the "Thumbnails" view, Windows will automatically generate an auxiliary file named "Thumbs.db"



Typical Validation Issues (IVd)

The "Thumbs.db" file will not be deleted if you switch back to "list" or "details" view …



… but it may remain invisible to you, if your File Explorer configuration prevents display of "hidden files and folders“.

Typical Validation Issues (Va)

- PDF properties of certain files are not allowed (e.g. PDF version, fast web view, bookmark & hyperlink properties)
- Possible reasons:
  - The document used was not eCTD-ready and some settings in the eCTD tool prevent it from being corrected, e.g. an EU electronic application form, a digitally signed PDF form or a password protected file.
- Remove password protection or explain in cover letter why this issue can not be resolved.

Typical Validation Issues (VI)

- Incorrect handling of Sequence/Related Sequence in the envelope
- Possible reasons:

  - Submission Unit is not ‘initial’ or ‘reformat’, but Related Sequence Number is empty in a GCC submission.
  - Submission Unit is ‘initial’, but Related Sequence Number is not empty and different from Sequence Number.

- Revisit regional eCTD specifications and correct envelope information.

Typical Validation Issues (VII)

- Have a strict and detailed workflow in place when it comes to eCTD creation – **including "minor" steps** like
  - **where to store** submissions before they are copied to disc
  - **check the final disc** before it is send to the agency (but mind that you can't validate eCTD lifecycle on the disc)
  - check at least Module 3 sections **3.2.P.5.2** and **3.2.P.5.3** for abridged filenames ("analy~.pdf")

Typical Validation Issues (VIIIa)

e-mail from a European ***Agency*** after having received an eCTD-sequence 0028:

> Dear Madame,
>
> During validation of your eCTD application we have observed some ***errors***, and your application
> has been deemed ***invalid***. You can see this, in the ***file report*** I have ***attached*** with this email.
> ***We need you to make a new sequence 0028***, where the errors are corrected.
> We use EURSvalidator developed by Extedo on request by EMEA. […]
> Kind regards,
> ***E.F.***

Typical Validation Issues (VIIIb)

all of ***agency's*** validation issues were connected to **lifecycle** problems:

The PDF file contains broken links. (No. 0038)

1 : Hyperlink, Page 3, Action GoToR, Target ../../../../../0003/m3/32-body-data/32p-

a hyperlink in a document in the submitted sequence 0028 targets to a document in sequence 0003.

index.xml

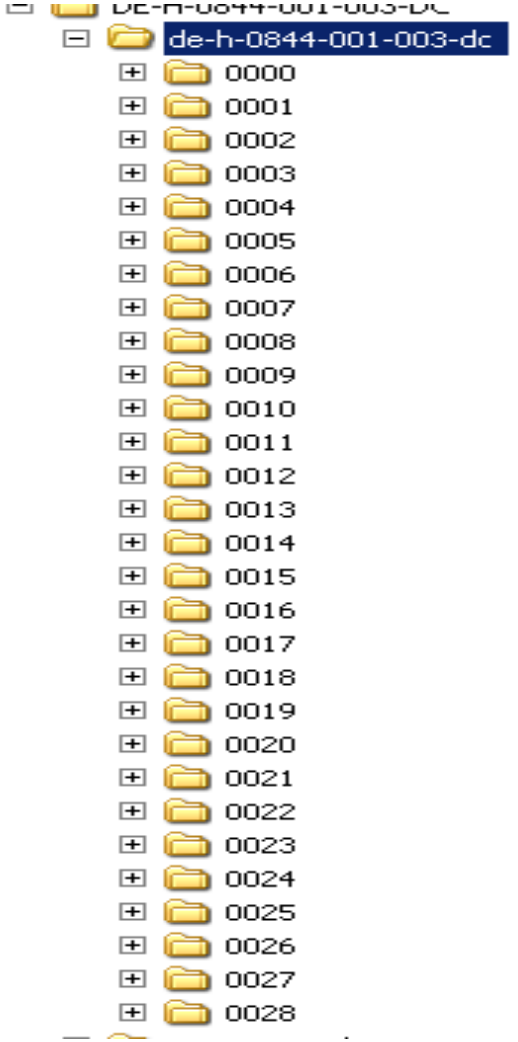
Not all modified file entries point to a valid document..

a document submitted in sequence 0028 ***replace***s or ***append***s a document in one of the prior sequences.

DIA

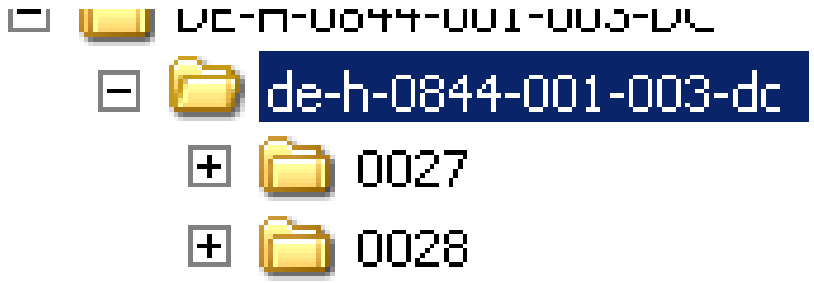
Typical Validation Issues (VIIIc)

We asked ***agency*** to confirm, that at the moment of validation all 29 (0000 to 0028) sequences were available in the same root directory, *i.e.* that the folder structure on the agency's file share looked like this:



Typical Validation Issues (VIIId)

Agency replied, that at the moment of validation only sequences 0027 to 0028 were available in the same root directory, *i.e.* that ***agency's*** file share structure looked like that:



Agency admitted, that it was their mistake, and …

… **kindly asked us, to resubmit sequences 0000 to 0026!**

Typical Validation Issues (VIIIf)

to the Applicants:

- Are you able to reproduce/regenerate all
  the individual sequences you've submitted so far?
- Are you sure that, if you regenerate your sequences out of your eCTD-System, the result
  will be identical to what you submitted originally?
- Will you still be able to reproduce/regenerate the
  sequences after a future eCTD-tool change?

Store a copy of each outgoing sequence in a proper electronic archive!

Typical Validation Issues (IXa)

e-mail from a European Agency to an applicant:

Dear Sir,

thank you very much for sending us the Cover Letter, Application Form and perfectly labelled jewel cases for your MAA No. ***abc***.
Before we can start technical validation, we would appreciate if you could also send us the CDs themselves. (The jewel cases were empty.)
Kind regards

X.Y.

after inspection of the applicant's RegOps Officer's CD drive it turned out, that the CD was still there.

KARL-HEINZ LOEBEL

Director, Regulatory Operations,
Pharmalex, Germany

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DIA