The eCTD regulatory dossier

Regulatory Pathways Training, DCVMN workshop

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GSK Vaccines
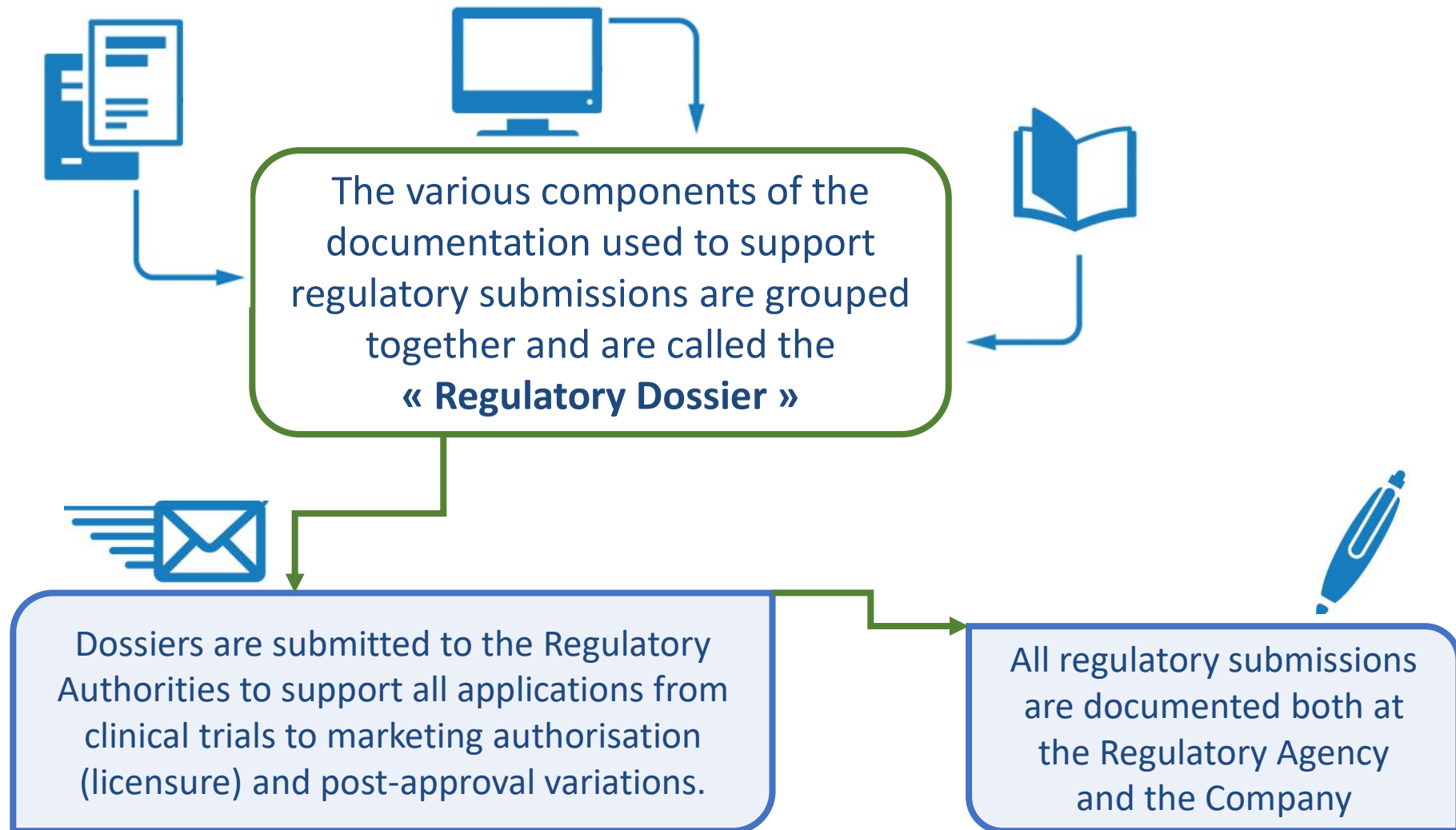
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Regulatory Dossier... a bit of history

- Concept of "applying" for new products licensure relatively recent
- Historically, drug preparation/control based on pharmacopoeias
- A few tragic cases led to specific legislation:
  - 1937: Elixer Sulfanilamide in the US:
    - 107 deaths due to diethylene glycol solvent
    - → **1938: US Food, Drug and Cosmetics Act**
      - pre-marketing approval of all drugs
      - instructions for use on the label
  - Thalidomide in EU:
    - sleeping aid and anti-emetic for treatment of morning sickness marketed from 1957 (essentially in Germany and Britain)
    - Drug shown to be racemic: one form teratogenic especially if taken during the first 25-50 days of pregnancy (malformation of limbs)
    - Safety tests in animals were performed but no testing in pregnant animals (not a pre-licensure requirement)
    - → **Directive 65/65/EEC, first EU requirements for licensure:**
      - No product can be marketed without an authorisation
      - Application for authorisation must contain specific information

What are Regulatory Dossiers ... ?

The various components of the documentation used to support regulatory submissions are grouped together and are called the **« Regulatory Dossier »**

Dossiers are submitted to the Regulatory Authorities to support all applications from clinical trials to marketing authorisation (licensure) and post-approval variations.

All regulatory submissions are documented both at the Regulatory Agency and the Company

Framework of a typical regulatory submission ...

Although there are different specific requirements around the world, Regulatory Authorities typically assess the following aspects of a regulatory dossier to safeguard public health

Quality: Providing assurance that well-controlled ingredients are used to develop robust, stable formulations which are manufactured to a consistent standard.

Benefit:Risk

Efficacy: Data from clinical and laboratory studies that show the product provides the claimed benefit.

Safety: The safety of a medicine relates to the risk posed by the medicine and the acceptability of the risk in the context of the treatment. In order to quantify risk, data are collected from human and animal studies and from use in the market. These data provide assurance that the medicine causes "no undue harm" to the patient. The science and activities associated with collecting safety data is called pharmacovigilance"
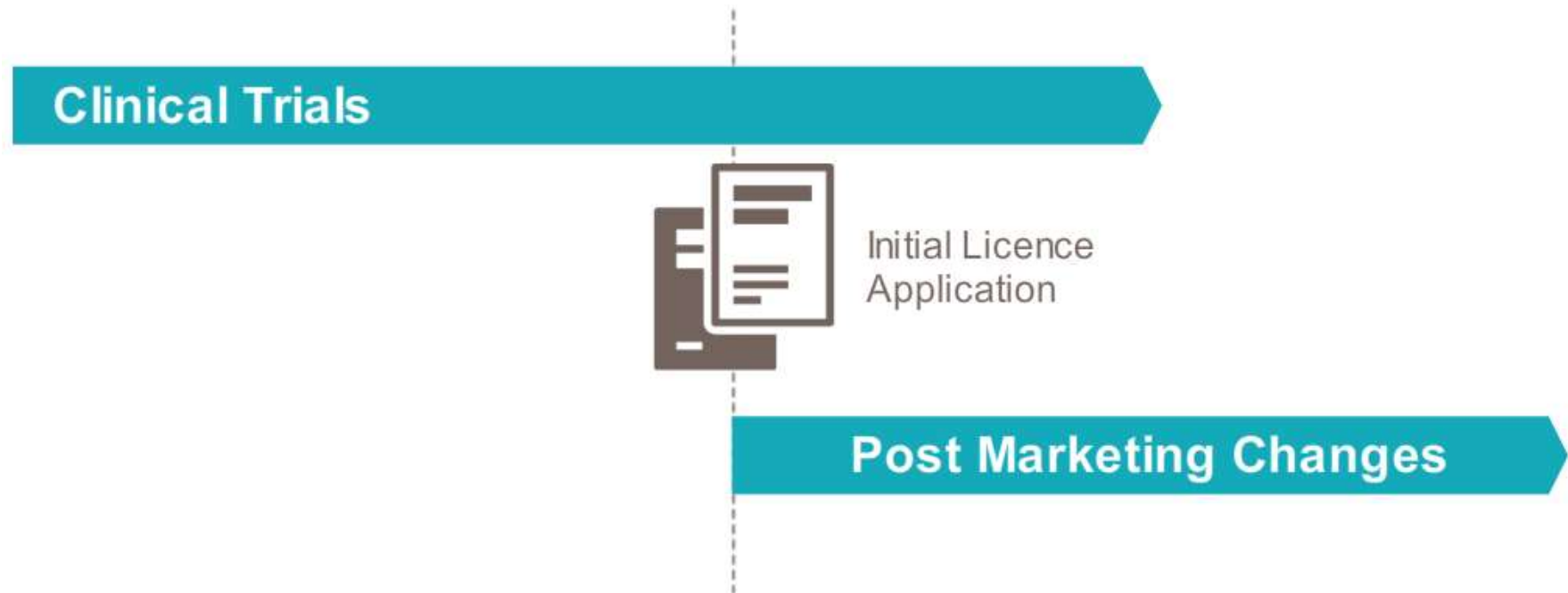
Framework of a typical regulatory submission …

The type of information submitted and level of detail will differ depending on the stage of development or commercial life-cycle of the product and whether or not the product is a generic product or the branded originator

Clinical Trials

Initial Licence Application

Post Marketing Changes

Marketing Authorisation Applications

A "marketing authorisation" (or license) is required to allow the placing on the market of a medicinal product in a particular country or region

The term used in Canada is **New Drug Submission** (NDS).

NDS

NDA/BLA

NDA stands for **New Drug Application** and this is the term used in the US and other countries like China. N.B. For biologicals the US term is **Biological License Application** (BLA)

MAA

MAA (in the EU) stands for **Marketing Authorisation Application.** The term is also used in other countries such as Australia
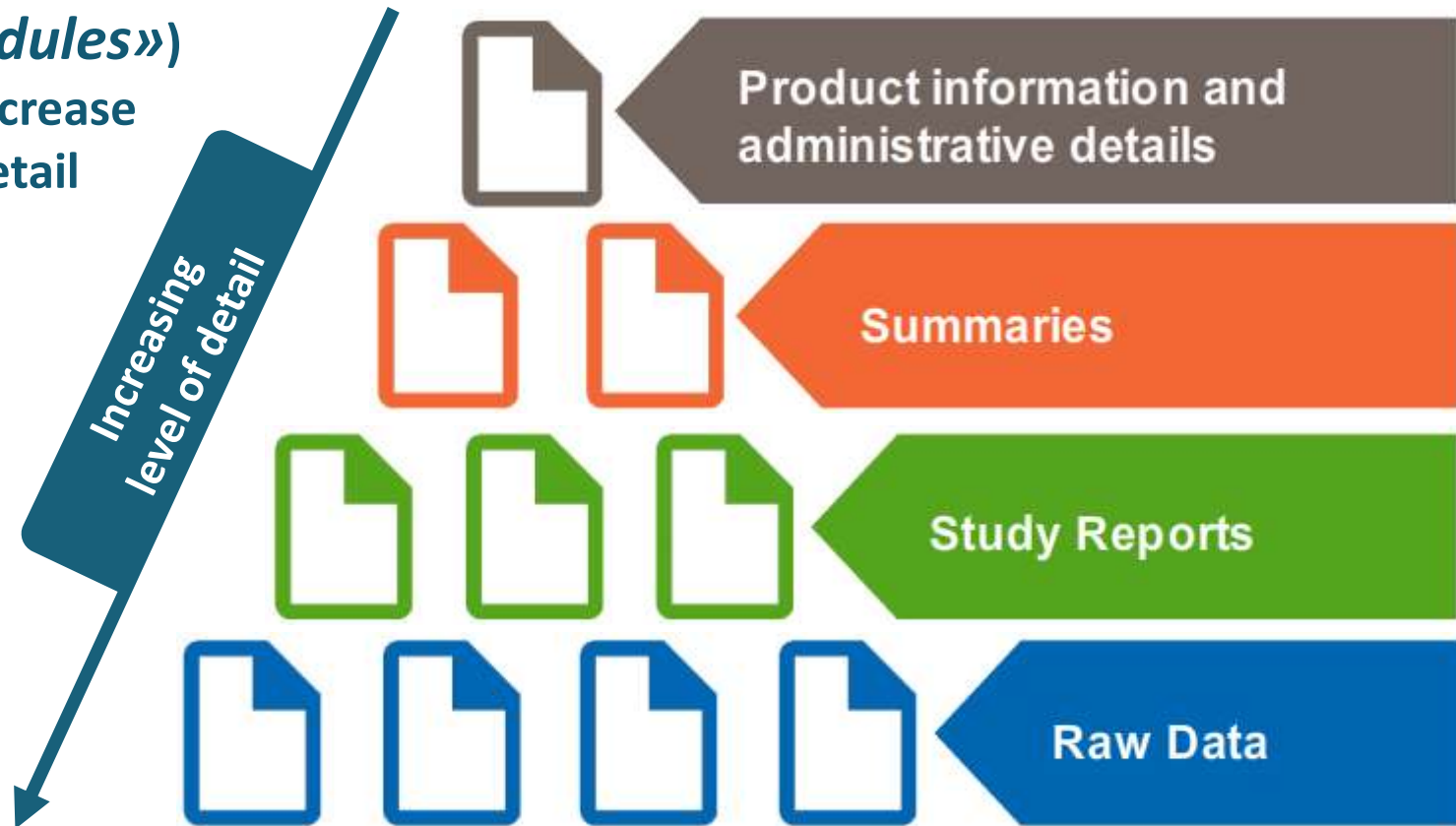
JNDA

JNDA stands for **Japanese New Drug Application**

Marketing Authorisation Applications

Example of recent Regulatory Dossiers

PCV vaccine
MAA: 31 volumes / 21,000 pages
Responses to CHMP questions: 15 volumes / 9,000 pages

Although regulatory submissions can now be made electronically, this photograph shows the typically huge amount of data included in a Marketing Authorisation Application (MAA)

More recently …

New vaccine
MAA: 1.006743 pages

... What is the *Common Technical Document (CTD)* ?

The Common Technical Document is a standard way of specifying how dossiers are **formatted and organised**.
*(N.B. The CTD does not define the actual **content** of a dossier)*

The CTD is used to format and organise Marketing Authorisation Applications as well as most post-approval applications.

The CTD was developed by **ICH** (the International Conference on Harmonisation) with representatives from regulatory bodies in Europe, Japan and the United States. It has now been adopted by several other markets around the world

The **eCTD** (electronic CTD) is the fully electronic application which is the most commonly used form for regulatory submissions today.

Background & History

- Original title/definition (since 1990): "**International Conference on Harmonisation** of Technical Requirements for the Registration of Pharmaceuticals for Human Use"
- New name since 23 October 2015: **"International Council for Harmonisation"**.
- Joint **regulatory/industry** project
- Based on **scientific consensus**
- **Commitment by Regulators** to implement ICH outcomes
- ICH Objectives: improve efficiency of development/approval of new medicines
  - ➤ Patients quicker access to new drugs
  - ➤ Reduction of unnecessary global development delays
  - ➤ Reduction of animal and human study duplications (non ethical nor economical use of resources)
  - ➤ Protection of Public Health

ICH

ICH membership

- **Founding Regulatory Members**
  - Europe: EC (European Commission) & EMA (European Medicines Agency)
  - USA: FDA (Food and Drug Administration)
  - Japan: MHLW (Ministry of Health Labour and Welfare) & PMDA (Pharm. And Med. Device Agency)
- **Founding Industry Members**
  - EFPIA (European Federation of Pharmaceutical Industries and Associations)
  - JPMA (Japan Pharmaceutical Manufacturers Association)
  - PhRMA (Pharmaceutical Research and Manufacturers of America)
- **Standing Regulatory Members**
  - Health Canada, Canada
  - Swissmedic, Switzerland
- **Regulatory Members**
  - ANVISA, Brazil
  - MFDS, Republic of Korea
  - HSA, Singapore
  - NMPA, China
  - TFDA, Chinese Taipei
- **Industry Members**
  - BIO (Biotechnology Innovation Organization)
  - IGBA (International Generic and Biosimilar Medicines Association)
  - WSMI (World Self-Medication Industry)

ICH

ICH observers

- **Standing Observers**
  - IFPMA
  - WHO

- **Legislative or Administrative Authorities**
  - ANMAT, Argentina
  - CDSCO, India
  - CECMED, Cuba
  - COFEPRIS, Mexico
  - CPED, Israel
  - INVIMA, Colombia
  - JFDA, Jordan
  - MMDA, Moldova
  - MOPH, Lebanon
  - National Center, Kazakhstan
  - NPRA, Malaysia
  - NRA, Iran
  - Roszdravnadzor, Russia
  - SAHPRA, South Africa
  - SCDMTE, Armenia
  - SFDA, Saudi Arabia
  - TGA, Australia

- **Regional Harmonisation Initiatives (RHIs)**
  - APEC
  - ASEAN
  - EAC
  - GHC
  - PANDRH
  - SADC

- **International Pharmaceutical Industry Organisation**
  - APIC

- **International Organisations regulated or affected by ICH Guideline(s)**
  - Bill & Melinda Gates Foundation
  - CIOMS
  - EDQM
  - IPEC
  - PIC/S
  - USP

ICH — Internationally harmonised Guidelines

Quality Guidelines
- Stability (6 guidelines)
- Analytical Validation (2 guidelines)
- Impurities (3 guidelines)
- Regulatory Acceptance of Pharmacopoeial Interchangeability
- Quality of Biotechnological Products (5 guidelines)
- Specifications (2 guidelines)
- Good Manufacturing Practice for Active Ingredients
- Pharmaceutical Development
- Quality Risk Management

Safety Guidelines
- Carcinogenicity Studies (3 guidelines)
- Genotoxicity Studies (2 guidelines)
- Toxicokinetics and Pharmacokinetics (2 guidelines)
- Toxicity Testing (2 guidelines)
- Reproductive Toxicology
- Preclinical Safety Evaluation of Biotechnological Products
- Pharmacology Studies (2 guidelines)
- Immunotoxicology Studies

Efficacy Guidelines
- Clinical Safety (7 guidelines)
- Structure and Content of Clinical Study Reports
- Dose-Response Studies
- Ethnic Factors in the Acceptability of Foreign Clinical Data
- Good Clinical Practice
- Clinical Trials of Special Populations (2 guidelines: geriatric and paediatric)
- General Considerations for Clinical Trials
- Statistical Principles for Clinical Trials
- Choice of Control Group in Clinical Trials
- Clinical Evaluation by Therapeutic Category (1guideline: Antihypertensive)
- QT/QTc Interval Prolongation and Proarrhythmic Potential

Multidisciplinary Guidelines
- Medical Terminology (MedDRA)
- Electronic Standards for Transmission of Regulatory Information (incl. eCTD)
- Joint Safety/Efficacy: Timing of Pre-clinical Studies in Relation to Clin Trials
- **Common Technical Document (CTD)**

ICH Background to the CTD

- CTD = logical follow-up of first ICH Phase (harmonised guidelines):
    - already considerable harmonisation of Content (scientific guidelines),
    - Progress to a common format acceptable in 3 Regions
- Differing regional requirements:
    - Japan : GAIYO
    - Europe : 4-part dossier with Expert reports and tabulated summaries
    - USA : FDA guidance on format and content of NDA & BLA
- Industry survey: converting NDA to MA = 10-20 weeks (10 FTE) + Feasibility study Oct 1996-June 1997
- started as an official ICH topic end 1997 and completed by end 2000
- Sections order and numbering revised in 2001

Original Scope and Objectives of the CTD

Scope

- Harmonised format for Registration Applications
    - acceptable by Regulatory Authorities in the 3 regions
    - **Does not define content** (e.g. what studies are required, etc.)

Objectives

- For Industry
    - Reduce time and resources needed to compile applications
    - Ease preparation of electronic submissions
- For Regulatory Authorities
    - Facilitate reviews
    - Improve communication with applicant
    - Simplify exchange of information between Regulators

C. T. D. Organisation in Modules

Module 1:
Geographically specific documents, proposed labelling, RMP (Risk Management Plan)

Module 2:
Summaries of Quality, Non-clinical and Clinical Data (summaries and overviews of modules 3, 4, 5)

Module 3:
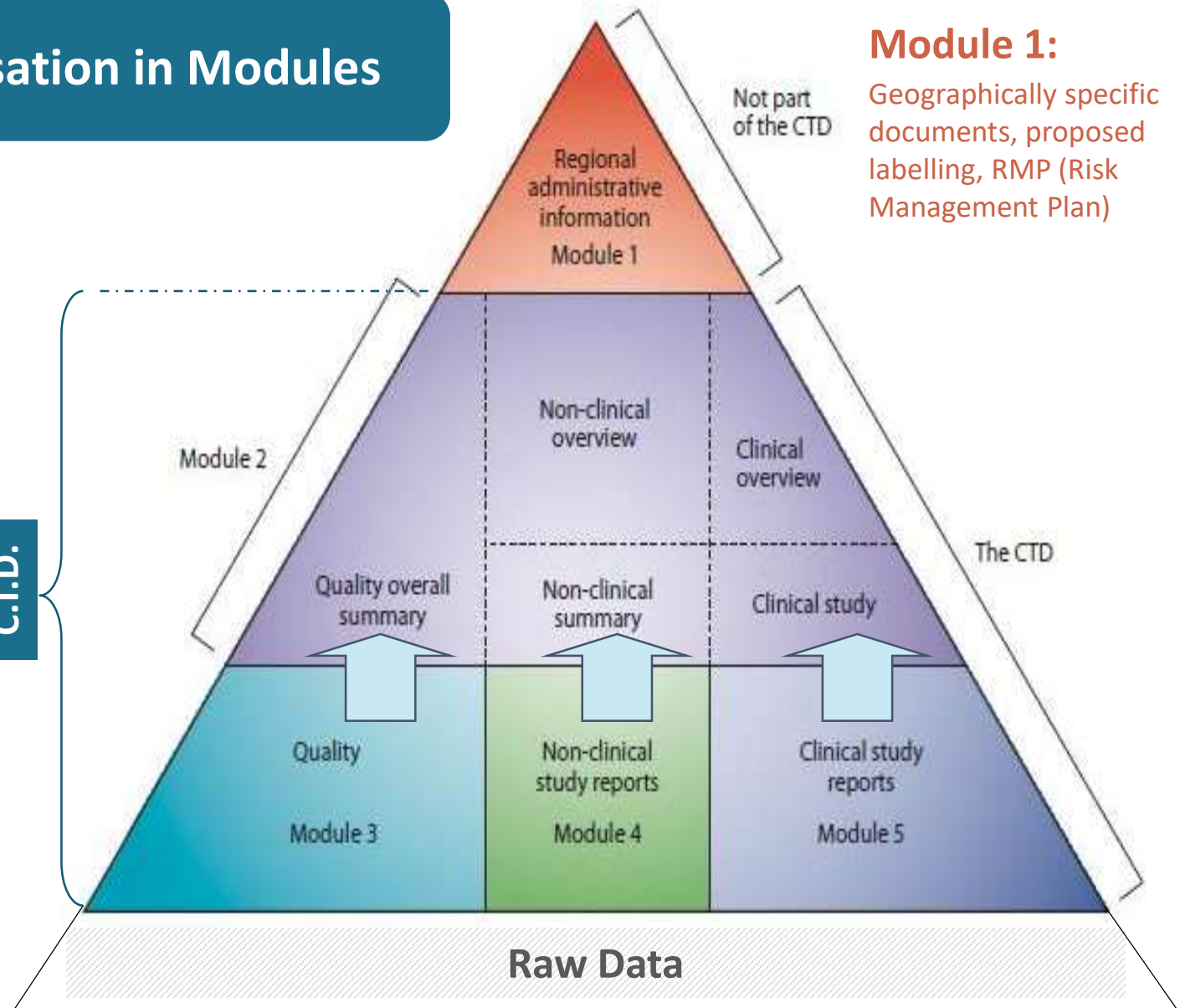Quality (Manufacturing data)

Module 4 :
Non-clinical Study Reports (Preclinical data & toxicology studies)

Module 5 :
Clinical Study Reports

https://www.ich.org/page/ctd

Worldwide acceptance of ICH CTD as Regulatory Dossier format

- In ICH Regions the CTD became official since July 2003, as:
  - in EU and Japan, as the " legally mandatory" format for new product applications
  - in the US, as the "strongly recommended" format for NDAs submitted to FDA (Food and Drug Administration)
  - in ICH Observers countries (Canada Switzerland)

- electronic CTD (eCTD):
  - eCTD specifications were formally adopted at ICH level in Nov. 2003
  - Since 2003, applicants have had the option of submitting an eCTD in parallel with paper submission CTD.
  - The electronic format (eCTD) has become the mandatory electronic submission format since 2014.

- With the expansion of ICH, the CTD is becoming the official standard for dossier format in more and more countries and regions around the world.

Worldwide acceptance of ICH CTD as Regulatory Dossier format

- *Of note: In several non-ICH Regions, the acceptance of ICH CTD format may be subject to differences/variabilities in implementation, e.g.*
    - *"ASEAN CTD" = format applicable in South-East Asia*
        - *ASEAN (Association of South East Asian Nations) includes Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam*
    - *"EAC CTD" = format applicable in East-African countries*
        - *EAC (East African Community) includes Kenya, Uganda, Rwanda, Burundi and Tanzania*
    - *"PANDRH CTD" = format for the Pan-American Network for Drug Regulatory Harmonization (PANDRH)*
        - *PANDRH includes among others: the Andean Community, the Caribbean Community, Central-American Countries, Argentina, Brasil, Paraguay, Uruguay, Venezuela.*
    - *N.B. There may also be differences in implementation of the e-CTD in the various non-ICH regions/countries.*

Electronic Common Technical Document (eCTD) Dossier Format

An eCTD is an electronic submission of (mostly) PDF leaf documents, stored in the eCTD directory structure, accessed through the XML backbone (index.xml) and with the files' integrity guaranteed by Checksum.
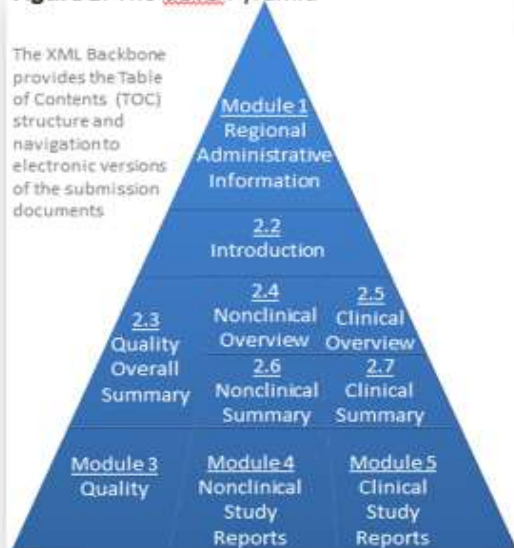
Highly organized electronic table of contents.

Integrated document and lifecycle management
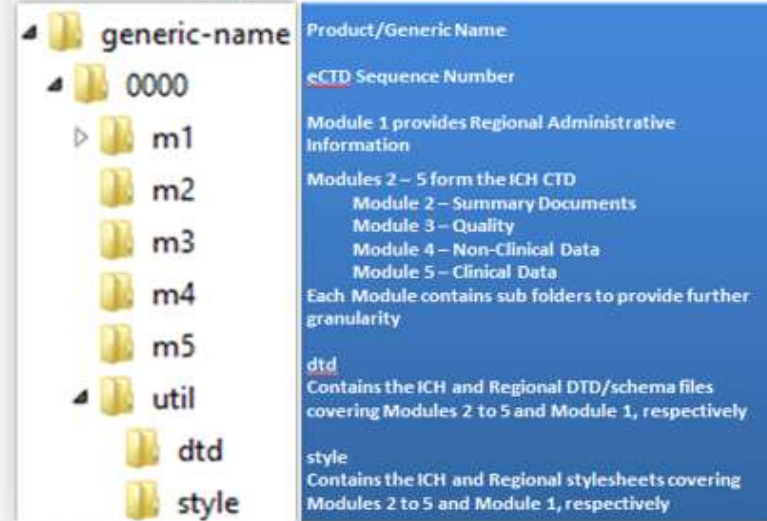
ICH standard for regulatory submissions

Mandatory for a number of HA e.g. FDA and EMA.
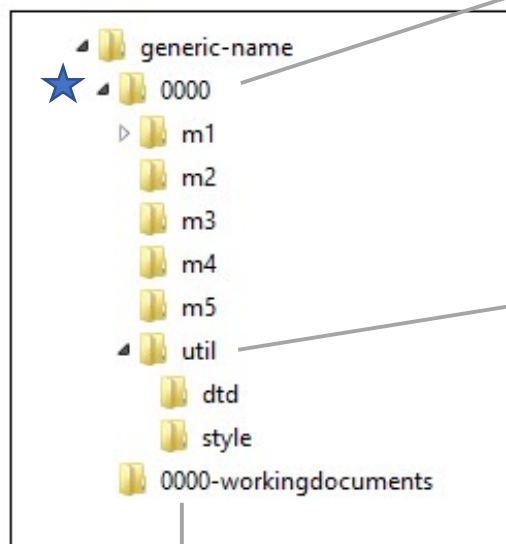
Figure 1: The eCTD Pyramid

The XML Backbone provides the Table of Contents (TOC) structure and navigation to electronic versions of the submission documents

- Module 1 Regional Administrative Information
- 2.2 Introduction
- 2.3 Quality Overall Summary
- 2.4 Nonclinical Overview
- 2.5 Clinical Overview
- 2.6 Nonclinical Summary
- 2.7 Clinical Summary
- Module 3 Quality
- Module 4 Nonclinical Study Reports
- Module 5 Clinical Study Reports

Figure 2: The eCTD Structure

- generic-name — Product/Generic Name
  - 0000 — eCTD Sequence Number
    - m1 — Module 1 provides Regional Administrative Information
    - m2 — Modules 2 – 5 form the ICH CTD
    - m3 — Module 2 – Summary Documents
    - m4 — Module 3 – Quality
    - m5 — Module 4 – Non-Clinical Data
    - util — Module 5 – Clinical Data
      - dtd — Each Module contains sub folders to provide further granularity
      - style

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

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

Composition of the eCTD

```
▲ 📁 generic-name
  ▲ 📁 0000
    ▷ 📁 m1
      📁 m2
      📁 m3
      📁 m4
      📁 m5
  ▲ 📁 util
      📁 dtd
      📁 style
    📁 0000-workingdocuments
```

eCTD Sequence Number

The initial submission submitted to eCTD format is generally 0000 (0001 in the US with most recent specification).
.
Subsequent Responses and Lifecycle maintenance submissions are sequentially numbered 0001, 0002 etc. and form their own submission packages

eCTD Util Folder

Dtd (document type definition)
        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

Move to eCTD brings value

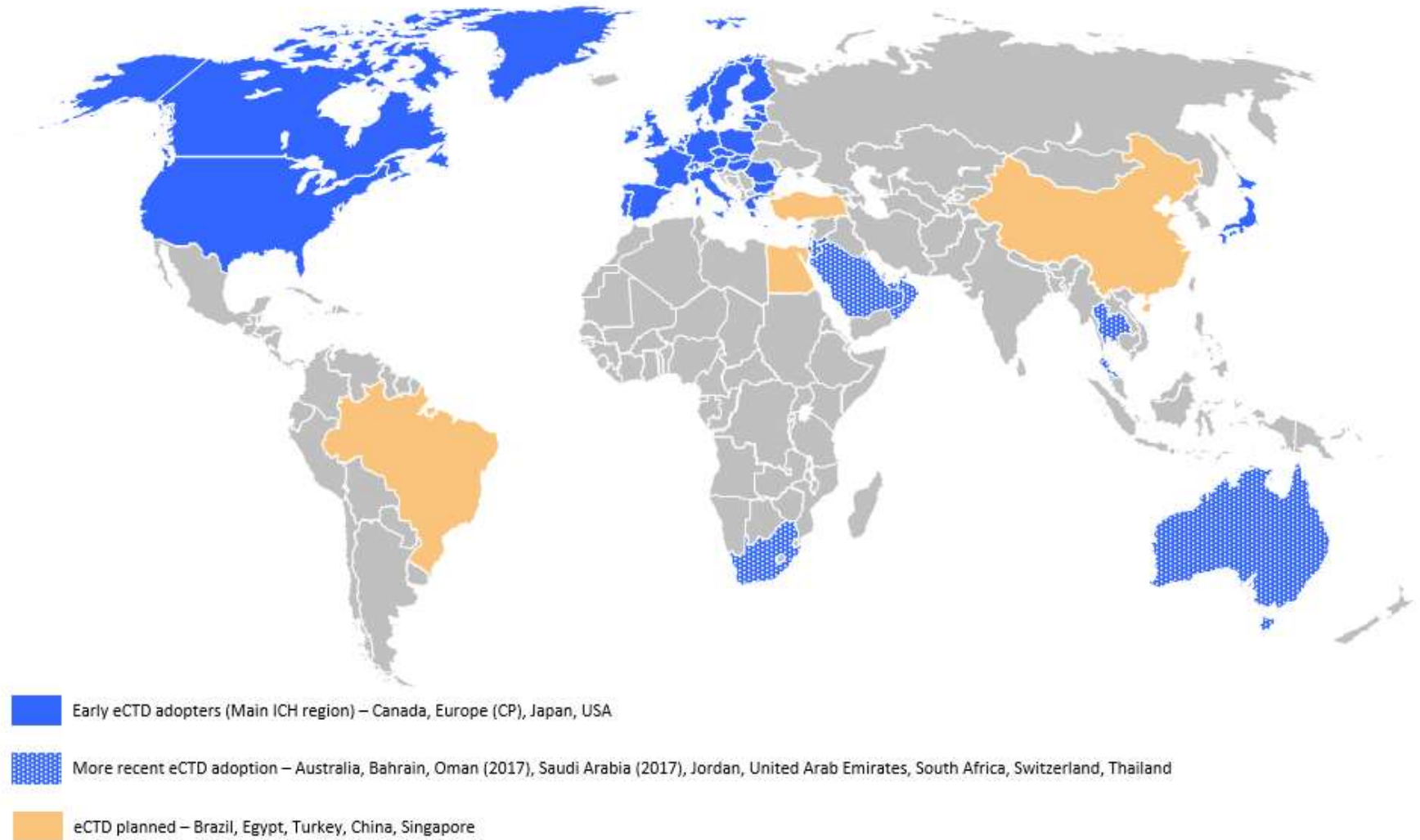**The adoption of ICH eCTD and recognises the many benefits, including:**

- Better information management, document storage, retrieval, archiving
- Electronic working, searching, cross referencing
- Management of product information in the dossier over time

Key recommendations:

- Collaboration – regulator<>industry<>software vendors
- Timelines – allow time for transition (minimum 12 months)
- Consistency with existing standards
- Baselines recommended only
- Implement eCTD as part of wider E2E process digitization
- Maximise use of technology – electronic gateways and automated upload, use of metadata.

Visual of eCTD Adoption mid 2020

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

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

eCTD planned – Brazil, Egypt, Turkey, China, Singapore

eCTD Technical Validation

- eCTD sequences are validated before Applicant dispatch and after Health Authority receipt.
- Most regions have the concepts of Pass/Fail and Best Practice 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.
  - 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**
  - 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
  - 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.

Suggested EFPIA eCTD adoption timelines
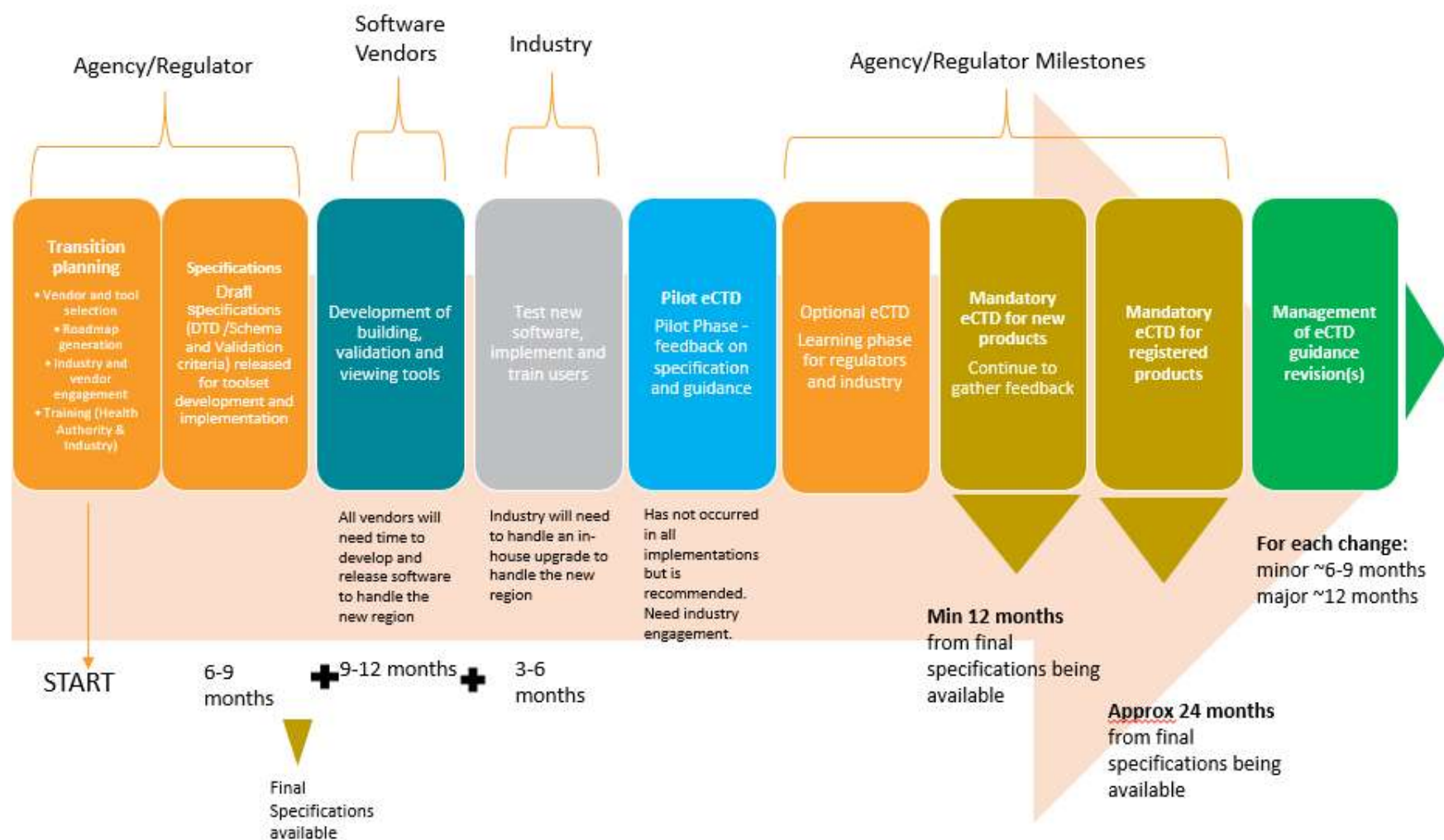
Critical success factors

- 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
- 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

Some challenges

- **eCTD adoption has provided Health Authorities and Industry with challenges;**
  - Software / IT infrastructure issues, vendor issues (regulator and industry)
  - Transition plans for new and registered products – must be carefully managed
  - Need clear communication and interpretation of requirements – ambiguity can cause issues
  - Management and implementation of revised specifications – all parties need the time to adopt
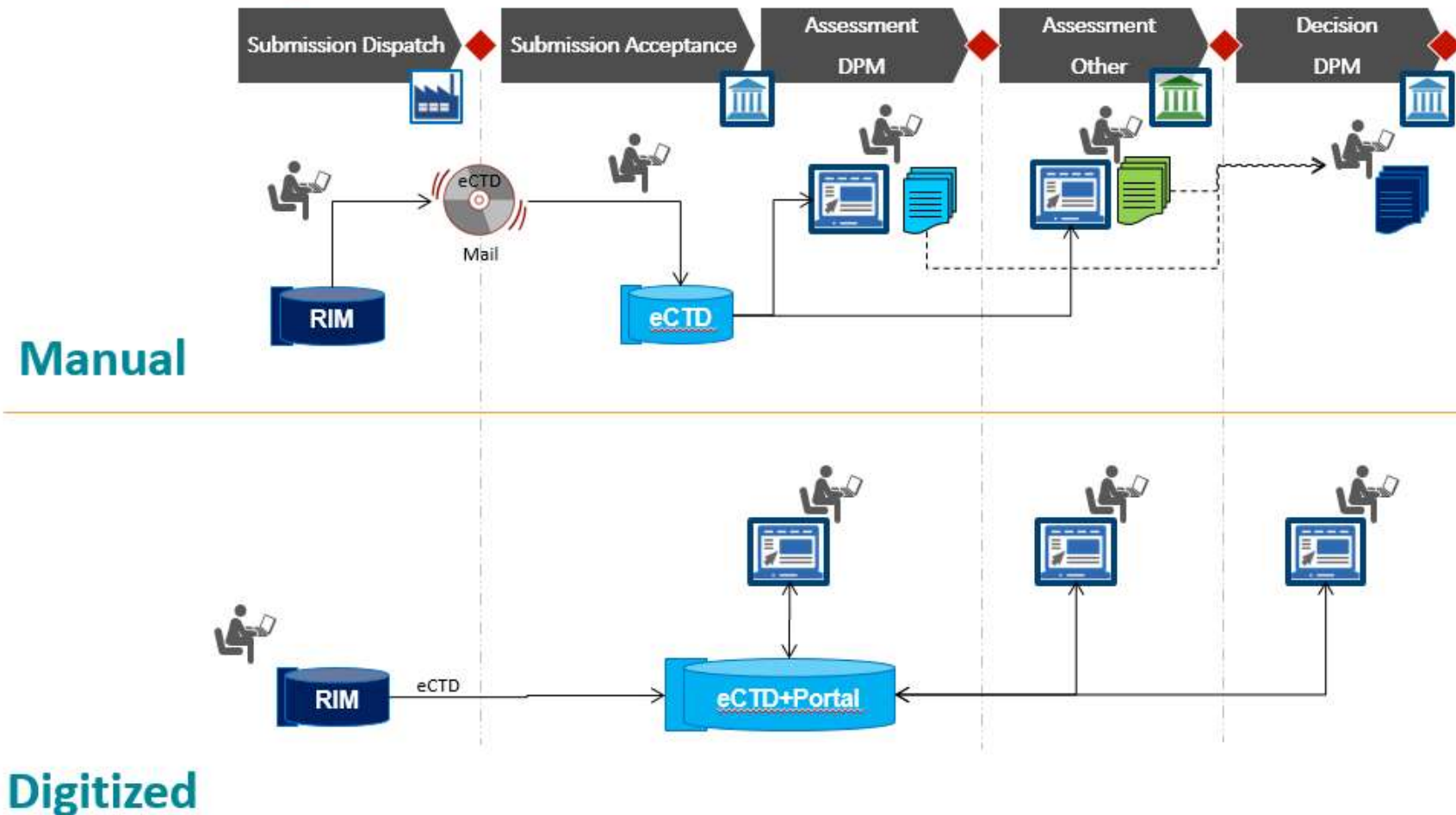
eCTD transition for new products

- 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

- Some authorities in the ICH region have adopted eCTD for new products only (e.g. Swiss Medic, TGA Australia, UAE, Thai FDA)
- Introducing eCTD for registered products also means deciding how to handle the non-eCTD history
  - EU, US, Japan
    - Use eCTD format for lifecycle dossiers without resubmitting original content, although baselines* recommended
  - Saudi Arabia, Oman, Bahrain
    - Require a 'baseline' of current approved information

- Industry recommends that the transition is introduced over a period of time to avoid HA and applicant surge of work and allow phasing for
  - Health Authority transition, Applicant conversion of existing content to CTD, selection of appropriate lifecycle dossiers

Manual vs Digitized eCTD End to End Process

Manual

Digitized

RIM = REGULATORY INFORMATION MANAGEMENT   ECTD = ELECTRONIC COMMON TECHNICAL DOCUMENT

End to end Process is the best option

Options for deployment of eCTD

1. **Maintain current manual process**

   - eCTD is delivered via CD from MAH
   - Assessments are made and shared offline (e.g. via email)
   - eCTD Platforms available "out of the box"

2. **Develop an eCTD gateway/portal with assessment workflow**

   - eCTD is uploaded by MAH via gateway/portal
   - eCTD platforms are linked to gateway/portal
   - Overall system is custom made for Tunisia ways of working

3. **Leverage "cloud" platform for eCTD and assessment workflow**

   - eCTD is uploaded (or shared) by MAH via cloud platform
   - Vendor-supported workflow and eCTD is "out of the box"
   - Limited configuration of solution and faster implementation

Opportunity to substantially enhance the regulatory submission and review process by...

... increasing pharma's regulatory affairs' effectiveness

- A central repository shall always have the last version of the regulatory submission
- Extensive translations of documents shall be minimized and automated
- Transcriptions, localizations, translations of submission documents shall be avoided
- Central repository version shall be used to automatically generate all regional submissions

... modernizing and simplifying the iterations with regulators

- Regulators worldwide shall have access to the same dossier version, at the same time (convergence)
- Automated workflow shall triage and route inquiries and responses
- Regulators' vision to collaborate (and specialize) at global level shall be powered by this platform (reliance and work sharing)
- Regulators will be able to keep up with new advances in regulatory technology (e.g. move to data submissions)

... leveraging existing proven technologies

- Use e.g. cloud technology to simplify access to information, while securing it
- Use a flexible platform able to:
  - ✓ easily orchestrate all diverse information sources
  - ✓ adapt to changes in regulatory frameworks (e.g. NLP, IDC-codes, IDMP)
  - ✓ adapt to changes in collaboration models
  - ✓ Protect data while sharing as needed

Ultimately increasing the capacity of regulators to process approvals = more therapies to patients

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.

Key Learnings from other Regions

- Need clear guidance, closely aligned to ICH

- Material readily available (e.g. on agency website)

- Transparent communication between Authority and Industry

- Advance notices of changes and plenty of time to comply

- Engagement with industry and vendors throughout process

Some additional thoughts

Managing Strengths and Dosage Forms

Trade Name	Formulation	Strength	Licence number
Mydrug	Powder for solution for infusion	1500mg	ABC/1234/01
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

eCTD 1

All dosage forms/strengths in its one eCTD application

Advantages

- Documents that are common are presented only once and therefore read only once by the assessor (e.g., Pharmaceutical Development for multiple tablet strengths)

- Any changes to drug substance, or safety related changes that affect the product, will require only one sequence

- All lifecycle is in one place - no need to jump between different applications which can be confusing

- Faster submission timelines and shorter preparation and reviewing time
- Reduced risk for technical and validation issues
- Easier ability to cross reference to other strengths

Managing Strengths and Dosage Forms: Recommendations

- Merge strengths *and dosage forms* where possible to reduce workload for industry and regulators

- Regional and ICH metadata (envelope, drug substance, manufacturer, drug product, dosage form, manufacturer) should be used to clearly describe what the eCTD application covers

Baseline explained

- A baseline is an eCTD sequence that contains the current and approved CTD formatted documentation for a registered product.

- Typically, a baseline would consist of the maintained information only – labelling and module 3

- Some agencies state a preference to receive m4 and m5

- Since a baseline is by definition content that has already been submitted and approved, no review is required at the regulator

- Baselines must be technically valid eCTD sequences, and pass all eCTD validation criteria

Baseline Pros and Cons

- Establishes current documentation describing product in eCTD format, at both regulator and MA Holder

- More logic in subsequent lifecycle submissions (replaces, deletes)

- A baseline can take significant resource and time to generate

- For applicants to deliver a baseline: previously submitted content has to be revisited and documents reorganised using eCTD restructure, renamed to align with eCTD conventions and for older products predating CTD, content has to be reopened to adjust granularity and re-authored.

- Some older documentation may be in 'paper' format, with no breaks between CTD sections

- Regulators typically do not review but it may be necessary for the regulator to compare the content of the baseline versus previously approved dossier components.

- Mandatory baselines could delay other urgent submissions if the baseline is mandatory

- Urgent submissions should always take priority over any requirement or recommendation to submit a baseline

eCTD for Currently Registered Products

- Industry recommends that Baselines are <u>recommended but not mandatory</u> to minimise effort and rework for Health Authority and Applicant.

- Industry recommends that the transition is introduced over a period of time to avoid HA and applicant surge of work and allow phasing for
  - Health Authority transition, Applicant conversion of existing content to CTD, selection of appropriate lifecycle dossiers

Term	Definition
Applicant	A pharmaceutical company or its agent that is submitting information in support of an *application*.
Applicant's Information	Regulatory information submitted by an *applicant* for, or to maintain, a marketing authorisation that falls within the scope of this guidance document.
eCTD application or also known as a dossier	A collection of electronic documents compiled by a pharmaceutical company or its agent in compliance with European legislation and guidelines in order to seek a marketing authorisation or any amendments thereof. An *eCTD application* may comprise a number of *regulatory activities*. In the EU an eCTD application may comprise several dosage forms and strengths, all under one invented product name. This is understood to be equivalent to a Global Marketing Authorisation according to Art. 6 para 2 Dir. 2001/83/EC as amended.
Procedure	A Community registration procedure for the authorisation of medicinal products in the European Community. There are 4 types of procedure that operate within the EC – Centralised, Decentralised, Mutual Recognition and National.
Regulatory Activity	A *single sequence or a collection of sequences* covering the start to the end of a specific business process, e.g. an MA application or Type II variation. To allow a more precise handling, the regulatory activity will be classified using a controlled vocabulary (submission type or regulatory activity type) and a free text field for a short narrative description.
Sequence	A single set of information and / or electronic documents submitted at one particular time by the applicant as a part of, or the complete application .Any collection of content assembled in accordance with the eCTD specification (ICH and EU) will be described using metadata as defined by the EU envelope. Sequences may be related to one another within one regulatory activity. The related sequence number should always be stated. In case of activities with only one sequence the same sequence number will be used.
Submission Type	The submission type describes the *regulatory activity* to which the content will be submitted.
Submission Unit Type	The submission unit type element of the envelope metadata set describes the content at a lower level (a "sub-activity") which is submitted in relation to a defined regulatory activity such as the initial submission, the applicant response to validation issues or list of questions or any other additional information.

Thank you

Key Abbreviations

API	Active Pharmaceutical Ingredient (Active Substance, Drug Substance)		ICH	International Conference on Harmonisation
ASMF	Active Substance Master File		IPC	In-Process Control
CEP	Certificate of the European Pharmacopoeia		LoA	Letter of Access (to DMF)
CHMP	Committee for Medicinal Products for Human Use (previously CPMP)		PAT	Process Analytical Technology
			Ph Eur	European Pharmacopoeia
CMC	Chemistry, Manufacturing & Controls		Q&As	Questions and Answers
CTD	Common Technical Document		QbD	Quality by Design
DMF	Drug Master File		QP	(EU) Qualified Person
DP	Drug Product		QOS	Quality Overall Summary
DS	Drug Substance		QWP	Quality Working Party (of CHMP/CVMP)
EDQM	European Directorate for the Quality of Medicines		SM	Starting Material (for chemical synthesis)
GMP	Good Manufacturing Practice		TSE	Transmissible Spongiform Encephalopathy