Course title: International financial regulation

Lesson 1. The Rational of International, EU and UK Regulatory Structures

Lecturer: PhD. Nargiza Dalmuradova

Outline

- EU Regulatory Environment
  - EU pharmaceutical legislation: basic principles
  - EU Clinical Trials Directive
  - EU Registration Procedures: CP & MRP/DCP
  - Post-Authorisation Variations
  - EU Paediatric Regulation: impact on development and registration
  - New Pharmacovigilance legislative requirements
- US Regulatory Environment
  - FDA & relevant legislation
  - IND & BLA
- Japanese Regulatory Environment
  - Law and relevant authorities (MHLW, PMDA, NIID)
  - Clinical Trials Notification & JNDA
- International Regulatory Environment
- Global Harmonisation

A representative sample of the slides that will be presented and discussed during the course is displayed hereafter.

EU Regulatory Environment

Evolution of the European Regulatory Environment since 1995…

Birth of the EMEA

1995 — EMEA Centralised Procedure; Mutual Recognition Procedure

2000 — Orphan Drugs Regulation

2003 — Annex I (to Directive 2001/83/EC) (CTD)

2004 — New Legisl. Title IV of Reg. 726/04 immediate

2005 — New Legisl. fully into force

2006 — Paediatric Regulation

2007 — Legisl. on Advanced Therapy

2008 — Enlarged Scope of CP

2010 — New Variation Regulation; New Pharmacovigilance legislation

2012 — Implem. of New PV Legisl.; PRAC (July 2012)

Enlargement (to 15 MS)

Enlargement to 25 MS (CY, CZ, EE, HU, LT, LV, MT, PL, SI, SK)

Enlargement to 27 MS (BG & RO)

Future... Accession of Croatia

Structure of the European Medicines Agency (EMA)

EMA Permanent Staff

EXECUTIVE DIRECTOR
Guido Rasi

- COMMUNICATIONS AND NETWORKING
- **HUMAN MEDICINES DEVELOPMENT AND EVALUATION**
- **PATIENT HEALTH PROTECTION**
- **VETERINARY MEDICINES AND INSPECTIONS**
- ADMINISTRATION

Experts appointed by NCA

- **CHMP** Committee for Medicinal Products for Human Use
- **CVMP** Committee for Medicinal Products for veterinary use
- **COMP** Committee on Orphan Medicinal Products
- **HMPC** Committee on Herbal Medicinal Products
- **CAT** Committee for Advanced Therapies
- **PDCO** Paediatric Committee
- **PRAC** Pharmacovig. and Risk Assessment Committee

NATIONAL COMPETENT AUTHORITIES (> 3 500 EUROPEAN EXPERTS)

CHMP (Committee for Human Medicinal Products)

Composition

Chairman (Dr. T. Salmonson; SE)

&

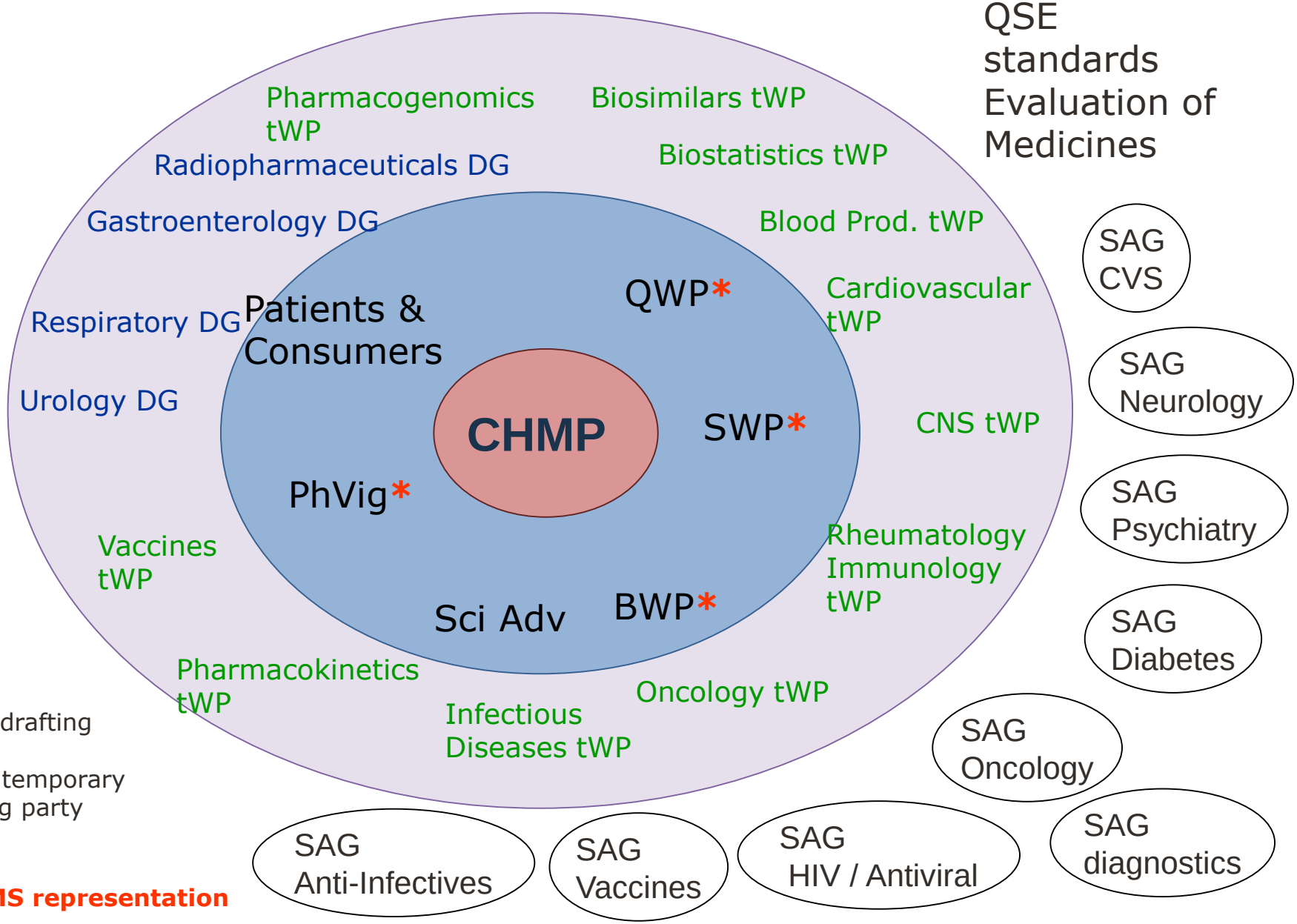
Vice-Chairman (Dr. I. Hudson; UK)

- **27 MSs + NO/IS (**EEA Countries**)** - 22 Languages (Working Language EN)
- **1** scientific expert **member** nominated by each MS **and 1 alternate**
- 1 scientific expert member from NO and IS and 1 alternate (**observers**)
- **5 co-opted members** as appointed by Management Board
- 3 years Mandate renewable

CHMP main tasks & responsibilities

- Delivering opinions to the European Commission
  - on new medicinal products/variation/renewal/line extension
  - on arbitration/referral procedures
- Advising on general EU guidelines/policies
- Scientific Advice & guidelines to companies
- Opinions on Compassionate Use to MSs
- Contribution to ICH process
- Establish Working Parties, SAGs & Expert Groups
- Delivering opinions to WHO

Working Party Constellation



DG = drafting groups
tWP = temporary working party

*** 1 / MS representation**

COMP (Committee for Orphan Medicinal Products)

Dr. Westermark

Composition

Chair and Vice Chair

+

1 member/MS

+

3 reps patient organizations

+

3 EMA reps

+ 3 patient organisations

+ 3 EMA

PDCO (Paediatric Committee)

Dr. D. Brasseur

Composition:

Chair and Vice Chair

+

5 CHMP members

+

1 member/MS

(not yet represented by member appointed by CHMP)

+

3 reps patient organizations

+

3 reps healthcare professionals

+ 3 patient organisations

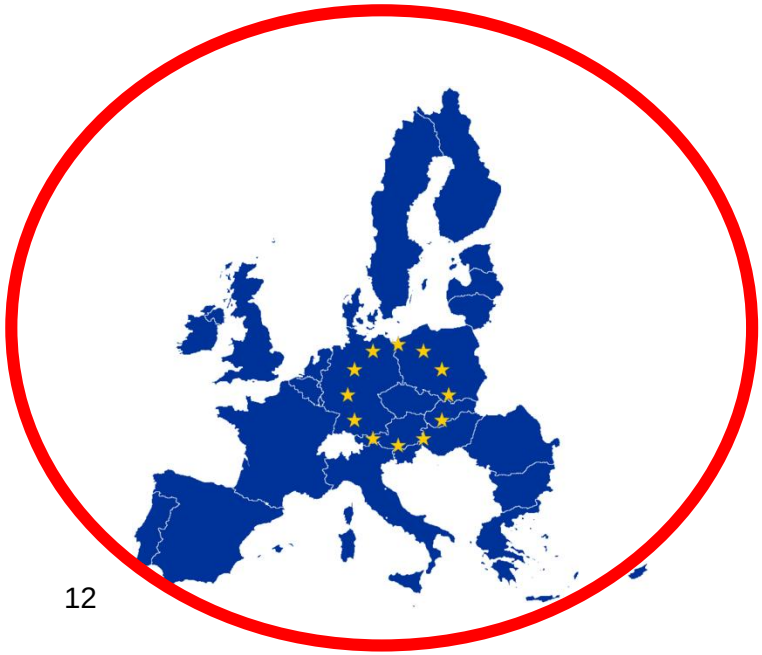
+ 3 healthcare prof.

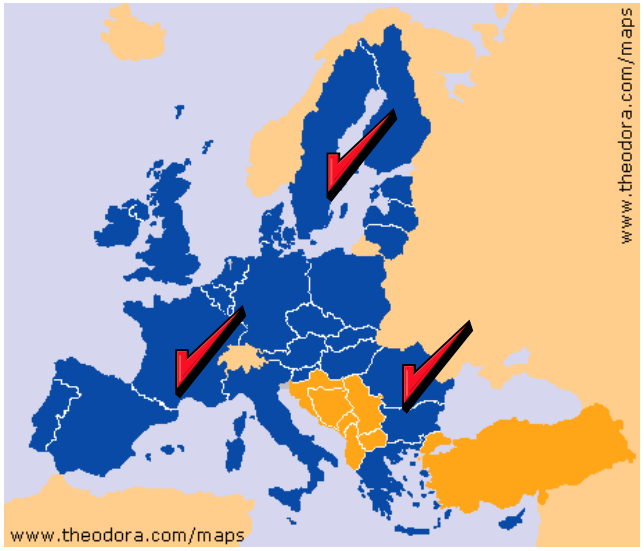
Registration in Europe Post Nov 2005 :
→ Three European Systems

Centralised Procedure (via EMA)

Mutual Recognition procedure

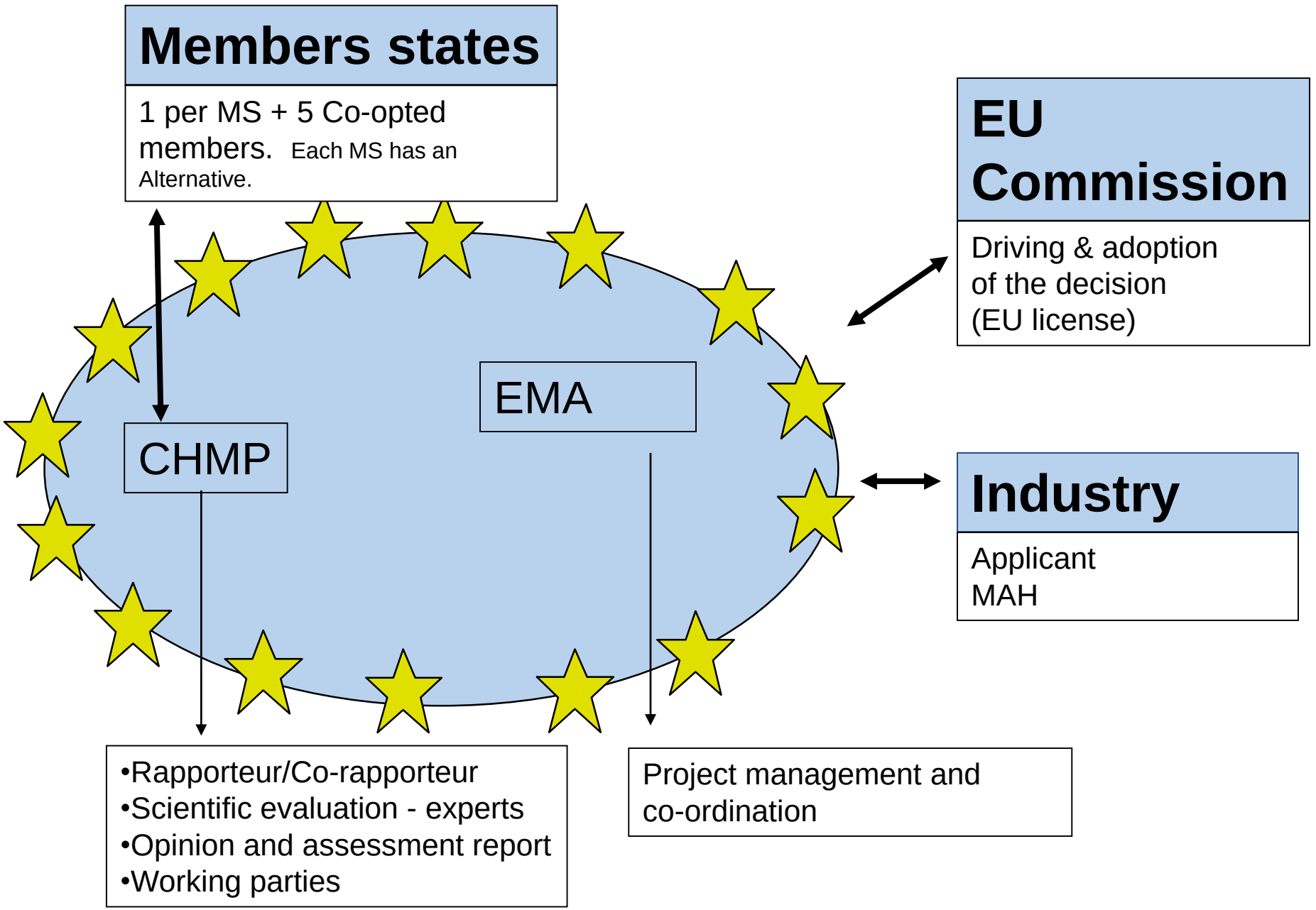
Decentralised Procedure





EU Centralised Procedure

- **Legal Basis:** Regul. (EC) No 726/2004 (also establishing "EMA" European Medicines Agency)
- **Principle: single application / evaluation → single authorisation**
  → direct access to all EU(27MSs) + Norway, Iceland and Liechtenstein
- **Scope:**
  - **Compulsory for:**
    - **Biotech** (recombinant DNA, gene expressed proteins, hybridoma & monoclonal antibodies)
    - New Active Substances in **Specific Therapy Areas**: AIDS, Cancer, Neuro-degenerative disorder, Diabetes, Auto-immune disease, other immune deficiencies, Viral diseases
    - **Orphan Drugs**
  - **Optional for:**
    - Any Other New Active Substance
    - significant innovation (therapeutic, scientific or technical)
    - in the interests of patients at community level
    - Generic of Centralised reference prod. (may use CP or MRP/DCP)


Members states
1 per MS + 5 Co-opted members. Each MS has an Alternative.
EU Commission
Driving & adoption of the decision (EU license)
EMA
CHMP
Industry
Applicant
MAH
•Rapporteur/Co-rapporteur
•Scientific evaluation - experts
•Opinion and assessment report
•Working parties
Project management and co-ordination

The 3 steps of the Centralised Procedure

Step I
Pre-submission to application
- Early advice
- Rapporteur/C-rapporteur appoinmt
- Assessment team
- Application
- Validation

-120 days

Step II
Scientific evaluation
- Assessment Reports
- List of Questions (+ clock stop)
- CHMP Opinion
- Possibility to appeal
- Transfer to EU Commission

210 days

Step III
Decision Making Process

67 days

Notify the EMA
Request Rapporteur/co-Rapporteur

Submit the MAA

Clock stop for answer to questions

Answer to questions
Oral hearing

CHMP Opinion

favourable

Draft EC Decision

EC Decision
Community Licence

Two options

Mutual Recognition Procedure

- Art. 28 para. 2 of Dir. 2001/83/EC
- For products with an existing MA

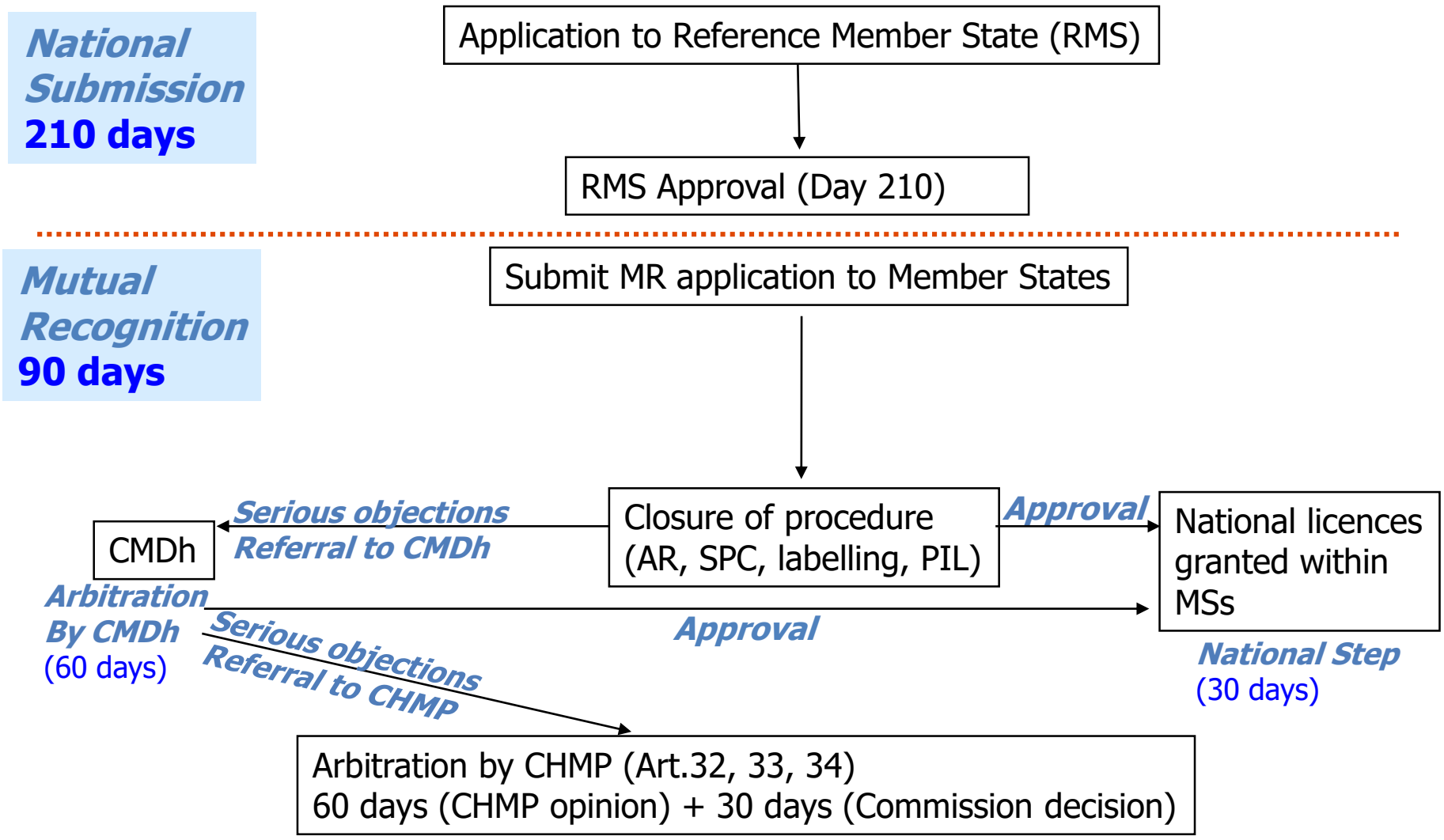
Decentralised Procedure

- Art. 28 para. 3 of Dir. 2001/83/EC
- Only possible, if no authorisation has already been granted
- Most significant difference with MRP = consultation between MS‘s before 1st MA issued

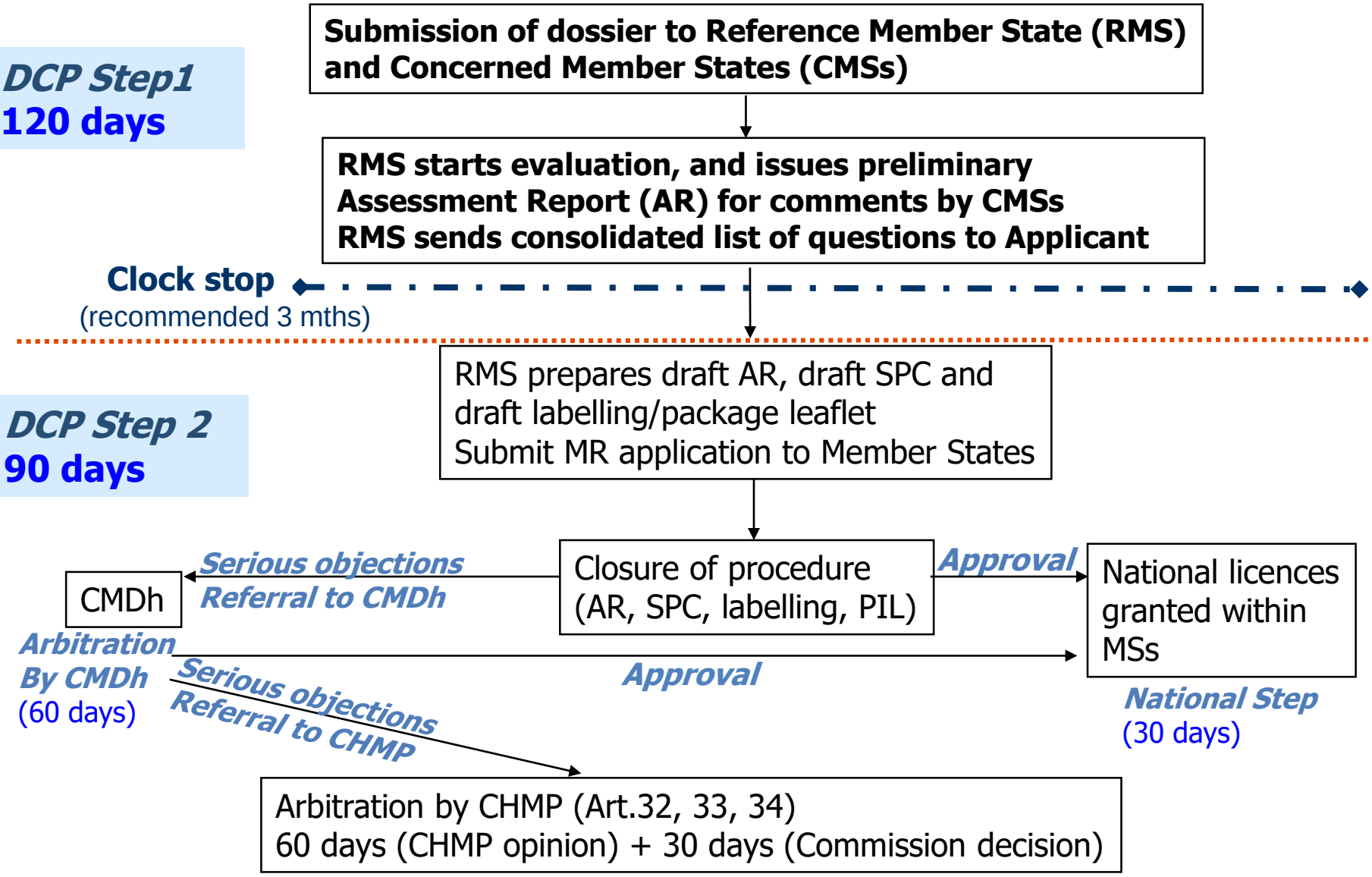
MRP & DCP: key authority stakeholders

- **CMDh** ("Coordination group for mutual recognition and decentralised procedure for human medicinal products"):
  - Mixed responsibilities: procedural, regulatory and scientific
  - One representative from each MS, appointed for 3 years (renewable)
    + observer from EMA and Commission
  - CMD(h) Chair appointed for 3 years
    + Vice-chair representative of MS that has presidency of Council
- **RMS** ("Reference Member State")
  - Selected by the applicant
  - Has to prepare the assessment report (AR)
  - Acts as central point between MS and MAH
- **CMS** ("Concerned Member State(s)")
  - All other MS's where the Company has submitted the dossier

Overview of the MRP



Overview of the DCP



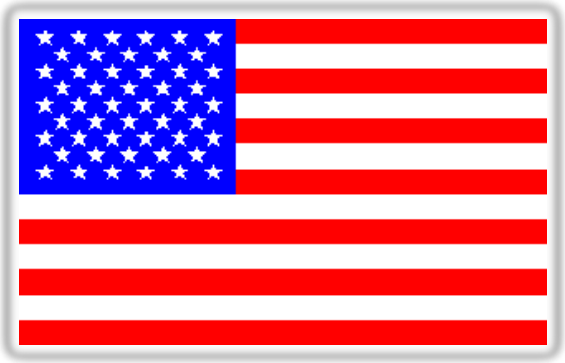
The “Pharmacovigilance and Risk Assessment Committee” (PRAC)

- Replacing Pharmacovigilance Working Party (PhV WP)
- Mandate: Risk detection, Benefit-Risk Assessment, Communication of risk and benefit/risk, Risk Minimisation and Analysis Impact, Design and Evaluation of PASS
- CHMP & CMDh to “rely upon” recommendations from PRAC but retain responsibility for benefit-risk assessments
- PRAC started in July 2012
- Membership:
  - 1 member (& 1 alternate) from each MS
  - Chair: June M. Raine (UK – MHRA)
  - Vice-Chair: Almath Spooner (Ireland – HPRA)
- Interaction between PRAC & CHMP:
  - About 30% of CHMP agenda would go to PRAC
  - Aiming that PRAC Rapporteur could come from same MS as CHMP Rapporteur
  - Chalenge with timing of PRAC opinions: i.e. trying to fit the PRAC 60 day review timeframe into overall timelines and still allow CHMP time to consider PRAC input before adopting their opinion

New requirements for the Marketing Authorisation Application (MAA)

- Pharmacovigilance System Master File (PSMF)
  - MAH must prepare and maintain "**Pharmacovigilance system master file**" (PSMF): replaces former "Detailed Description of Pharmacovigilance System" (DDPS), and must be held at MAH site
  - Summary of the Pharmacovigilance System must be included in the MAA dossier
  - Full PSMF to be provided within 7 days of request from a competent authority
- Risk Management Plan (RMP)
  - 'detailed description of risk management system'
  - RMPs to be included in MAAs for all new products
    - N.B. Authorities can impose need for Risk Management System on already authorised products if concerns about Benefit/Risk balance
  - Format and content of RMPs addressed in Commission's implementing measures

US Regulatory Environment



The US Regulatory Environment (1)

The US Food and Drug Administration (FDA)

- FDA's Role and Responsibilities:
  - FDA is regulating drugs, foods, cosmetics, biologics, medical devices
  - FDA is responsible for administration, enforcement, interpretation of US drug law and has power to establish regulations which have the force and effect of law
  - FDA has developed policies, procedures and regulations to implement its Reglatory initiatives, some going beyond the intent of the original laws

Drug Registration in the US = one of the most rigorous systems in the world

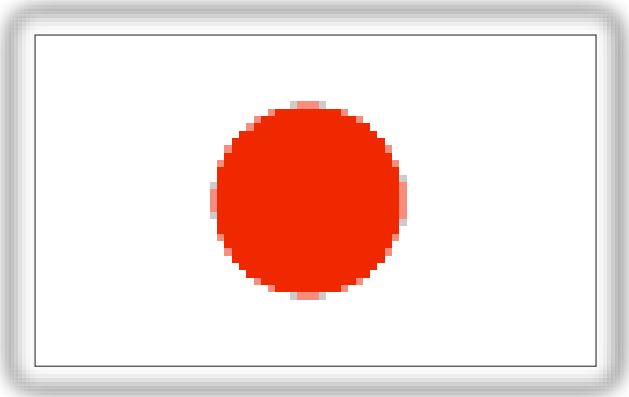
The US Regulatory Environment (2)

- Overview of FDA Organization – top level
  - Office of the Commissioner (OC)
  - Office of Regulatory Affairs (ORA)
  - Centers for Product Jurisdiction
    - **CDER (Center for Drug Evaluation and Research)**
    - **CBER (Center for Biologics Evaluation and Research)**
    - CDRH (Center for Devices and Radiological Health)
    - CVM (Center for Veterinary Medicine)
    - CFSAN (Center for Food Safety and Applied Nutrition)
    - NCTR (National Center for Toxicological Research)

The IND Process :
What is an IND? Where are regulations found?

- IND = Investigational New Drug application
- Seeks permission to test a new drug or biologic in humans
- Usually begins in Phase I; can begin in Phase II or III if have adequate human experience
- FDA's review of IND focuses on:
  - Phase I: Patient safety
  - Phase II/III: also includes assessment of the scientific quality of the clinical evaluation (data supportive or not for BLA?)
- IND Regulations are contained in Title 21, CFR, Part 312

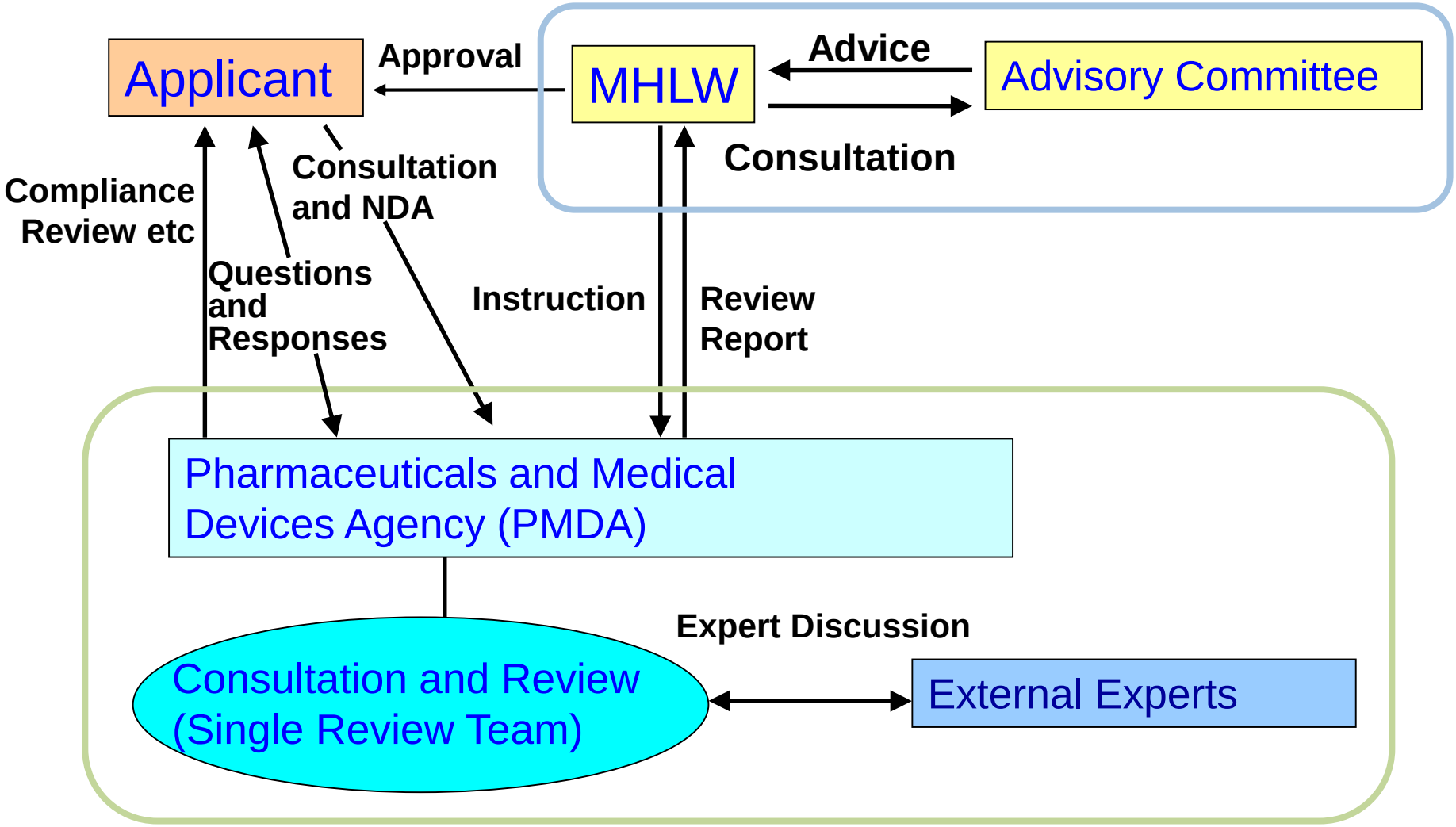
Japanese Regulatory Environment



Japanese law and relevant authorities for medicines registration

- Pharmaceutical Affairs Law (PAL) – April 2005
- MHLW (Ministry of Health, Labour and Welfare)
  - Responsibility for approvals and licensing
  - http://www.mhlw.go.jp/english/index.html
- PMDA (Pharmaceuticals and Medical Devices Agency)
  - Responsibility for scientific review (incl. audit for GMP, GLP, GCP)
  - Branch under MHLW, created in 2004
  - http://www.pmda.go.jp/english/index.html
- NIID (National Institute of Infectious Diseases)
  - Responsibility for national testing
  - http://www.nih.go.jp/niid/index-e.html

Relationship between MHLW and PMDA



INTERNATIONAL REGULATORY ENVIRONMENT

Scope

More than 70% of the world's population are:
Asia Pacific and Emerging Markets (APEM)

Key markets

- Asia Pacific:
  - India, Philippines, South Korea, Taiwan
- China / Hong Kong / Macau:
  - China
- Latin America :
  - Argentina, Brazil, Chile, Mexico
- Middle East and North Africa (MENA):
  - Egypt, Pakistan, Saudi Arabia, Turkey
- Sub Saharan Africa (SSA):
  - South Africa

Models for drug regulatory assessment

Countries can be categorised in 2 licensing models:

- model of licensing system based upon submission of evidence of registration in reference countries
- model of licensing system based upon a full assessment of new drug applications (including biological products)

Global Harmonisation Initiatives

ICH Definition and Background

- *"International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use"*
- Joint **regulatory/industry** project
- **EU**, **Japan** and the **United States**
- To improve (through harmonisation), efficiency of development/registration of new medicinal products
- Based on **scientific consensus**
- **Commitment by regulatory parties** to implement ICH recommendations

ICH Structure / Organisation

- **6 official parties (co-sponsors) directly involved :**

  Authorities and research based industry from

  - **EU:** - European Commission + EMA and CHMP
    - EFPIA (Eur.Feder.Pharmac.Industries&Associations)
  - **Japan:** - MHLW (Ministry of Health and Welfare)
    - JPMA (Japanese Pharmaceutical Manuf. Association)
  - **USA:** - FDA (US Food and Drug Administration)
    - PhRMA (Pharmaceut. Research and Manuf. of America)

- **Official "Observers"**
  - World Health Organisation (WHO)
  - European Free Trade Area (EFTA)
  - Canada (Health Protection Branch)
- **"Interested Parties" also involved**
  - Pharmacopoeias (Eur.Ph., J.P., U.S.P.)
  - other industry sectors (OTC and Generics)

ICH CTD (Common Technical Document)

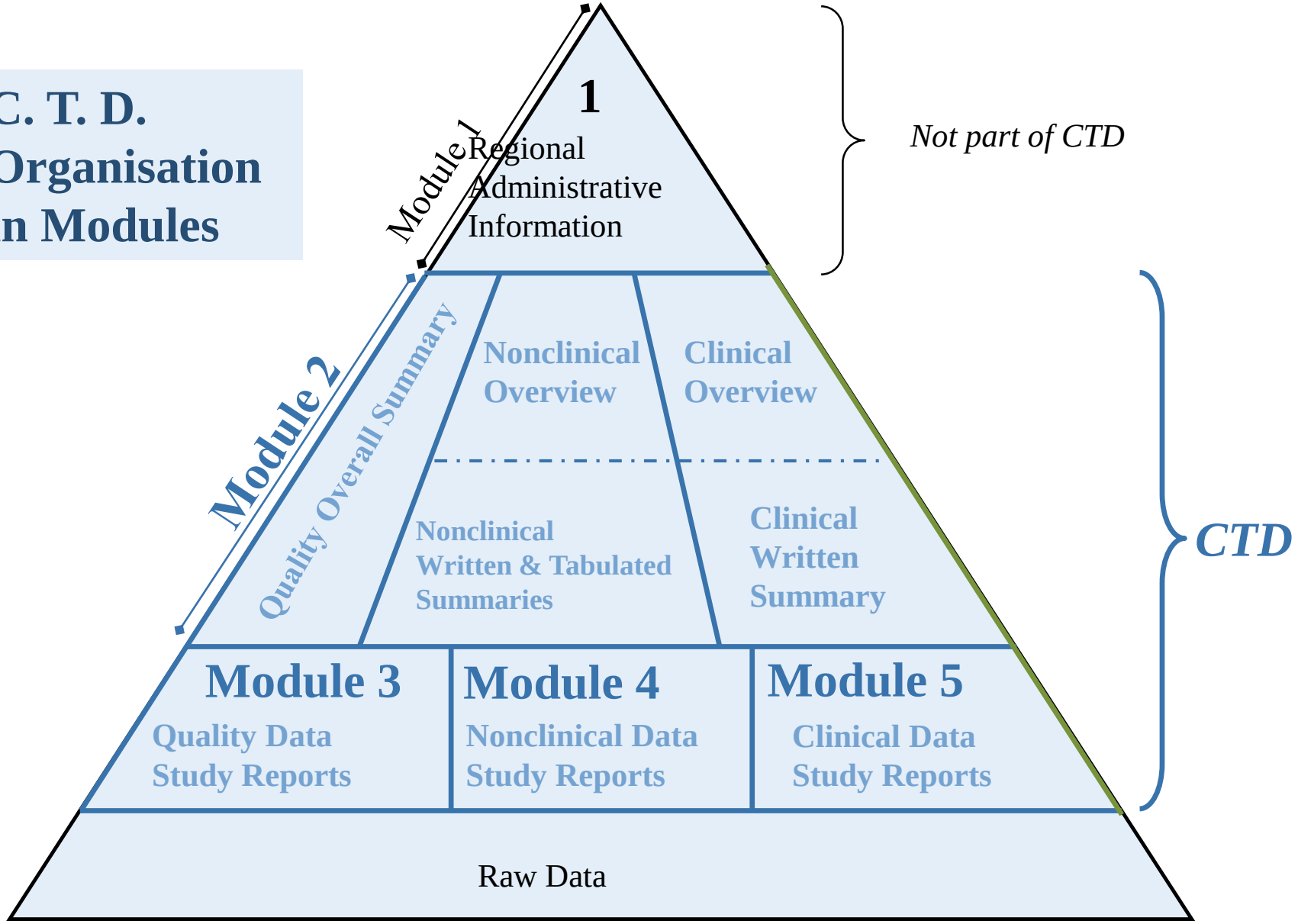
Scope

- Harmonised format for Registration Applications
  - Acceptable by Regulatory Authorities in the 3 regions
  - **Does not define content** (e.g. what studies are required, etc.)
  - Applicable to: - new pharmaceutical products (incl. biotech)
    - abbreviated (abridged) applications and variations

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



ICH Now and in the Future

- **New areas to develop ICH guidelines:**
  - Post-marketing pharmacovigilance
  - Pharmacogenomics
  - Biomarkers
  - Gene Therapy
- **Continued Harmonisation: prevention of new interregional disharmony**
  - Avoid unilateral development of requirements in specific areas

…Globalising ICH

- ICH Global Cooperation Group (**GCG**)
  - Representatives from other Regional Harmonisation initiatives
    - APEC (Asia-Pacific Economic Cooperation)
    - ASEAN (Association of the Southeast Asian Nations)
    - GCC (Gulf Cooperation Council)
    - PANDRH (Pan American Network for Drug Regulatory Harmonization)
    - SADC (Southern African Development Community)
  - Evolution in ICH and understanding that some non-ICH countries are now major contributors/consumers to the global pharmaceutical market
- **Regulators Forum -** started in 2008
  - Including representatives from **Australia, Brazil, China, Taiwan, India, Russia, Singapore and South Korea** most of which are not part of *Harmonisation Initiatives* already
  - Key areas of focus: API GMP; clinical trials; pharmacovigilance

Reference and source

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