Key Issues after the EU-Enlargement and New Legislation

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Drugs in Germany

- big (German-speaking) market (~ 100 Mio. people)

- 60,000 approved drugs with :
- ~ 1000 usable approvals with standardised master texts ("Muster")
- ~ 10,000 "freshly" appr. "old products" ("Nachzulassung")
- ~ 20,000 MRP-ready approvals (Assessment Reports)

- big market for homeophatics and herbals

- important medium-sized (and cooperative !) companies

- all global players in the market

- no pricing negotiations within approval procedure up to now

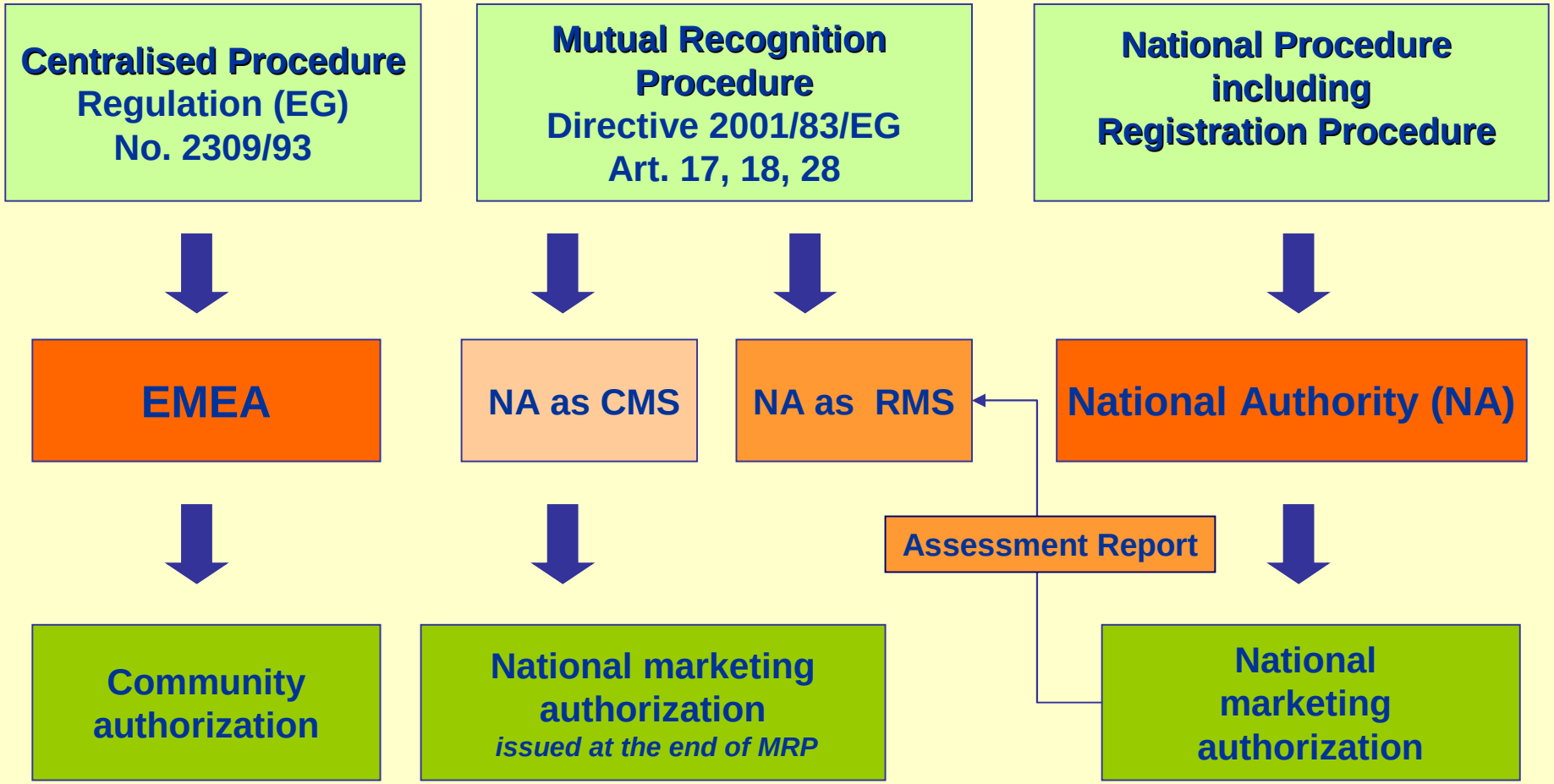
Drugs in Europe (Selection)

DE	UK	SE	DK
~ 82,4 million*	~ 59 million*	~ 8,9 million*	~ 5,4 million*
~ 57 000** marketable drugs *within the competence of the BfArM 94%; PEI 6%* *incl. Parallelimports* *incl. registrated homeopathic products*	~ 26 000 marketable drugs *incl. Parallelimports* *incl. registrated homeopathic products*	~ 6400 marketable drugs *without Parallelimports* *without homeopathic/herbal products*	~ 4650 marketable drugs *incl. Parallelimports*

*Inhabitants

** human AM

Different Types of Marketing Authorization Procedures



Scope for Centralised / Decentralised Procedure

centralised

Council Regulation (EEC) No. 2309/93 - Annex

new drugs for: AIDS, oncology & neuro-

vegetative diseases (e.g. Alzheimer's), diabetes: obligatorily CENTRALISED

…. and in the future more ?

decentralised

Generics, Bio-Generics?
centralised and decentralised
line-extension

national

FOR ONE MEMBER STATE ONLY
bibliographic approval;

Reference Member State

Timetable for the Mutual Recognition Procedure

- **Nationale Authorisation with Assessment Report**
- **Start of Procedure in compliance with the Best Practice Guide (MRFG)**
- **Day 1 - 50 ➡ Receive comments (RMS/MAH) of CMS**
- **Day 51 - 60 ➡ Agreement on Response Document (MAH and RMS)**
- **Day 61 ➡ Distribution of Response Document by MAH to RMS/CMS**
- **Day 75 ➡ “Break-out Session" parallel to MRFG-Meeting**
- **Day 85-89 ➡ "final position" CMSs**
- **Day 90 ➡ End of Procedure**

Concerned Member State

REALIZATION OF THE REQUIREMENTS OF THE BEST PRACTICE GUIDE

- **CHECK IN PROCEDURE**
  - AUTOMATIC VALIDATION TIME → **10 WORKING DAYS**

- **POTENTIAL SERIOUS HEALTH ISSUE** → **NOT LATER THAN DAY 50**
  ALWAYS BEFORE DAY 50

- **OBJECTIONS AND ANY ISSUES OF CLARIFICATION SHOULD CAREFULLY SCREENED WITHIN THE NATIONAL AGENCIES**

- **AGREEMENT ON THE SPC BEFORE** → **DAY 90**

- **NATIONAL AUTHORISATIONS TO BE ISSUED WITHIN** → **30 CALENDAR DAYS**

Need for Definition: "Serious Risk to Public Health"

- do national views / definitions differ from case to case and from country to country ?
- are national views always objective?
- are national views potentially "historical" ?
- are national views applicable to European harmonisation / single market ?
- are national views "for home use" only
    - or a "mission" to other countries?
    - Conclusion: A European definition is highly necessary.
- the theme is on Commission agenda

Important Aspects of the Review

- **Streamlining of EU-Committees (number of members; selection process; responsibility)**
- Importance of clear definitions
- **Scope for centralised / decentralised procedures**
- Renewal versus pharmacovigilance

European Medicines Regulation

- **Centralised MA plus special (Marketing) Protection**
- **„Free Movement“ of Goods throughout the European Union**
- „Parallel Import“ of nationally authorised medicines
- **„Parallel Trade“ of medicines authorised by the EU**
- „Mutual Recognition“ of MA issued nationally by other Member States (plus Decentralised Procedure)
- As medicines are „special goods“, Member State Veto remains in place to protect the people of a Member State, when so required for reason of public health
- (Partial) achievement of **harmonised labeling, PIL and SPC**, **legal status** (mostly national domaine / implementation)
- Creation of a „European Reference Product“

European Medicines Regulation

Basis for „Vision“: Motion of the European Commission
(concerning intended amendment of Community Legislation)
Goals placated in 2001 / slightly modified in 2002:

- Protection of public health
  Fast access to new „innovative“ medicines for patients (scope)
  Improvement of public information (DTCA), grasp and description of added therapeutic value, if any
- Achieving the „Single Market“ - Need for improving mutual recognition
- Improving the competitiveness of EU-industry - „Stick and carrot“ approach (protection) - Simplifying administration (renewals, sunset clause, regulatory deadlines)
- Rationalisation and simplification to improve coherency and transparency
- ***EU-Enlargement: meeting this challenge***

Key Elements in European Medicines Regulation

Impact on National Competent / Regulatory Agencies

- Regulatory Agencies/Authorities
- Competent Agencies/Authorities
- Regulatory / Competent Agencies/Authorities
- How to create for the First Time a **"Corporate Identity"** for the Commission together with European Regulatory Agencies ?
- **Focusing on the changes to the Centralised Procedure (to be expected)**
- **Where is the Centralised Procedure going in the future ?**

European Medicines Regulation

Key

- To unlock doors ?
- To open doors ?
- To lock doors ?

- **Unlock**: clinical trial authorisation systems
- **Un(b)lock**: full participation of new Member States
- **Open**: opportunity for European Reference Product !
- **Lock**: force companies into De- / Centralised Procedure
- **Do we have a clear view?**
  - On a clear day you can see .....

European Medicines Legislation

Networking and Partnership between EMEA and “old” national competent authorities in Supporting and Executing the **Centralised Procedure**

- From experience and applying the currently operated Centralised Procedure no need is seen for drastic changes for reason of EU-Enlargement!
- Pharmaceutical industries and competent authorities have achieved the Enlargement. This includes the obligation of new Member States to adapt as well as the obligation of old Member States to facilitate and support this process.
- **Translation into the additional languages may be the most difficult single issue to be tackled** (e.g. Maltese)!

New European Medicines Regulation

Regulation (EC) 2309/93 (rev) - Title IV: The EMEA: responsibilities and structure

Election of members:

- § CHMP's (via Man. Board ?)
- § COMP (via ????)
- § CHMP-add. (via ????)
- § Secretariat (sci. role ?)
- § Executive Director (impact on CHMP work ?)
- § Management Board
- § Commission (impact on CHMP work ?)

- § EMEA: The Agency .....
- § EMEA/Secretariat
- § Sci. Working Party providing scientific advice
- § CHMP
- § (Co-) Rapporteur System
- § Accreditation of nationally or directly appointed experts
- § Scientific Advisory Groups
- § QRD/PIPIT

New European Medicines Regulation

Impact on the Centralised Procedure "Package"

TITLE II (implementation 2005)

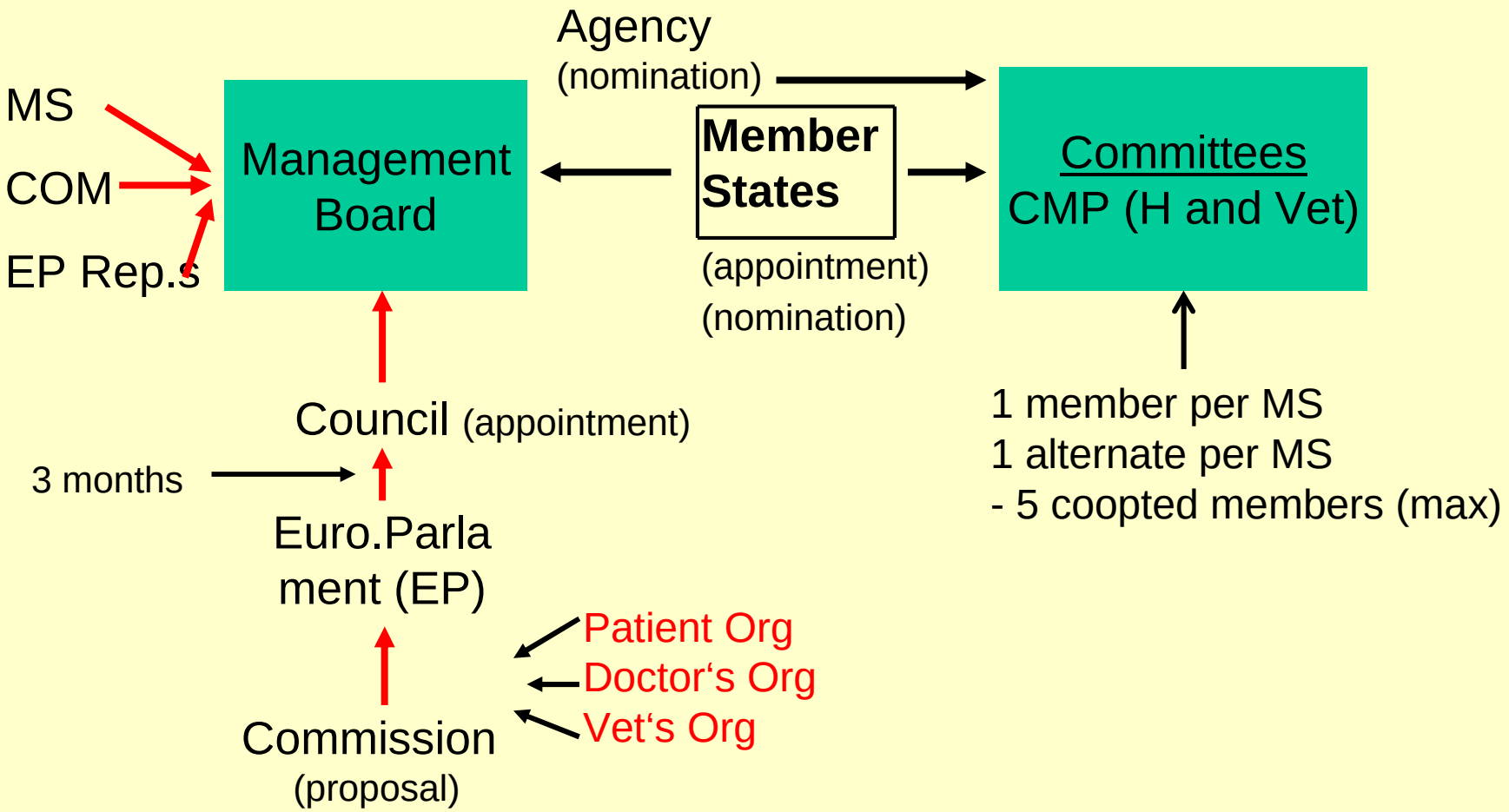
- (Scientific) Advice
- Dossier Assessment
- Interaction with the Applicant
- Time to CHMP Opinion
- Exec. Dir. may request opinion
- Added therapeutic value
- Exceptions from the "Rules"
  - Derogation (specific obligations, exceptional circumstances, accelerated assessment, compassionate use)
  - Definition of "non-Annex products"

TITLE IV (implementation 2004)

- The Agency .....
- Coordination of nationally provided scientific resources for MA, supervision and PhV
- CHMP : to prepare "Opinions"
- Commission may request opinion
- EMEA/Secretariat/Exec. Dir.
- Working Party(-ies) / Sci. Advis. Groups (new therapies /advice to applicants)
- (Co-) Rapporteur System
- Accreditation of nationally or directly appointed experts
- Q-Systems

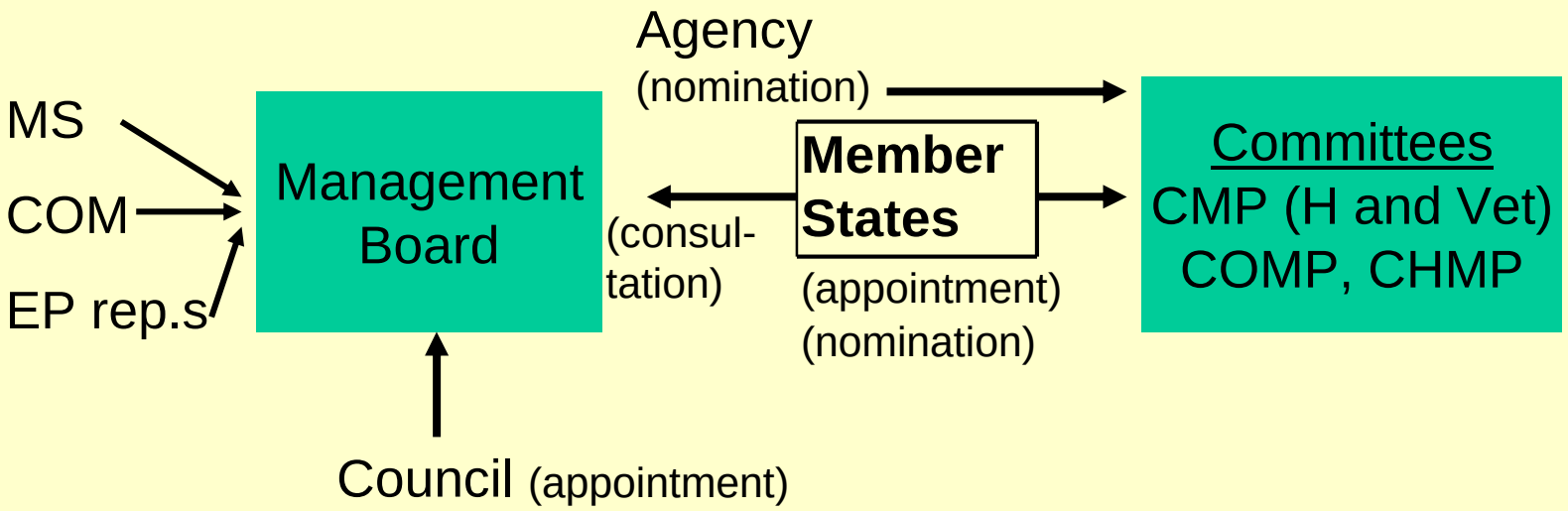
Committees (CMP (Human and Vet))

Dependencies and Relationships



Committees (CMP (Human and Vet))

Appointment of Members



What are the rules applicable for the appointment of the „new“ CMP (H and Vet)? What are the rules for the COMP and the CHMP ?? Which Management Board will be (ab-) used ??? Which Regulation will be applied ????

Describing the Hierarchy or Upside-down Model?

- Whereas CMP (H and Vet), COMP and CHMP are expressly mentioned as being part of EMEA (Art. 61), the remainder of the Regulation only addresses the two CMP‘s concerning composition, appointment and duties.

  The CHMP is also entitled to the (CO-) Rapporteur system and to using national experts

  Do such apparent inconsistencies indicate the need for the next Codification process ?

Describing the Hierarchy or Upside-down Model? continued

- CHMP‘s members shall ensure coordination between Agency, Member States, and CMP‘s consultative bodies !
  Exec. Dir. shall ensure appropriate coordination between the four Committees !
- CHMP‘s members shall represent the national competent authorities !
- Member States may not give instructions incompatible with their own individual / Agency responsibilities ! Members shall be independent !

Describing the Hierarchy or Upside-down Model? continued

- The CHMP‘s members shall rely on the scientific resources available to the national marketing authorisation bodies.
  Where do the experts nominated/appointed by the Agency come in ?

- Consultative scientific advisory groups will issue an „opinion“ based on the (Co-/Rapp‘s) draft Assessment Reports – the time-frame has to be ensured by the CHMP‘s chairperson (?)

CMP (Human) Opinion

§ Any Procedure leading to a CHMP Opinion is - in fact or in substance of impact and workload – a quasi

„Centralised Procedure“

which will be forwarded to the Commission for the Decision-making procedure

CMP (Human) Opinion

- Marketing Authorisation procedures („Lifetime“)
  Observe: change in „Scope“ (Art. 3 and Annex – as of 2005)
  Including any new need for re-assessing the risk-benefit balance (Art. 5 – as of 2005)
- EU designated Orphan Medicinal Products
  (Regulation: Annex – as of 2005)
- Products not (to be) marketed in the EU
  (WHO Cooperation - Art. 57/58 as of 2004 – but in accordance with Art. 6-9 – as of 2005)
- Compassionate Use, exceptional circumstances, specific obligations, accelerated assessment
  (Art. 14 - as of 2005)

CMP (Human and Vet) Opinion

- At the Commission‘s request: any other scientific opinion concerning the evaluation of medicinal products or the starting materials used
  (Art. 57.1 (o) – as of 2004)
- At the Exec. Dir. or Commission‘s request: any scientific matter concerning the evaluation of medicinal products
  (Art. 5.3 – as of 2005)
- Mutual recognition disagreement
  (Art. 5.3 – as of 2005), all other „Article Procedures“, and „Urgent Safety Opinions“ (Art. 20 – as of 2005)
- Resolution of „Conflict“ with other Community Institutions
  (Art. 59 – as of 2004).

Facts and Fiction

- **Fact**: a new Committee for old procedures, and for somewhat „varied administrative aspects“
- **Fiction**: meeting the challenge of EU Enlargement („Whereas“, … -no. 3 and 24: mention CP; Art. 61: describes new CMP (H and Vet) composition, appointment, etc.)
- **Fact or Fiction**: New „Consolidated“ Regulation text had to be compiled in „hand-made“ fashion
- **Other TITLES** of the Regulation contain the „beef“, but remain far from implementation

New European Medicines Regulation

Impact on and Relevance for Patients, ...

- Re-setting compulsary and optional use of CP ....
- Re-dressing composition and appointment of Management Board and Scientific Committees ....
- Increasing the power of the EMEA-Secretariat within the adminstrative and scientific system ....
- Widening the access of the EMEA Executive Director to the Scientific Committees tasks ....
  - may have been the wrong playgrounds
  - what becomes available in 2005 may be of lesser importance for patients, innovation, etc.
  - creation of a „Corporate Identity“ for the full complement of old and new European Regulators might have proven a better and faster road to success

New European Medicines Regulation

Centralised Procedure : Summary

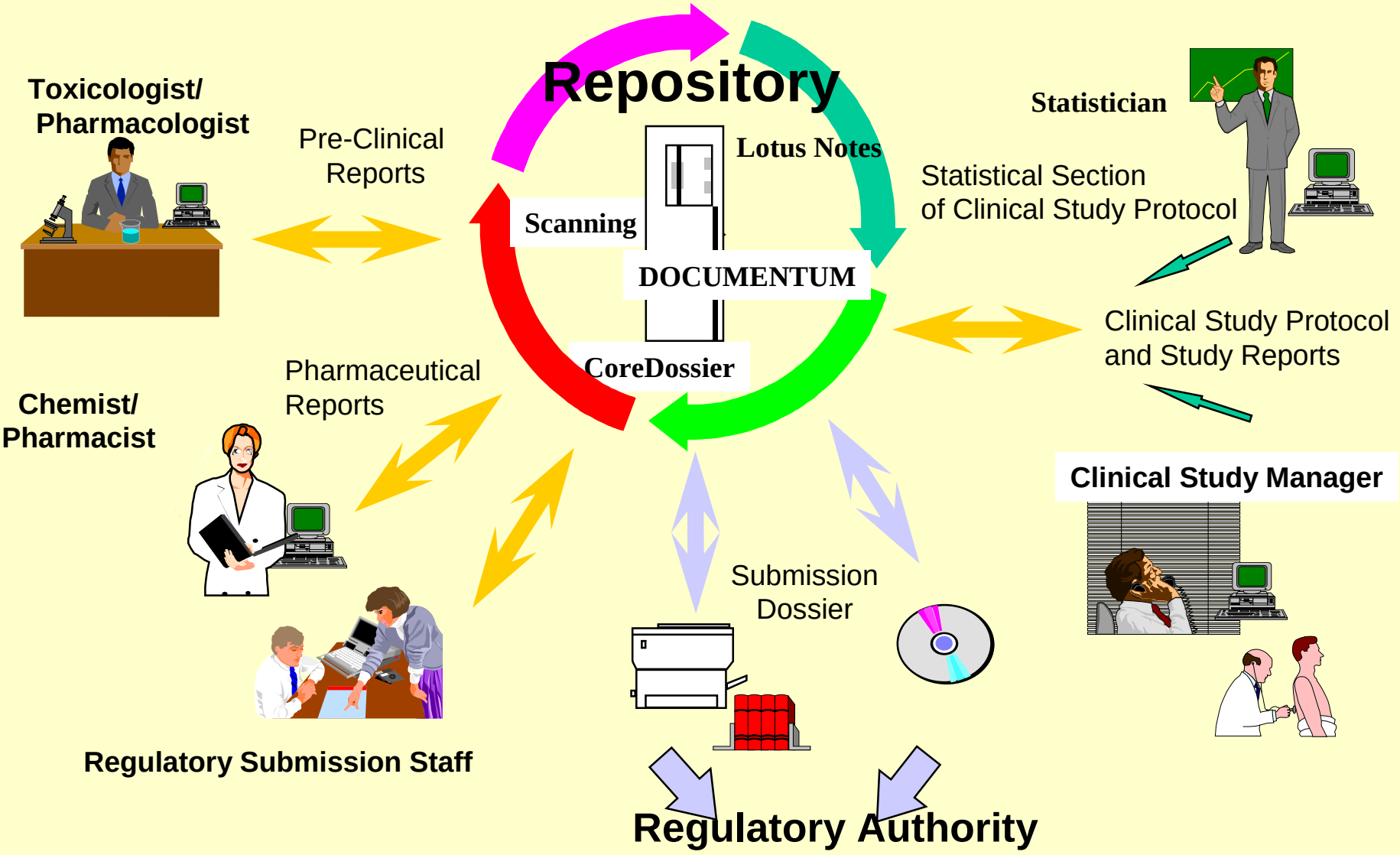
- Widening the scope of the Centralised Procedure to eventually encompass all NAS (and yet other types of products)
- Shift from Mutual Recognition to Centralised Procedure (replacing MR by Decentralised Procedure)
- Increasing the types of „quasi“ Centralised Opinions
- Increase in workload for the CHMP

- Urgent need to develop European Regulatory Authority „Corporate Identity“

European Electronic Systems

- Examples:
  - E-CTD
  - CTS/ EUDRA-TRACK
  - EUDRA-NET
  - EuroPharm

Vision


Repository
Lotus Notes
Scanning
DOCUMENTUM
CoreDossier
Toxicologist/
Pharmacologist
Pre-Clinical
Reports
Statistician
Statistical Section
of Clinical Study Protocol
Clinical Study Protocol
and Study Reports
Chemist/
Pharmacist
Pharmaceutical
Reports
Clinical Study Manager
Submission
Dossier
Regulatory Submission Staff
Regulatory Authority

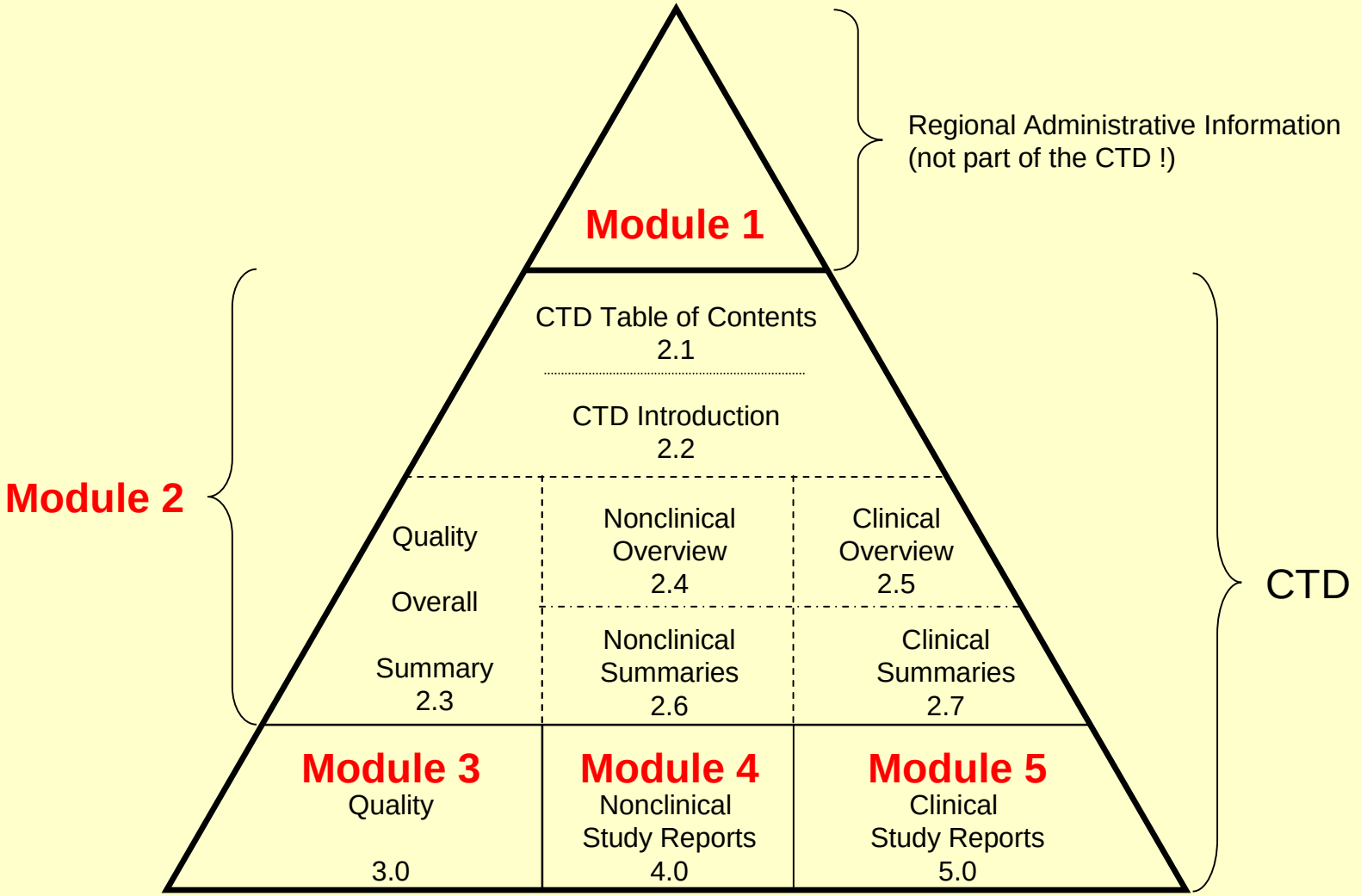
Common Technical Document

The Common Technical Document (CTD) aims to harmonis/ze, as far as is possible, the structure and content of the technical information submitted in support of marketing authorizations

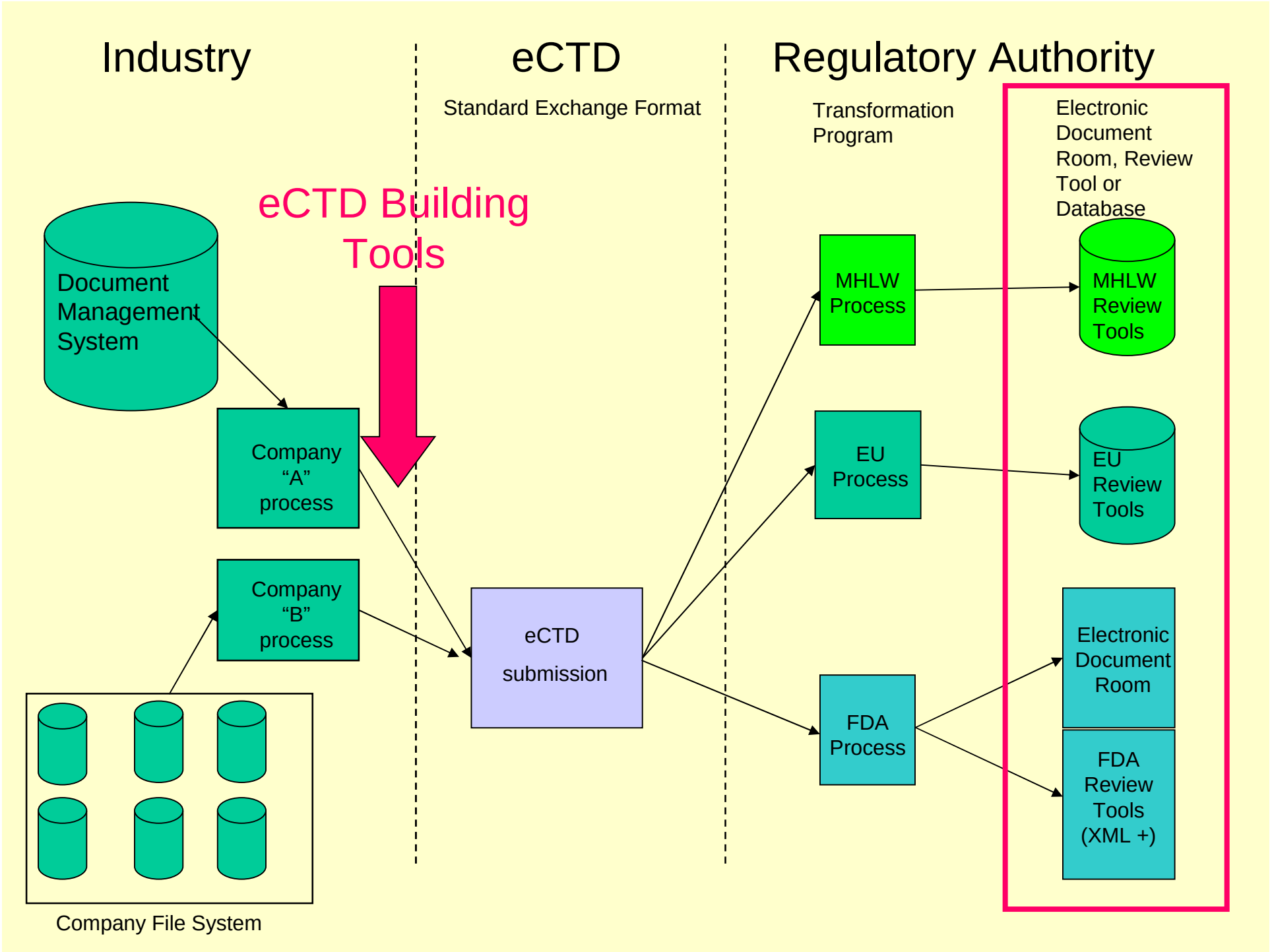
What is needed for an eCTD

- Directory structure
- Documents to submit (Leaf documents)
- XML backbone
  - XSL e**X**tensible **S**tylesheet **L**anguage (for viewing only)
  - DTD **D**ocument **T**ype **D**efinition
- Metadata
  - md5 checksum
  - Attributes (Lifecycle Management)
  - ID
  - Href
  - Title
  - File names
  - …

Organisation of CT-Documentation



Actual Version (EU) http://pharmacos.eudra.org/F2/eudralex/vol-2/B/ctd_06-2004.pdf

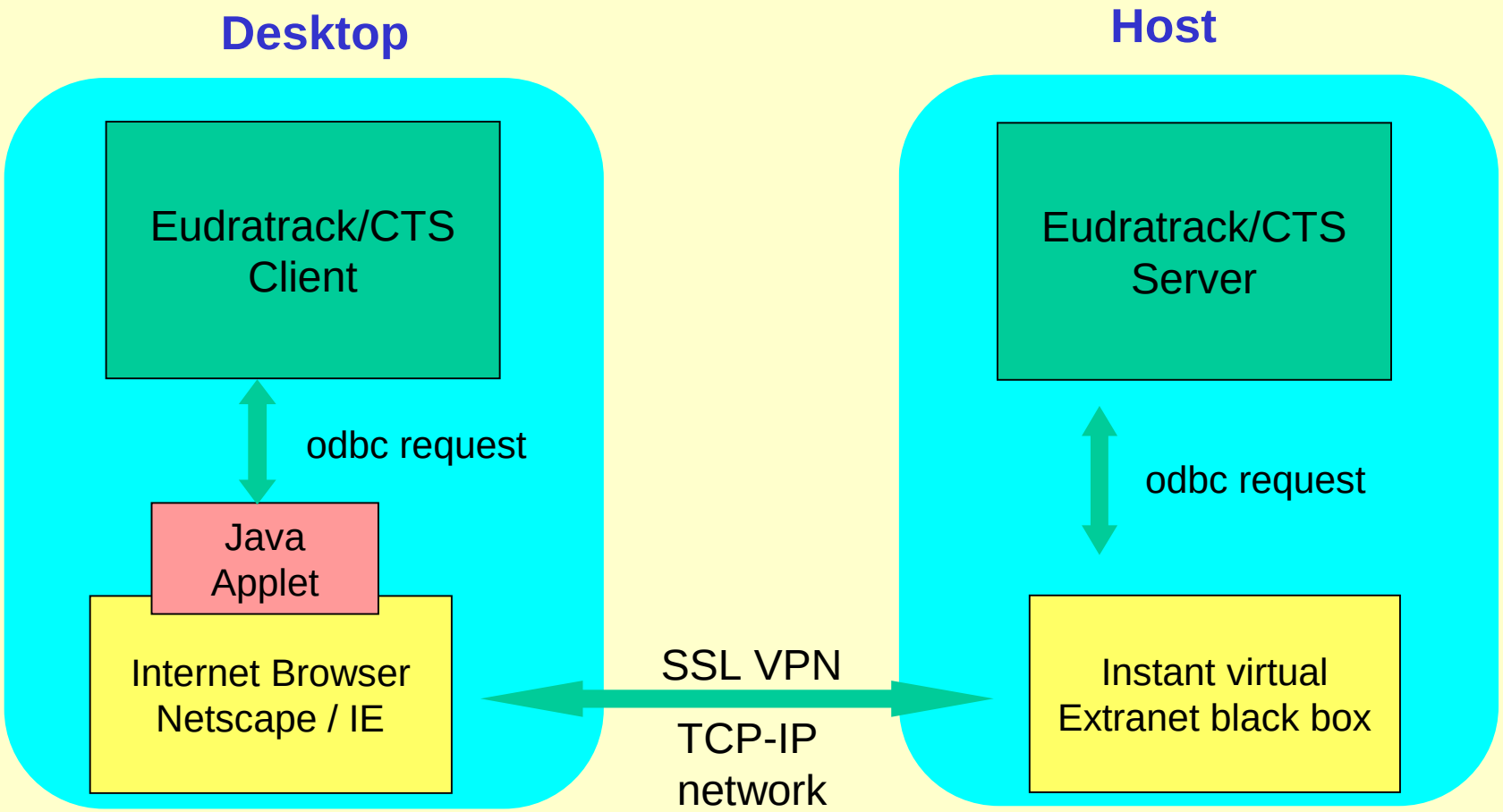

Industry
eCTD
Standard Exchange Format
Regulatory Authority
Transformation Program
Electronic Document Room, Review Tool or Database
eCTD Building Tools
Document Management System
Company "A" process
Company "B" process
Company File System
eCTD submission
MHLW Process
EU Process
FDA Process
MHLW Review Tools
EU Review Tools
Electronic Document Room
FDA Review Tools (XML +)

Implementation Status - EU

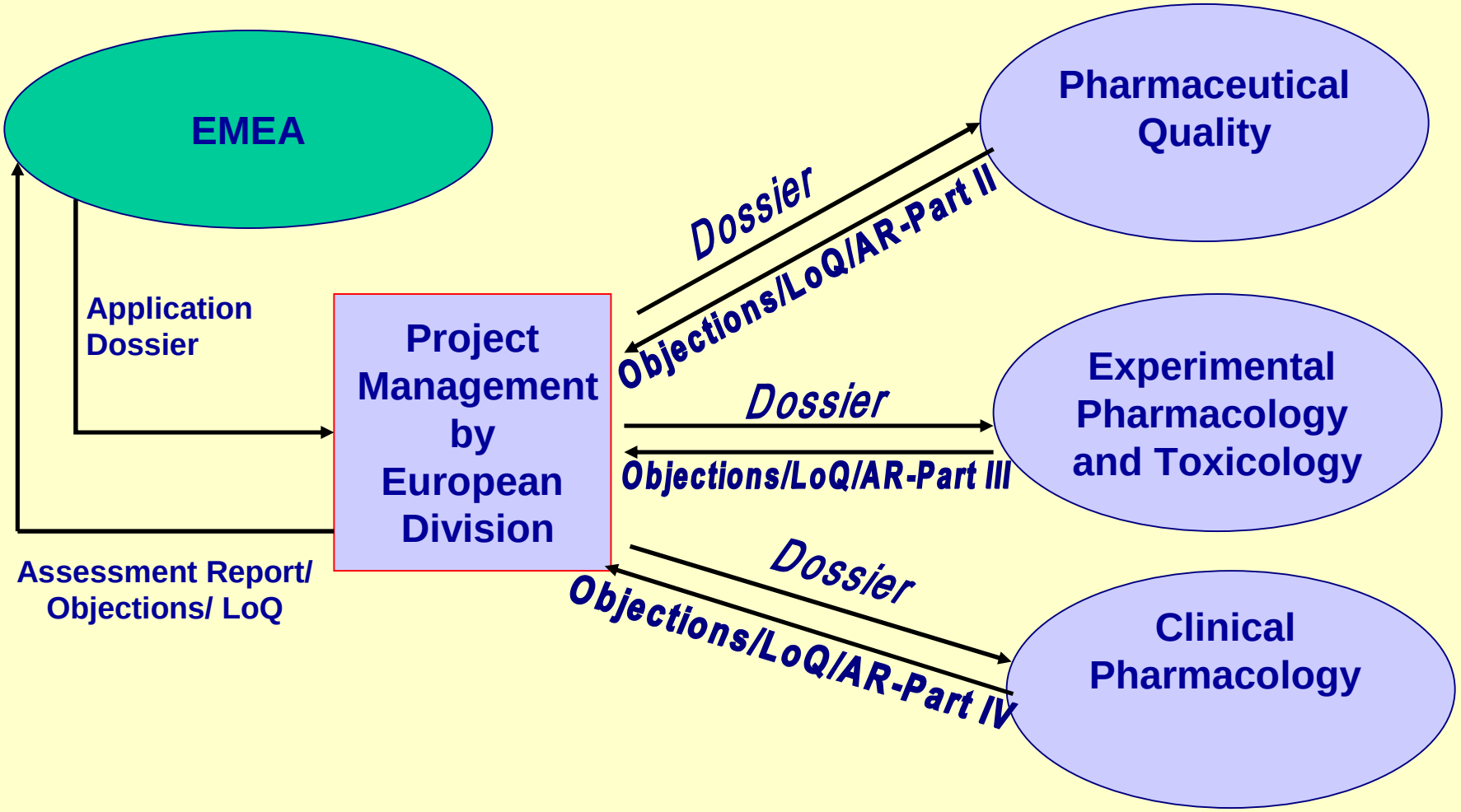
- Regional Guidance
  - step 5 adopted in November 2002 by CPMP for implementation
  - not mandatory, optional as of June 2003 in parallel with paper submissions
  - final version of Module 1 specification issued by NtA
  - final version of MAA form specification issued by NtA
- Joint EU and Trade Associations Working Group
  - Sample eCTDs used to test different submission scenarios and procedure types
- Website http://esubmission.eudra.org

CTS (EUDRA-TRACK)

(technical overview)



Organisation of Review Process – Centralised Procedures



EuroPharmDatabase

- An European database of information relating to all medicinal products on the market in the European Union, or undergoing clinical trials;
- In all official languages of the European Union

Basis

- Assistance in protection of Public Health
- Facilitate Competent Authorities Tasks
- Requirement of Legislation
- Council Regulation (EEC) No 2309/93;
- The proposal for a regulation of the European Parliament and Council (“The review”); and
- Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents (Official Journal L145, 31/5/2001 P. 0043 – 0048);

Article 57.1

- The Agency shall provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use, which is referred to it in accordance with the provisions of Community legislation relating to medicinal products.
- To this end, the Agency, acting particularly through its committees, shall undertake the following tasks:

Article 57.1 (k)

- **creating a database** on medicinal products, to be **accessible to the general public**, and ensuring that it is updated, and managed independently from pharmaceutical companies; the database shall facilitate the search for information already authorised for **package leaflets**; it shall include a section on medicinal products authorised for the treatment of **children**; the information provided to the public shall be **worded in an appropriate and comprehensible manner**;

Article 57.2

§ The database provided for in paragraph 1 (k) shall include the **summaries of product characteristics**, the **patient or user package leaflet** and the information shown on the **labelling**. The database shall be developed in stages, priority being given to medicinal products authorised under this Regulation and those authorised under Chapter 4 of Title III of Directive 2001/83/EC and of Directive 2001/82/EC respectively. The database shall subsequently be extended to **include any medicinal product placed on the market within the Community**.

Article 57.2 (cont.)

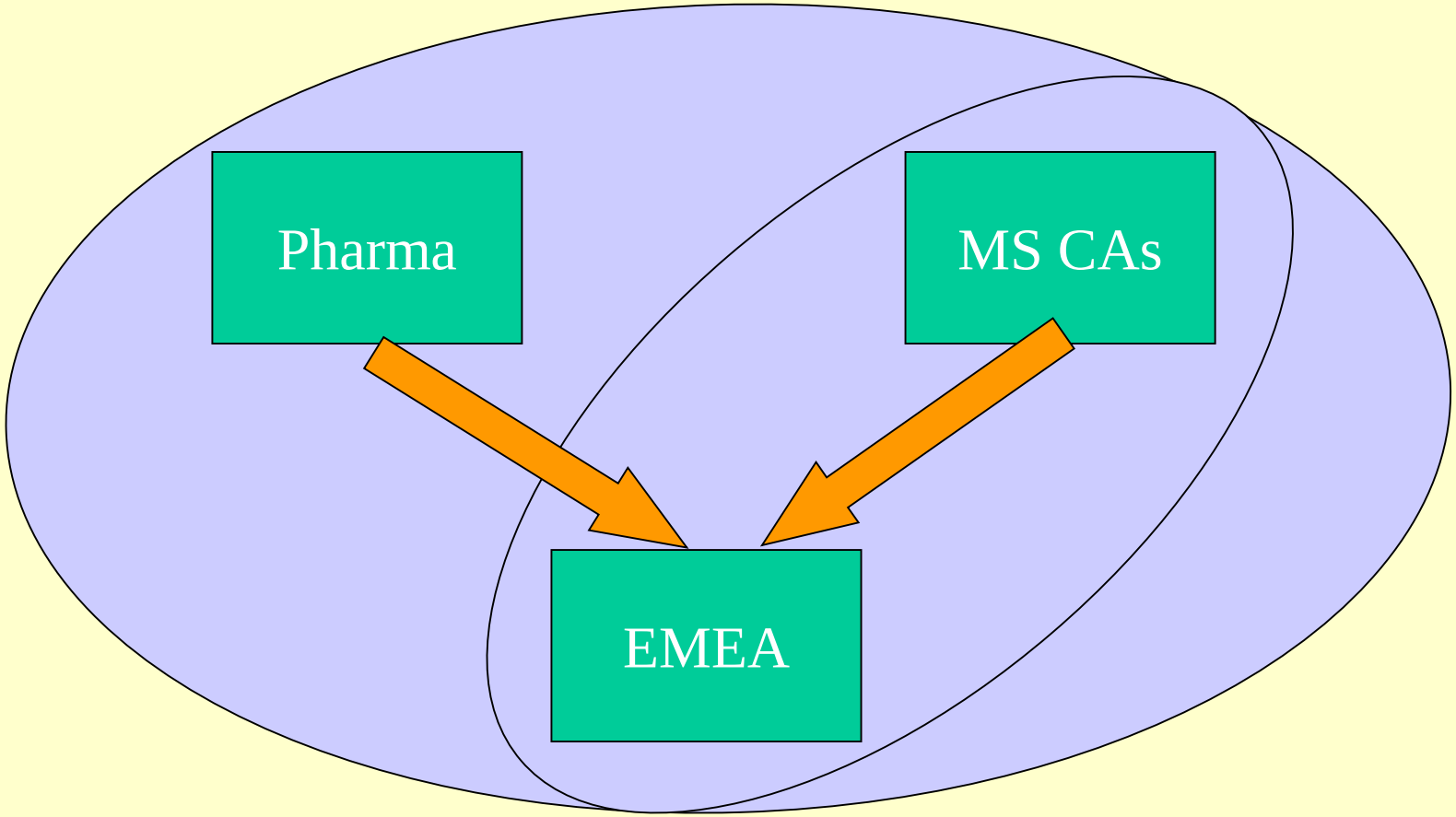
- Where appropriate, the database shall also include **references to data on clinical trials currently being carried out or already completed**, contained in the clinical trials database provided for in Article 11 of Directive 2001/20/EC. The Commission shall, in consultation with Member States, issue guidelines on data fields which could be included and which may be accessible to public.

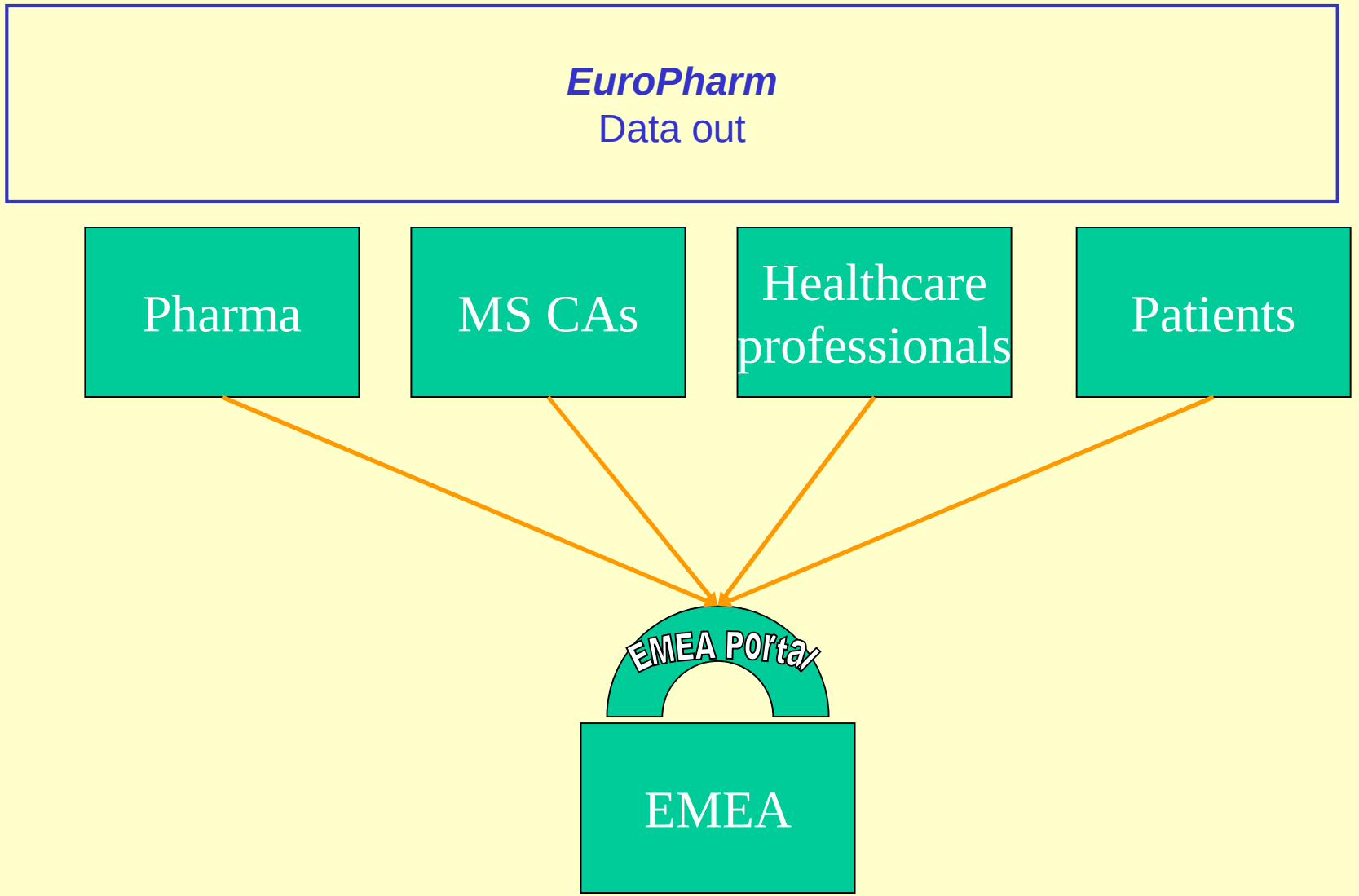
Stakeholders

- Competent authorities
- Health Authorities
- European Commission (DG ENTR; DG SANCO)
- Patients
- Health professionals
- Companies in the pharmaceutical sector
- International organisations (WHO; The Council of Europe, CEN)

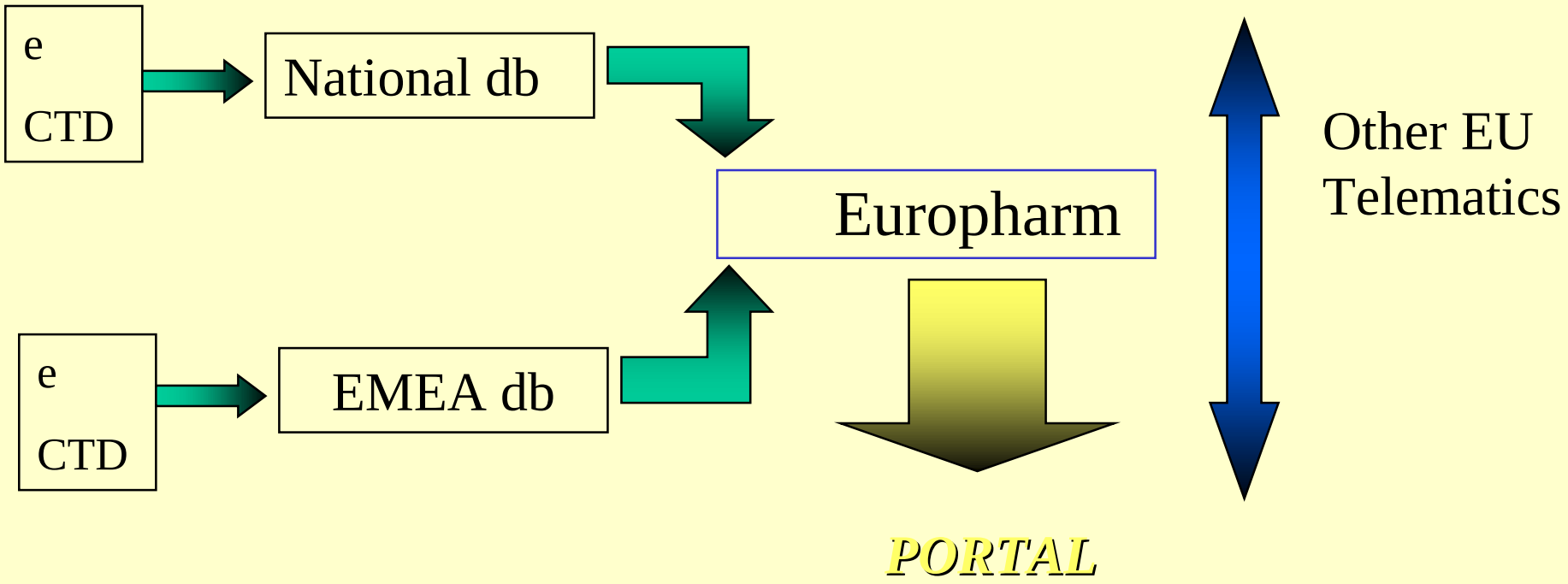
EuroPharm

Data in

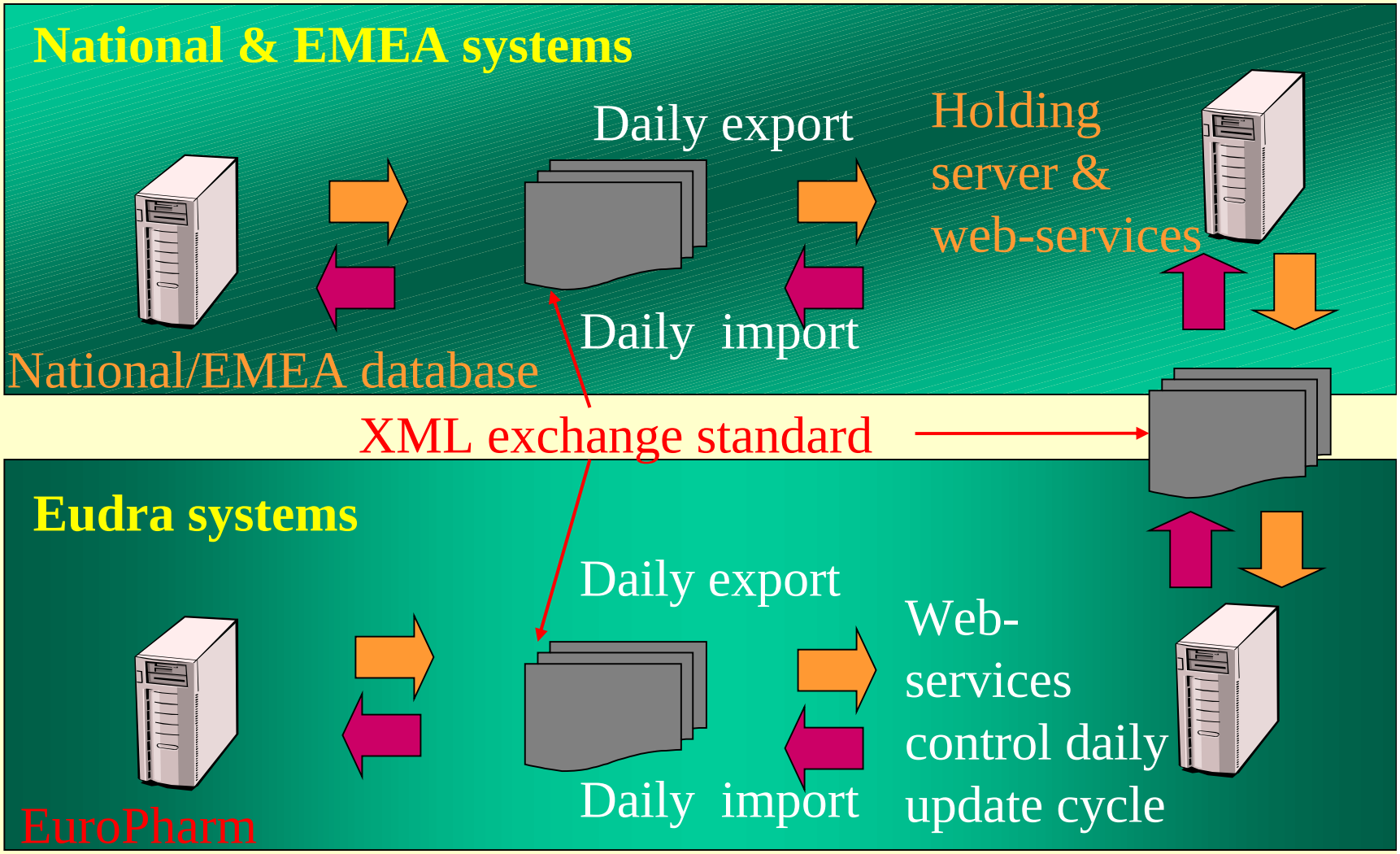



EuroPharm
Data out
Pharma
MS CAs
Healthcare professionals
Patients
EMEA Portal
EMEA

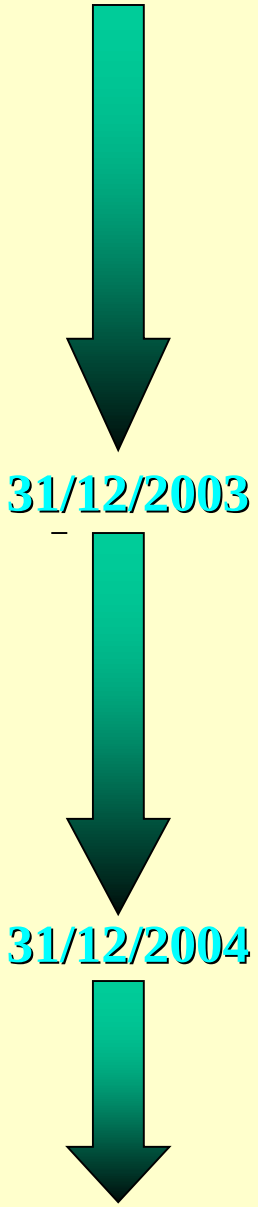
Europharm- central piece of EU-Telematics system



EuroPharm updating mechanisms



Phased approach



Core data model	Business case v 0.x
Reference core data model	Prototype
Reference extended data model	Specification
Mapping of reference data model to CA databases	1st production version: EuroPharm
	Iterations through to completion

Agencies Have to Define Their Position for the Future:

- Centres of excellence for agencies or "full provider" ??
  - according to approvals :
  - MRFG – RMS / Centralised - Rapporteur
  - according to projects / indications (e.g. antibiotics, HIV)
  - according to topics (Notes for Guidance, Points to Consider, Working Parties)
  - Which way electronic submission will go?

Who and how will survive of the 25 agencies?

Importance of European Procedures
- Future -

For 2004*, 33 new substances were expected within the Centralised Procedure but 200 „orphans“ are „on the horizon“ in the next few years.

What is the future ??

How to get a rapporteurship from a smaler „cake“ ??

What‘s about the new members and their „slice“ ??

(costs ? , fees ?, 240 EMEA - employees must be paid!)

* source: T. L nngren, Rome 27.11.03, no final data aviable up today

Agencies

- Are part of different social systems
- Are involed in the effective and secure use of drugs
- Are – besides industry and universities - the third independent collumn of drug-development
- Are in discussion and critisised :
- Approval too slow
- Approval too fast
- Hurdles too high
- Hurdles too low

Non German Examples :

- 1995: The Republican speaker of the House of Representatives, Newt Gingrich referred to the FDA as "job killers: its excessive reviews, he claimed, delayed the launch of new drugs and thereby forestalled growth for the pharmaceutical industry.
- 1998 Kleinke, J.D. : Is the FDA approving drugs too fast? Probably not - but drug recalls have sparked debate. BMJ (317), 899.
- 2003 Singh, D. : Medicines Control Agency slated by Commons committee: "... ...", (BMJ (327), 10.

A big Problem for Europe: Harmonis/zation of SPCs

§ EU Commission opinion:

Article 7a of Dir. 65/65 EEC requires MRP for generic products.

Problem: when the originator`s product SPC is not harmonised, national MA`s were granted based on different dossiers, the MRP is not possible nor are national procedures in more than one country

Effords undertaken since EMACOLEX meeting in August 2002

Follow-up after Community Referral Article 11 „Harmonis/zation“

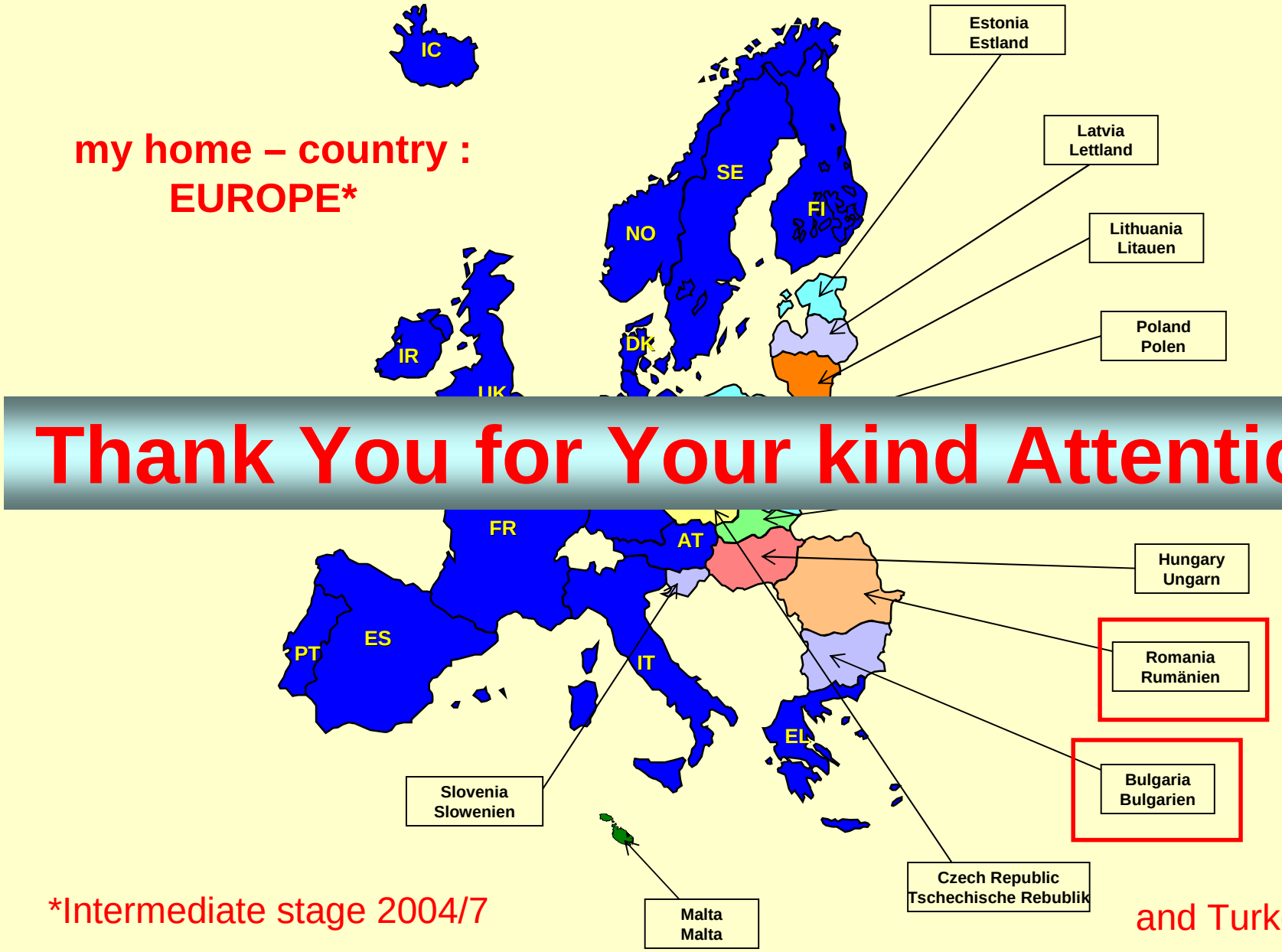
How to „ harmonis/ze“ (If we even not agree on the spelling ?)

The procedure harmoniz/ses the "Summary of Product Characteristics" especially Parts III and IV of the Dossier (pharm-tox, clinical)

Not Part II, Quality. This part of the SPC can remain unharmonised

However, the authorisation holder is seriously advised to harmoniz/se voluntarily or to file the Quality Dossier as a 'European Dossier'

my home – country :
EUROPE*



Thank You for Your kind Attention !

*Intermediate stage 2004/7

and Turkey ?