Overview of global registration of vaccines

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Outline of the presentation

- The objective of medicines regulation
- The regulatory System
- The regulatory Functions
- Overview of marketing authorization function
- Marketing approval process in various countries
- Harmonization attempts
- Comparison of CTD module 1, some examples

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Objectives of the regulatory oversight of medicines including vaccines

- Ensure that medicines circulating in countries are of standard quality, are safe and effective
- Exercise control over the medicines that are marketed in the country through registration in order to prevent to the extent possible, the circulation of substandard or counterfeit products
- Be able to monitor the safety profile of products, i.e. occurrence of adverse reactions their investigation and management
- Be able to monitor the qualityand effectiveness of products once they are introduced in the market and throughout their lifecycle

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The beginnings of regulatory strengthening activities at WHO

When the WHO activities to strengthen regulatory capacity started in the late 90's, vaccines supplied through the UNICEF or the PAHO centralized procurement mechanisms were used in receiving vaccines without any in-country regulatory oversight

- Reception, storage, distribution and use was directly managed by EPI.
- Many of the receiving countries did not have a developed NRA capable of regulating Biological Products
- Vaccines were prequalified by WHO and this was sufficient seal of quality for acceptance

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The beginnings of regulatory strengthening activities at WHO (2)

However, from WHO's perspective,

Ideally, all countries should

- Have a «SYSTEM» in place to regulate the circulation of medicines in their territories,

  and….

- Exercise a number of selected functions to oversee their quality, safety and efficacy, depending on the characteristics of the country

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What is a Regulatory System and why is it needed?

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The Regulatory System

- Defines the responsible Institutions for regulatory oversight of medicines, as well as their respective functions, roles and organizational structure
- Defines the scope of products covered
- The legislation, at different levels, (law, regulations, decrees) provide the legal framework on which the regulatory system is built.
- The highest level is represented by the law, which provides the overall and very general guidance. Regulations, decrees, procedures, etc provide increased level of detail as to the way in which the system works.

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The Regulatory System (2)

- The highest level is represented by the law, which provides the overall and very general guidance.
  - Being the overarching framework of the regulatory system, laws need to be general enough to allow for flexibilities
  - Flexibilities allow to follow alternative regulatory pathways under special circumstances
- Regulations, decrees, procedures, etc provide increased level of detail as to the way in which the system works, and in which way the law is to be applied and enforced.

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The Regulatory System (3)

Every effort should be done to develop a «ROBUST» regulatory system that will take into account different situations and conditions of use of the vaccines

Different provisions embedded in the regulatory framework are required to provide the necessary flexibility to achieve this

Transparency, well defined and published processes and procedures applied in a consistent manner, established fees, etc are key elements of a robust system

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The Regulatory functions

Six **functions** have been identified as important for the regulation of vaccines

However,

- ✓ not every country needs to develop them all
- ✓ Strategies used by countries to ensure adequate performance of each function may vary (different routes lead to Rome).

The aim is to exercise an effective and efficient regulatory oversight of the products while making the best use of existing resources and available knowledge about the products' quality, safety and efficacy.

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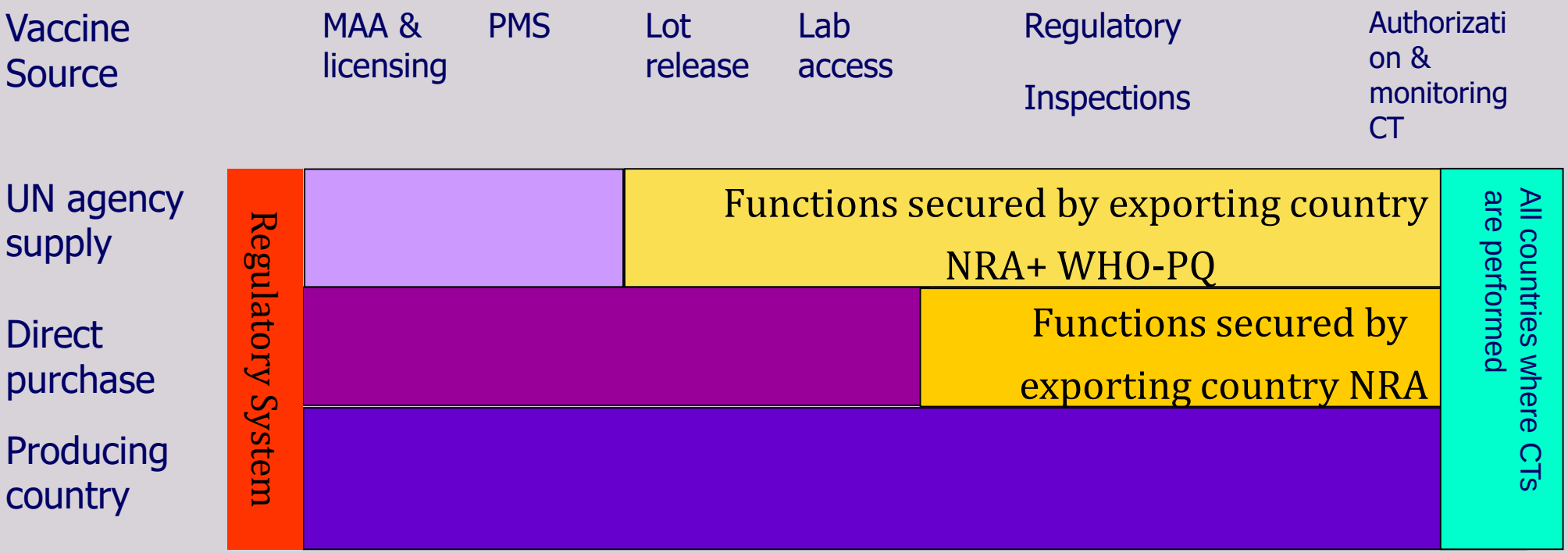
WHO recommended functions according to vaccine source
(*prioritization strategy)*



Summary of recommended functions

Producing countries: All six critical functions need to be established

Non- producing countries sourcing vaccines through United Nations procurement agencies need to establish Marketing Authorization and Post-Marketing Surveillance

Countries procuring vaccines directly need to establish Marketing Authorization, Post-Marketing Surveillance, lot release and laboratory access

All countries that are target to performance of clinical trials need in addition to establish Authorization and Monitoring of Clinical Trials

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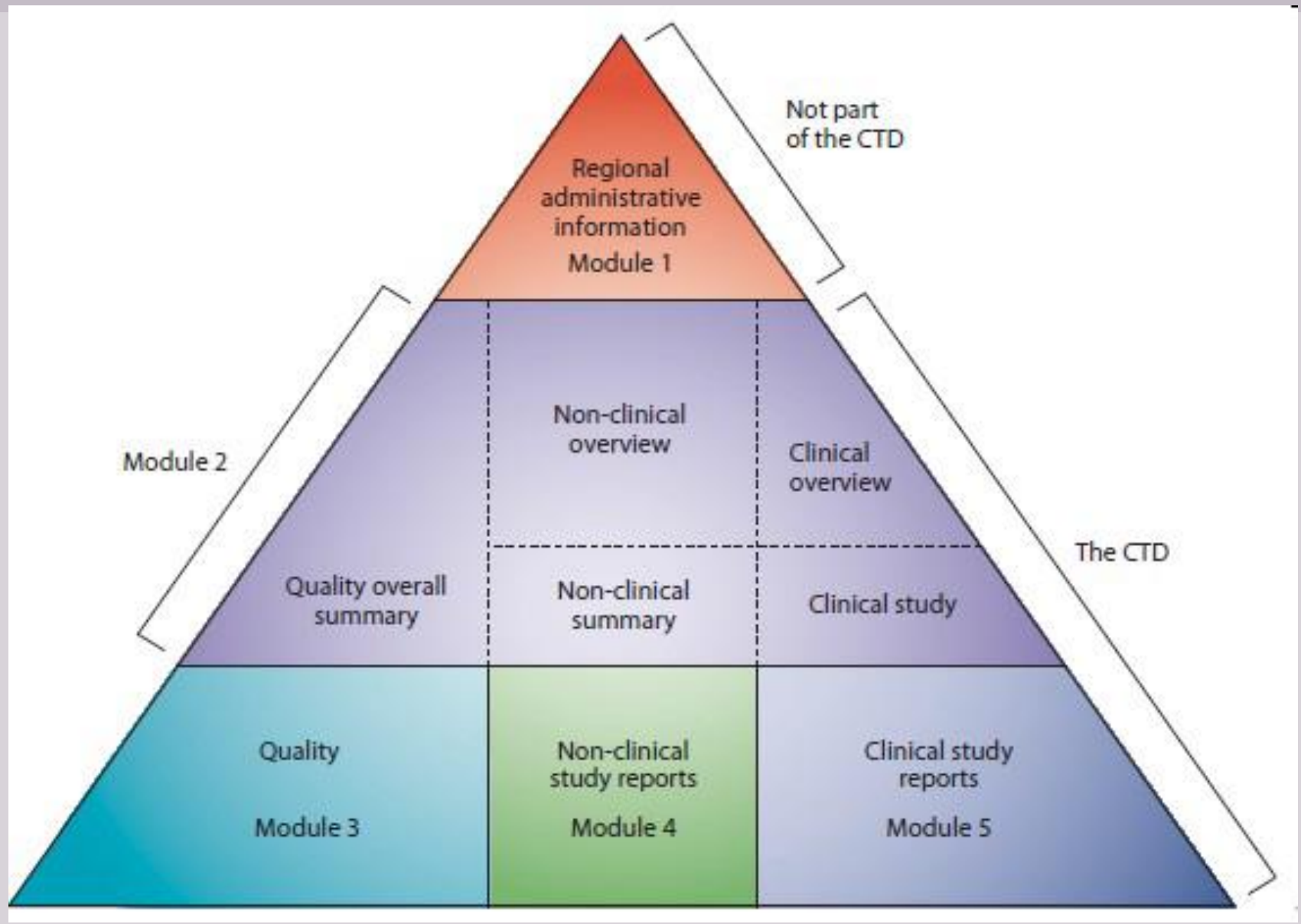
Marketing Authorization

- ✓ A medicinal product can only be marketed in a specific country or region if it has been approved/authorized by the appropriate governmental body/is in that country or region, granted a marketing authorization.
- ✓ The company interested in the MA needs to demonstrate the product quality, safety and efficacy
- ✓ In Japan, EU and US there is a common/harmonized format in which the documentation on Q,S & E is submitted. This is the CTD (common technical document) and more recently the eCTD
- ✓ The process for evaluating the product and granting the MA is however not exactly the same in these countries/region
- ✓ EU and US focus their evaluation and decision making process on the dossier review, Japan however has a different approach

ICH Common Technical Document



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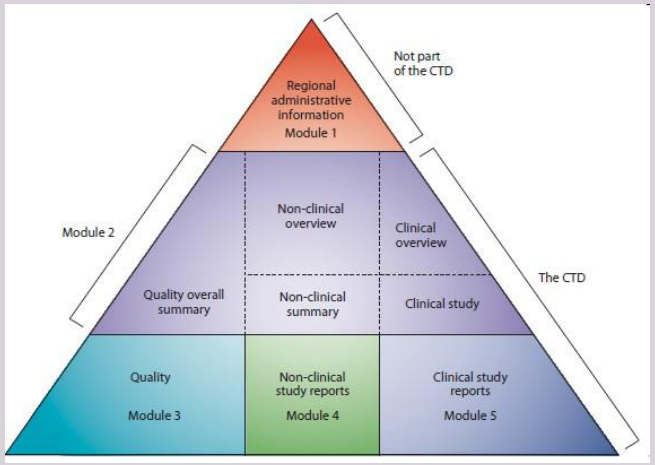
Common Technical Document



- ✓ Module I contains region specific information that is not common between the ICH parties including: application forms, mock-ups of labelling and packing information in local language and legal documents required for MA
- ✓ Modules 2-5 are harmonized
- ✓ ASEAN CTD does not include module 2
- ✓ Module 1 is the source of headaches for manufacturers since this is different for each country and region in the world.

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General steps for product licensing/registration

- ✓ The general steps for data review is similar in the three ICH countries/regions and include:
- ✓ Application by the manufacturer to the responsible authority
- ✓ eCTD technical validation followed by a formal content validation
- ✓ Start of procedure
- ✓ Assessment by regulatory experts
- ✓ Q & As phase
- ✓ Decision pro/Con on approval
- ✓ Inform the applicant about the decision
- ✓ Publication of the decision on the website

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Note; the specific steps followed may vary according to the local laws and regulations

Market Approval Process in USA, EU and Japan

The process in US and Europe does not necessarily include inspection or testing.

The process in Japan is in two steps. First the manufacturer requires a manufacturing/marketing license which is subject to a GMP inspection and only after this “license” has been granted the manufacturing/marketing license holder can submit the manufacturing/marketing approval application to start the dossier evaluation process

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Market Approval Process in Canada

ICH Common Technical Document (CTD) (in place since 2003)

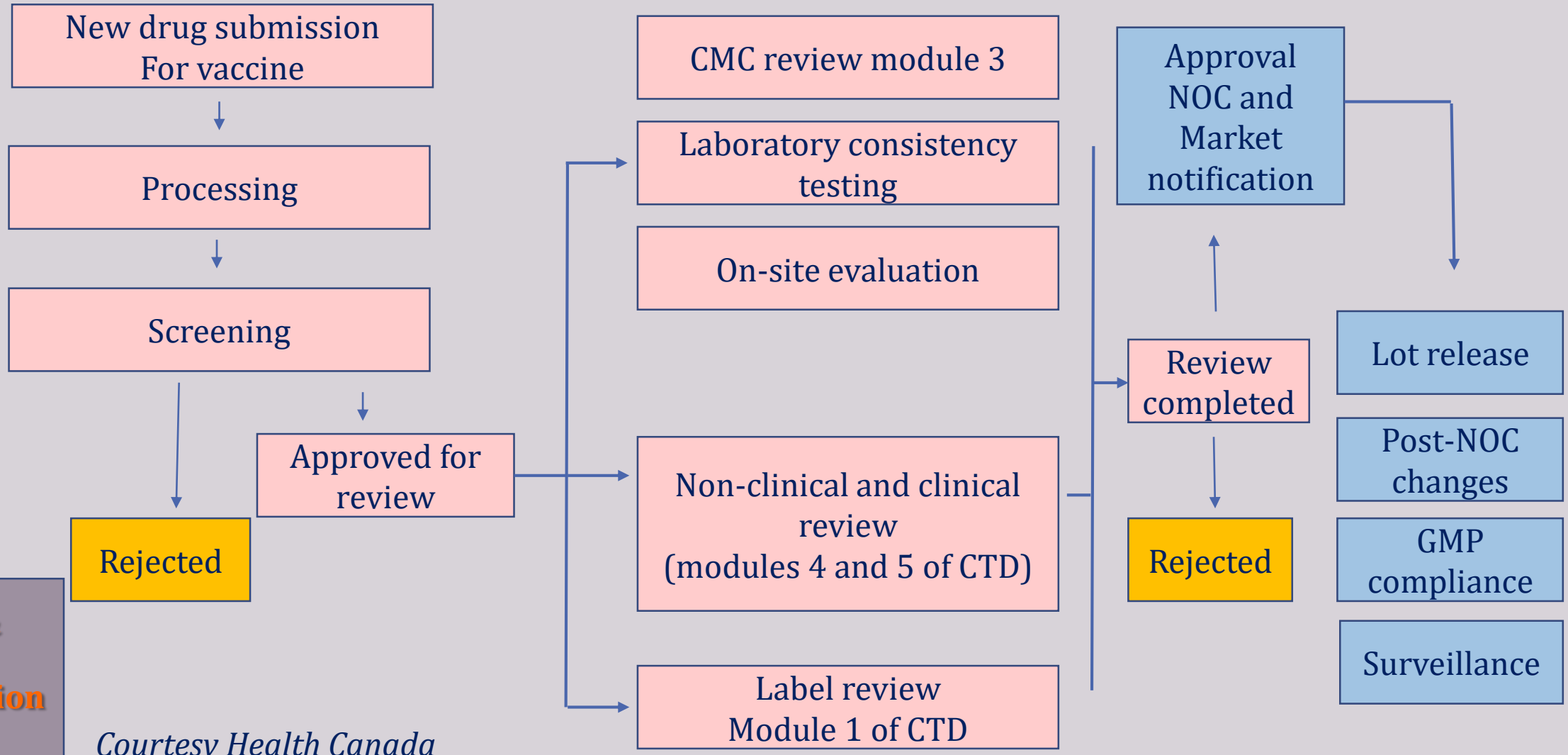
Submissions are structured and formatted as per the International Conference on Harmonisation (ICH) Common Technical Document (CTD)

- Applies to pharmaceuticals and biologics (including vaccines)
- Includes regional administrative (ie country specific) and general filing requirements

CTD Format

- Module 1 **(country specific): Administrative** and Prescribing Info
- Module 2: CTD Summaries (Quality, Nonclinical, Clinical)
- Module 3: Quality
- Module 4: Nonclinical Study Reports
- Module 5: Clinical Study Reports

Market approval process for a vaccine submission in Canada



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Courtesy Health Canada

Summary of Market Approval process

CTD review	Site inspection	Consistency testing
EU		
USA		
Japan		
Canada		

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Harmonization vs dis-harmonization of requirements

- ✓ The ICH CTD and eCTD or its adaptations have been adopted by numerous countries in the world
- ✓ The establishment of the CTD by ICH has been a huge step towards harmonization of requirements across the globe
- ✓ However, module 1 remains non-harmonized and different countries and regions require very different documentation that creates high workload and investment of resources by the manufacturers who are willing to export their products
- ✓ The process followed by countries for MA evaluation also differs. EU and US, base their assessment on the review of the CTD, Japan requires a previous license of the facilities, Canada requires licensing of the establishment, an on-site evaluation (for Biologics only) and testing of batches
- ✓ Other countries introduce more variables to this already complicated picture

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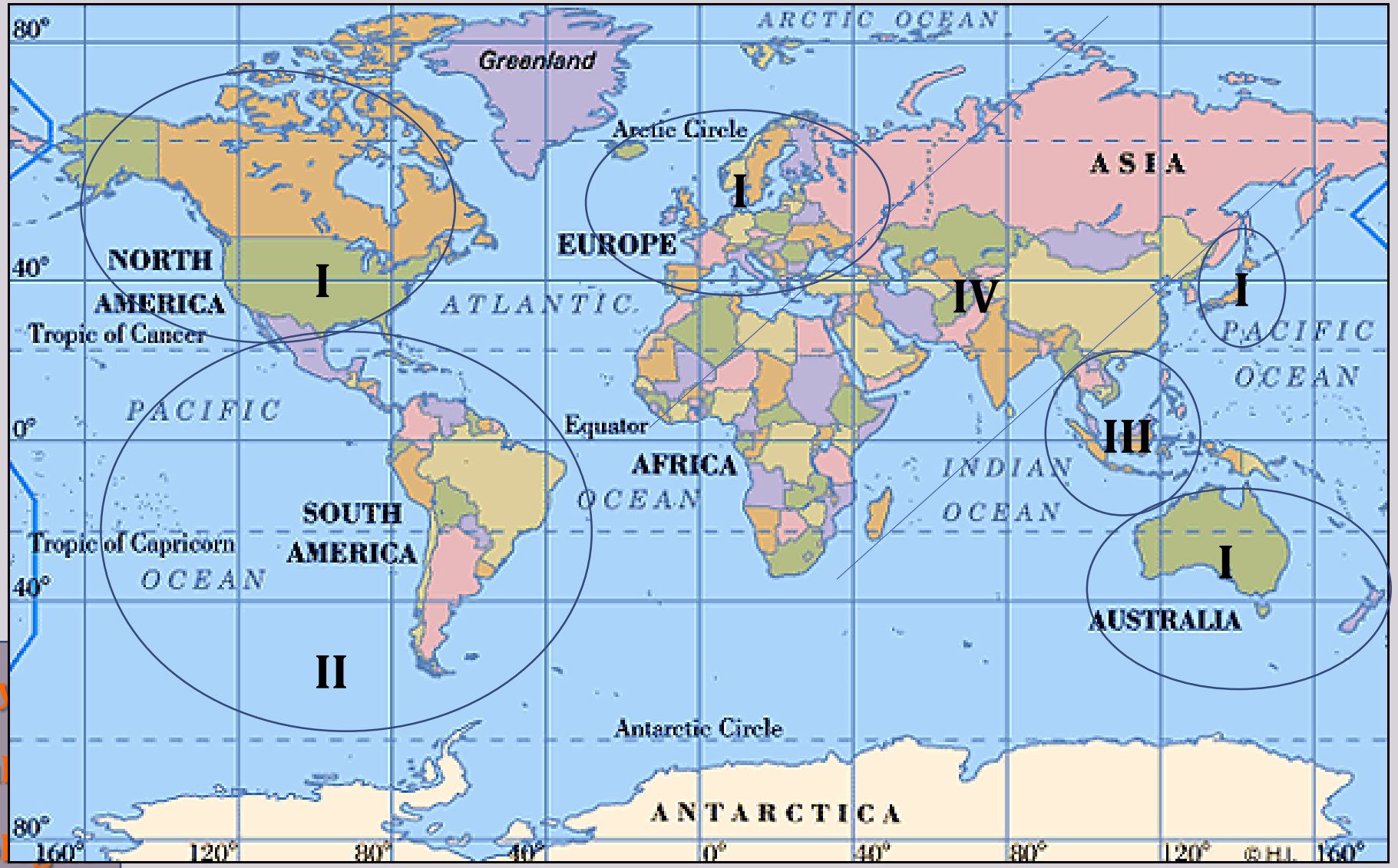
Worldwide distribution of MA dossier formats



I ICH CTD

II PAHO CTD

III ASEAN CTD

IV Diversity of formats

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Comparison of CTD module 1 PAHO and India

PAHO	INDIA
1.1 Table of contents (modules 1 to 5)	1.1 Comprehensive table of contents (Modules 1 to 5)
1.2 Application form 1.2.16 Legal documents: Doc. Recogninzing technical director or equivalent, authorization of representative, CPP, certificate of GMP, Batch release Certificate, patent certificate, trademark certificate (optional), etc	1.2 Administrative information 1.2.1 to 1.2.2.5 legal and Statutory documents (some to be notarized) including Form 44 and Treasury Challan, License and Approvals, Copy of Site Master File, Certificate of Analysis from CDL Kasauli
1.2.1 Proprietary, commercial or trade name of vaccine	1.2.4.1 Proprietary, commercial or trade name of drug product
1.2.2 Non-proprietary name or common name of vaccine	1.2.4.2 Non-proprietary name or common name of drug product
1.2.3 Concentration	1.2.4.3 Composition (as per label claim)
1.2.4 Dosage Form	1.2.4.4 Dosage form
1.2.5 Senior Executive Officer / Senior Medical or Scientific Officer 1.2.7 Vaccine Proprietary 1.2.8 Manufacturer of active ingredients 1.2.9 Manufacturer of the finished product 1.2.10 Other manufacturers involved in the production process	1.2.3.1 Name, address, telephone, fax, e-mail of manufacturer of drug product 1.2.3.2 Name, address, telephone, fax, e-mail of the responsible official 1.2.3.5 Name, address, telephone, fax, e-mail of the manufacturing premises holding Market Authorization of the drug product (for imported drug products) 1.2.3.6 Name, address, telephone, fax, e-mail of manufacturer of drug substance 1.2.3.7 Name, address, telephone, fax, e-mail of other manufacturer(s) involved in the production process
1.2.6 Legal Representative in Country	1.2.3.3 Name, address, telephone, fax, e-mail of the authorized agent
1.2.11 Official responsible for releasing batches of finished product	1.2.3.4 Name, designation, address, telephone, fax, e-mail of the official responsible for releasing batches of drug product

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Comparison of CTD module 1 PAHO and India (2)

PAHO	INDIA
1.2.12 Commercial presentation of vaccine	1.2.4.8 Commercial presentation
1.2.13 Route of administration	1.2.4.7 Route of administration
1.2.14 Storage conditions	1.2.4.9 Conditions of storage or conservation
1.2.15 Strength of each unit of dose	1.2.4.5 Strength per dosage unit. 1.2.4.6 Dispensing requirements
1.3 Summary of Product Characteristics and Product Labeling 1.3.1 Summary of product characteristics	1.2.4.10 Summary of product characteristics as per Annex C
1.3.2 Product labelling 1.3.2.1 Primary package label 1.3.2.2 Secondary packaged label 1.3.2.3 Package insert 1.3.2.4 Final packaging	1.2.4.11 Product Labeling (should conform to the specifications under the Drugs and Cosmetics Rules 1945) a. Primary package label b. Secondary package label c. Package insert (in English)
1.3.2.5 Monograph for health professionals or information for prescription in extended or reduced form	1.2.4.11 Monograph for health professionals or information for prescription
1.3.3 Samples 1.3.3.1 Samples of finished product (in accordance with legislation of each country) 1.3.3.2 Summary protocol of batch production and control	1.2.5 Summary protocol of batch production and control 1.2.14 Samples
1.4 List of countries where the product has been licensed and summary of approval conditions	1.2.6 List of countries where MA or import permission for the said drug product is pending and the date of pendency 1.2.7 List of countries where the drug product has been licensed and summary of approval conditions. 1.2.8 List of countries where the drug product is patented. 1.2.9 Domestic price of the drug followed in the countries of origin in INR.
1.5 Information regarding experts	1.2.12 Information about the expert(s)/ Information regarding involvement of experts, if any
1.6 Environmental risk assessment	1.2.13 Environmental risk assessment
	1.2.10 A brief profile of the manufacturer's research activity 1.2.11 A brief profile of the manufacturer's business activity in domestic as well as global market.

Comparison of CTD module 1 EU and Jordan

EU	JORDAN
1.0 Cover letter	1.0 Cover Letter.
1.1 Comprehensive table of content	1.1 Comprehensive Table of Contents (Module 2-5).
1.2 Application Form (Administrative data) 23 Annexes need to be included under item 1.2	1.2 Application Forms (JFDA forms):
1.3 Product Information	1.3 Product Information
1.3.1 Summary of Product Characteristics, Labelling and Package Leaflet Proposal for packaging, labelling & package leaflet	1.3.1 SPC (Summary of product characteristics), Labeling, Package leaflet.
1.3.2 Mock up	1.3.2 Mock-up.
1.3.3 Specimen	1.3.3 Specimen (one registration sample)
1.3.4 Consultation with Target Patient Groups	NA
1.3.5 Product Information already approved in the Member States. SPC already approved in the member states	NA
1.3.6 Braille	NA
1.4 Information about the Experts Expert reports. Signature of experts	NA
1.4.1 Quality 1.4.2 non-clinical 1.4.3 Clinical	NA
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 Authorization	1.4 Specific Requirements for Different Types of Applications: 1.4.1 Information for application type (Generic, Bio-similar ……..). 1.4.2 Information for submission type (Technology Transfer, under license …..)
1.8 Information relating to Pharmacovigilance	1.5 Information related to Pharmacovigilance
1.8.1 Pharmacovigilance System 1.8.2 Risk-management System	1.5.1 Pharmacovigilance System. 1.5.2 Risk-management System.

Comparison of CTD module 1 EU and Jordan (2)

EU	JORDAN
1.6 Environmental Risk Assessment	1.6 Other information
1.6.1 non-GMO 1.6.2 GMO	1.6.1 List of Similar Product Available in Local Market. 1.6.2 NA to vaccines 1.6.3 Declaration from the manufacturer about the ingredient/s from human or animal origin included in the composition of the product and their source and the related certificates (*TSE CEP*). 1.6.4 List from manufacturer to declare the worldwide registration status: (registered\Marketed (date), under registration, rejected (with reason) 1.6.5 Technical Contract (Open part) in case of contract manufacturing. 1.6.6 Health authority approval of the latest Plasma master file (if the product contain plasma derivatives)
1.7 Information relating to Orphan Market Exclusivity	1.6.7 Certificates
1.7.1 Similarity	1.6.7.1 Certificate of Pharmaceutical product (CPP)according to WHO format Certified and Legalized. 1.6.7.2 SmPC certified and legalized from country of origin (excluding generics). 1.6.7.3 Price certificates:(for Exported products) 1.6.7.4 Prices certificate: (for local products) 1.6.7.5 JFDA approval certificate for the Manufacturing site/s (for the same production line)(or copy of the request letter for approval (date and number)
1.9 Information relating to Clinical Trials	
Responses to Questions	
Additional data	

General comments on CTD module 1

- ✓ India's CTD was based on PAHO's CTD. However, significant differences in contents and numbering system between module 1 for both CTDs,
- ✓ Jordan CTD is based on EU CTD. However, significant differences in contents (not so much in numbering system),
- ✓ Thailand FDA CTD is based in EU CTD. Module 1 of both CTDs are quite comparable.
- ✓ ICH CTD is harmonized for EU, USA and Japan. However, module 1 is quite different for the three of them
- ✓ In addition to collecting the required administrative information, US FDA uses the regional section of the CTD as a catalogue of various correspondence associated with the submission, from presubmission meeting requests to submission withdrawals.
- ✓ Furthermore, other countries have their own module 1 format and contents and still other do not use a CTD format. Hence, huge scope for future work on alignment worldwide.

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Thank you

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