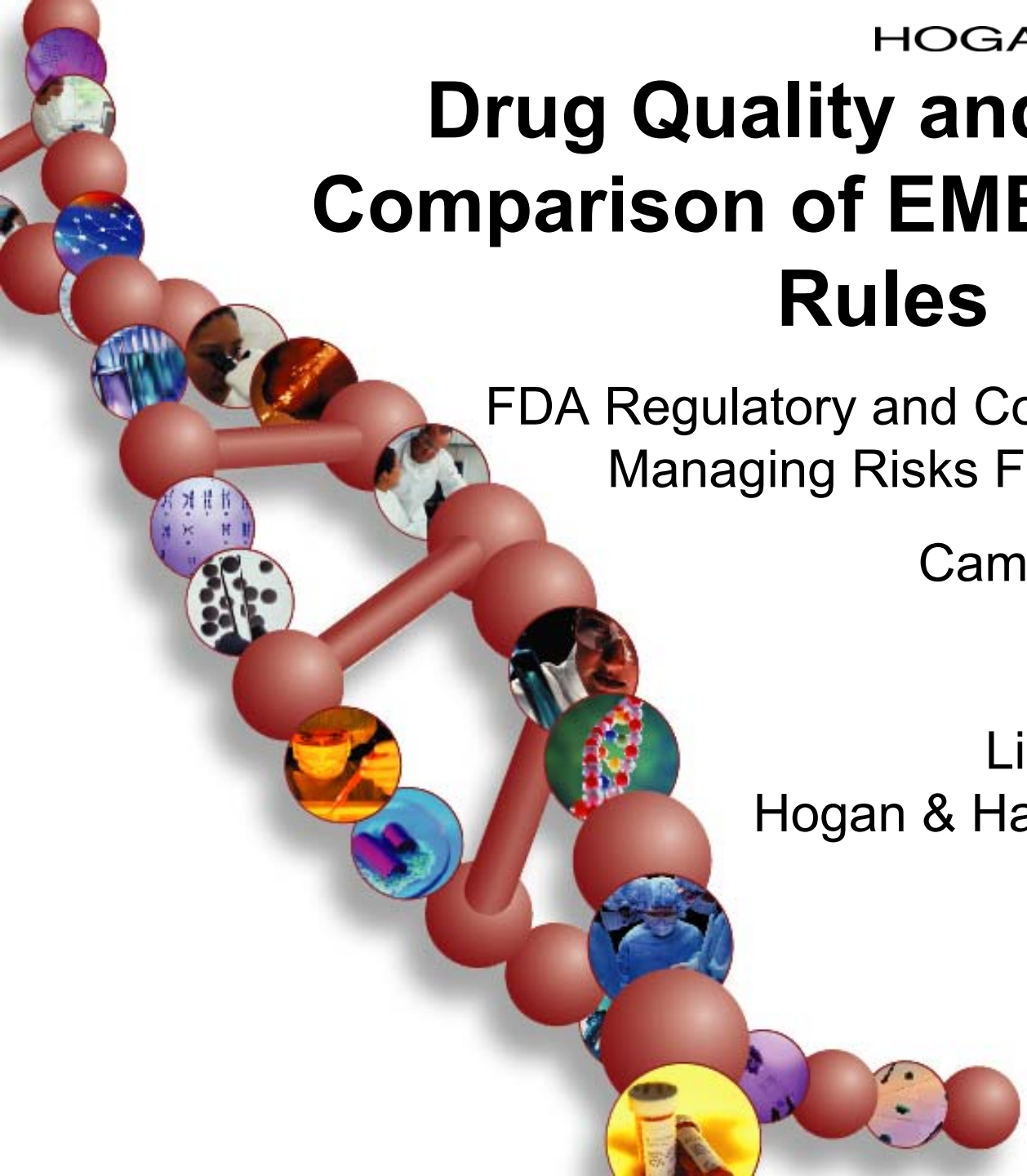

Drug Quality and Safety: Comparison of EMEA and FDA Rules

FDA Regulatory and Compliance Symposium:
Managing Risks From Pipeline to Patient

Cambridge, Massachusetts

August 25, 2005

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What we will discuss

Comparing the EU and the U.S. re drug regulation
  - How is the EU different?
  - How is it similar?
- EU 101
  - Glossary
  - Key players
  - Recent regulatory changes
  - Centralized vs. decentralized approvals
- EU regulation of drug safety and quality in a product's life cycle
- EU response to drug safety crisis

How is EU regulation different?

- Looking over the Atlantic ≠ looking in a mirror.
- There is no United States of Europe.
- There is no EU FDA.
- Since 1995, there has been a European Medicines Agency (EMEA).
- Yet each of the 25 Member States has one or more drug regulatory agencies.
- Although today 70% of new products enter via EMEA route, most products on the EU market were approved by Member State agencies.

Isn't the EMEA like the FDA? Not quite.

The EMEA is a secretariat for a network of experts.

- It does a first-rate job with its resources, attracts talented staff, and is rewarded for success by ever-expanding responsibilities.
- Although there are (largely) uniform rules on testing, clinical trials, applications, pharmacovigilance, and GMPs, enforcement is by Member States with coordination by the EMEA.
- Review of EMEA/centrally authorized product occurs chiefly in the national regulatory agency of where the rapporteur works.
- European Commission role in authorization

In the EU, coordination is a challenge

- Multiple agencies
- Multiple languages
- Multiple regulations, some hard-to-find
- Variant cultures and prescribing practices
- Rx v. OTC classification unharmonized
- Drug companies' marketing portfolios may vary widely from country to country
- Parallel trade complicates quality control efforts (you don't know where in EU product marketed)
- Price controls, formularies, health technology assessments add regulatory layers at MS level

EU regulators have some tools that are not universally available in the U.S. In the EU:

- No direct-to-consumer (DTC) advertising
- Mandatory patient package insert leaflets
- Unit of use packaging
- “Behind the counter” OTC drugs common
- Possibility of marketing suspensions while safety concerns are investigated
- Proposal for EMEA/European Commission to assess penalties for non-compliance with requirements, e.g. omissions from applications, failure to report or do studies
- Trade association advertising code bodies can regulate members (antitrust issue in the U.S.)

FDA has some advantages, especially in times of crisis

- No need to coordinate among 25 sovereign countries
- Quasi-independence within U.S. government
- Single approval and enforcement agency
- Authority to approve is delegated within FDA except: imminent hazard withdrawal [Sec.HHS] or appeals from denials or withdrawals [Commissioner, after a hearing]
- Appeals are rare; generally companies cease marketing and/or recall product if FDA requests it
- FDA has investigators and relationships with U.S. attorneys nationwide, adding credibility to its requests
- FDA doesn't depend on U.S. states to act and, re imports, Customs helps FDA but FDA calls the shots
- FDA has fairly good handle on what's on US market
- Single pharmacovigilance system

How are the U.S. and EU similar:

- Common regulatory objectives
- There is conscious effort to eliminate unjustified differences and harmonize
- Regulatory affairs officials in companies are striving toward global submissions and uniform reporting obligations
- ICH guidelines lead the way, e.g. Common Technical Document and pharmacovigilance
- Thanks to ICH, the differences today are principally organizational not substantive.

EU 101

- Legal instruments
- Glossary
- EU Pharma: Key Players
- Centralized procedure (EMEA)
- Decentralized procedure/mutual recognition
- Member State role
- Recent regulatory changes

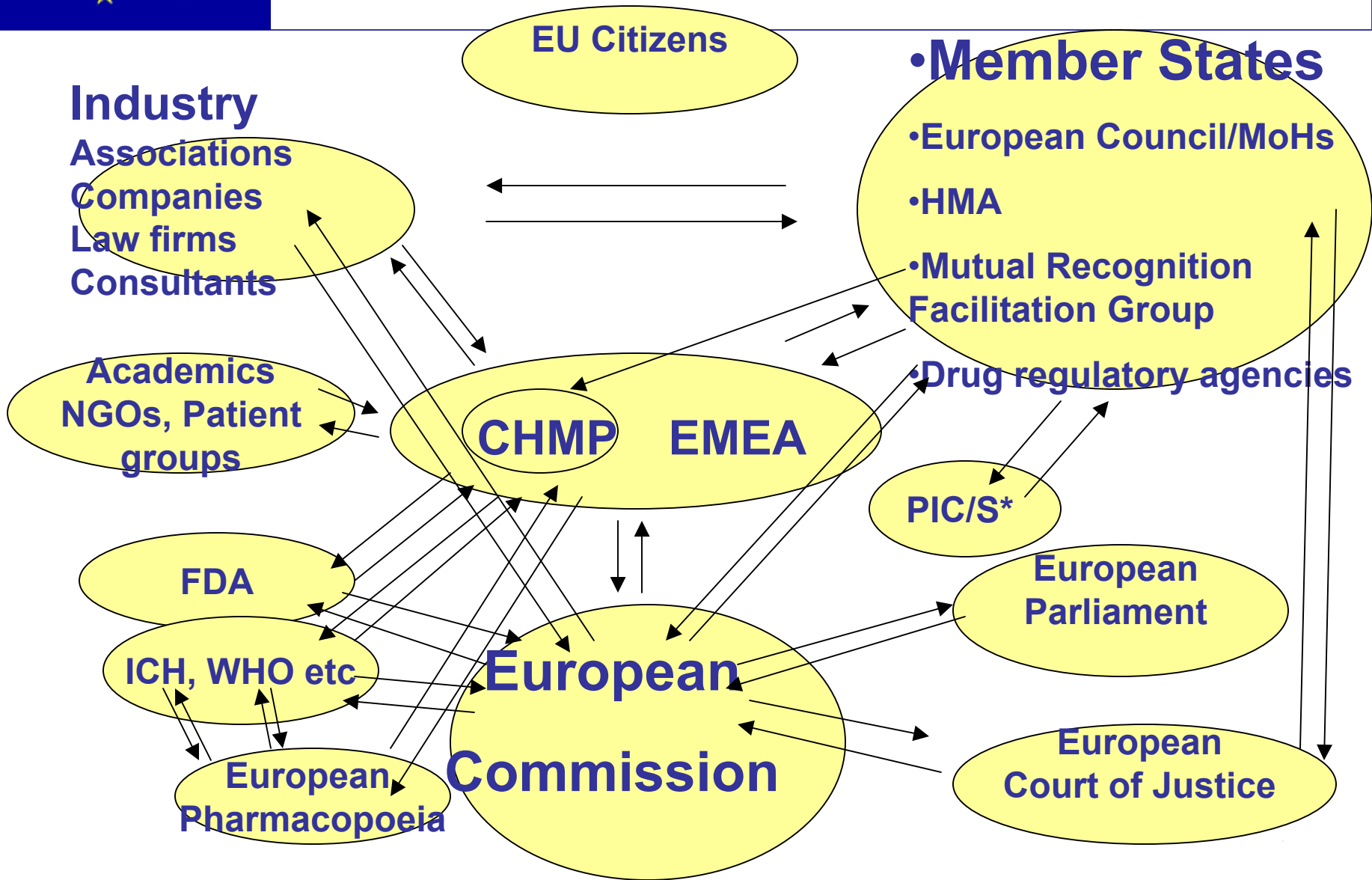
EU 101: legal instruments

- A **directive** is mandatory, aimed at member states which then must "transpose" the directive into national legislation. Examples:
  - Community Code on Medicinal Products (1→25+3 laws!)
  - Clinical Trials Directive (1 →25+3 laws!)
- A **regulation** is mandatory and self-executing without need for member state transposition (1 law!)
  - Example: Regulation on the EMEA; variation regulations
- A **recommendation** is non-mandatory (rare)
- A **decision** is mandatory but narrow in scope
  - Example: Market authorizations based on EMEA
- A **guideline**: no legal status. Example: Notice to applicants. See recent EMEA procedure.

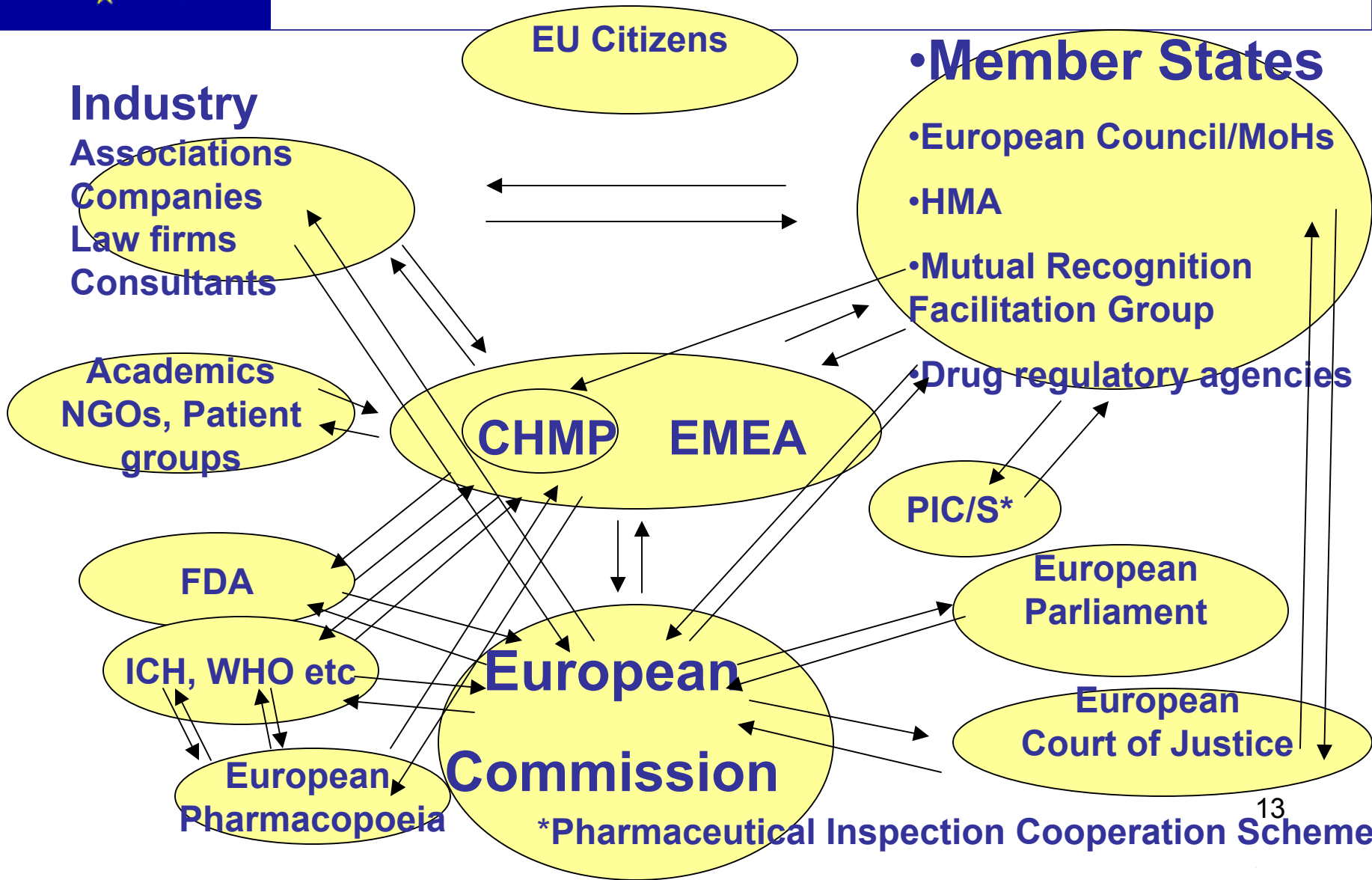
Glossary

- CHMP: Committee on Human Medicinal Products
- CMSs: Concerned Member States
- Competent authority/DRA: drug regulatory agency
- CTD:Common Technical Doc
- EP: European Pharmaco-poeia (or EU Parliament)
- ERMS: European Risk Management Strategy
- GCPs: Good clinical practices
- HMA: Heads of Medicines Agencies
- ICH: International Conference for Harmonization
- MA: Marketing authorization
- MAA: MA application
- MAH: MA holder
- MoHs: ministers of health
- MRFG: Mutual Recognition Facilitation Group
- PhVWP: PharmacovigilanceWP
- PIC/S: Pharmaceutical Inspection Cooperation Scheme
- PSUR: Periodic Safety Update Report
- QP: Qualified person
- Rapporteur: point person
- RMS: Reference Member State
- MSs (Member States)

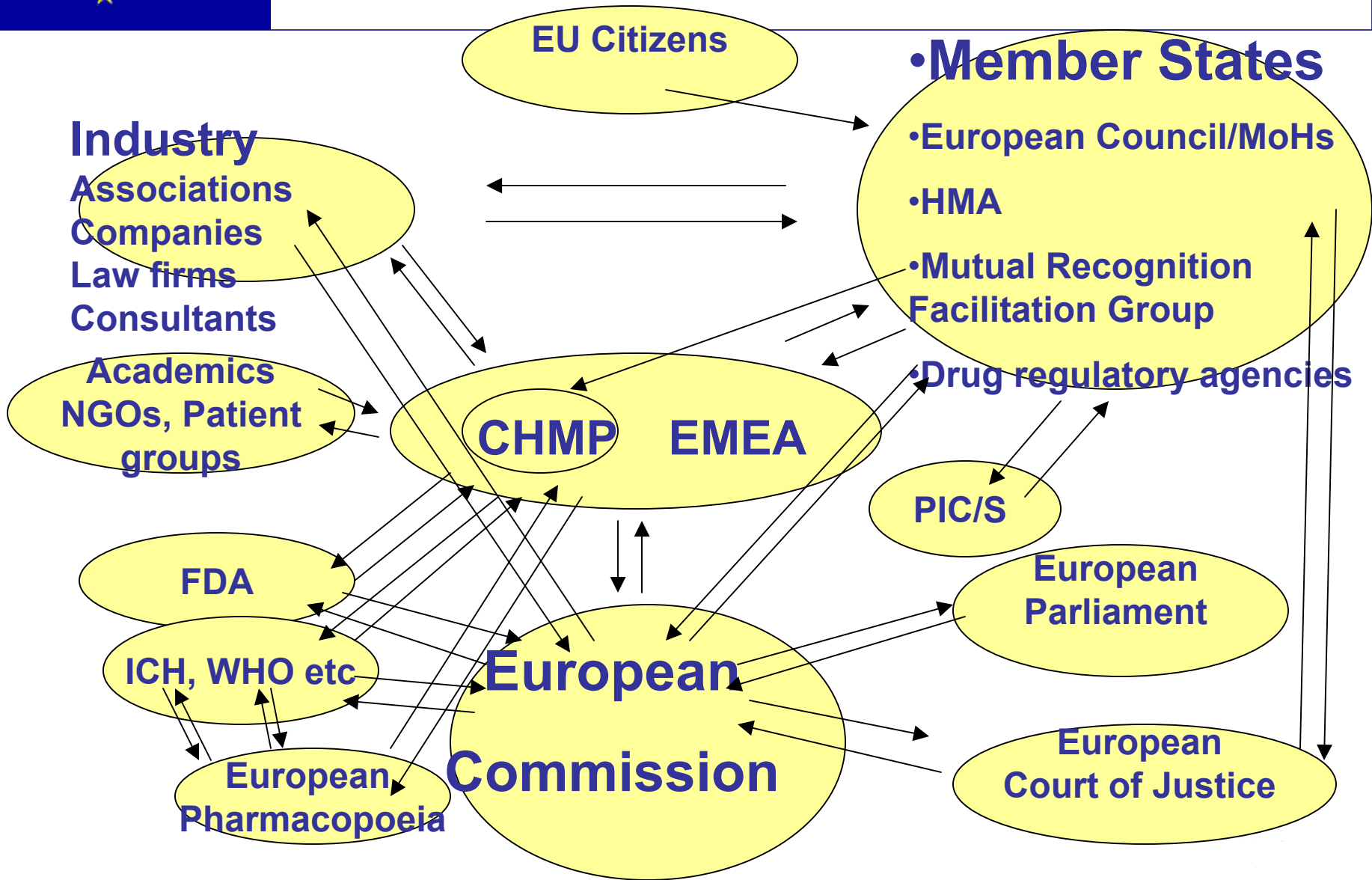
EU Pharma: Key Players



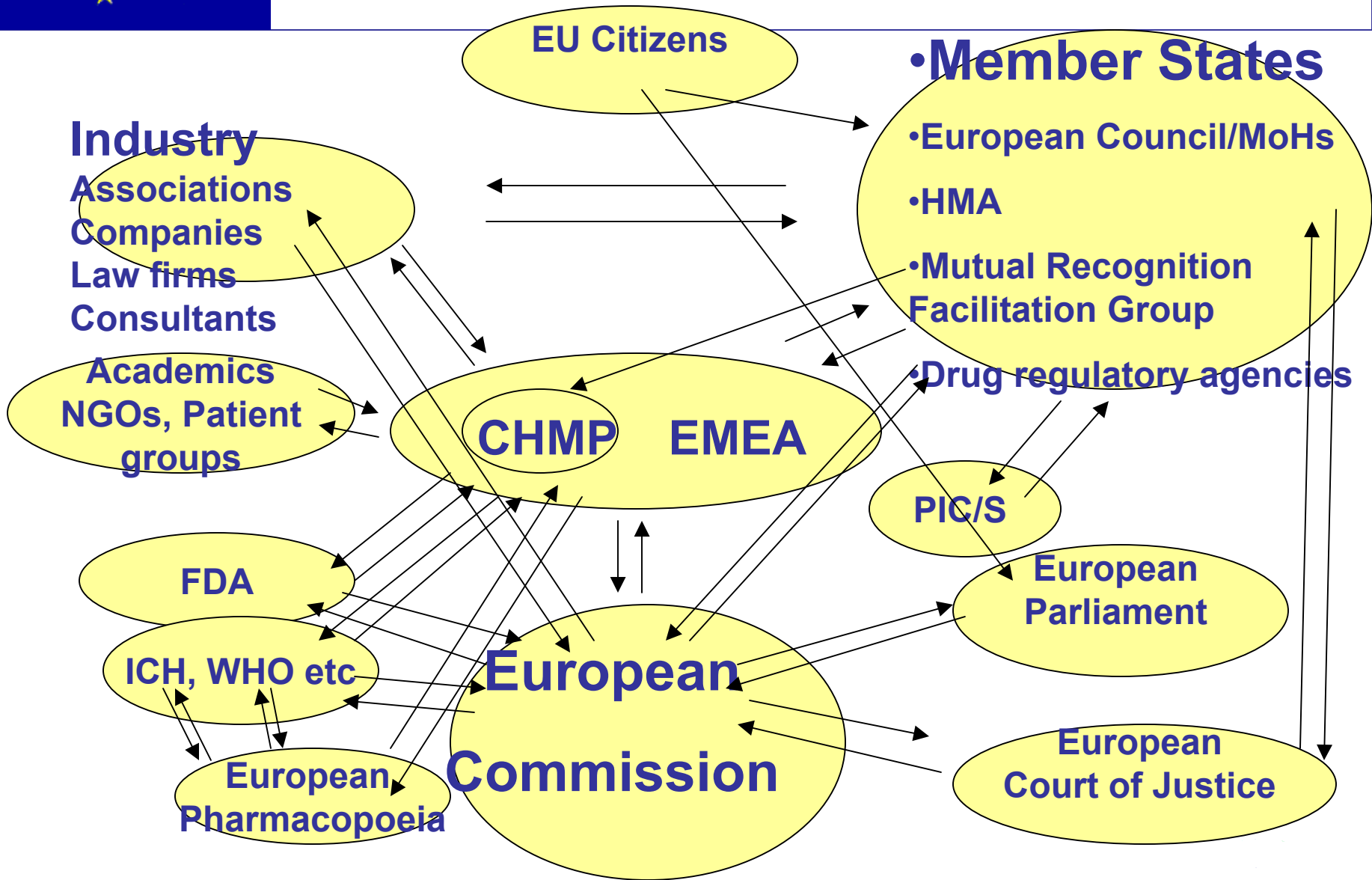
EU Pharma: Key Players



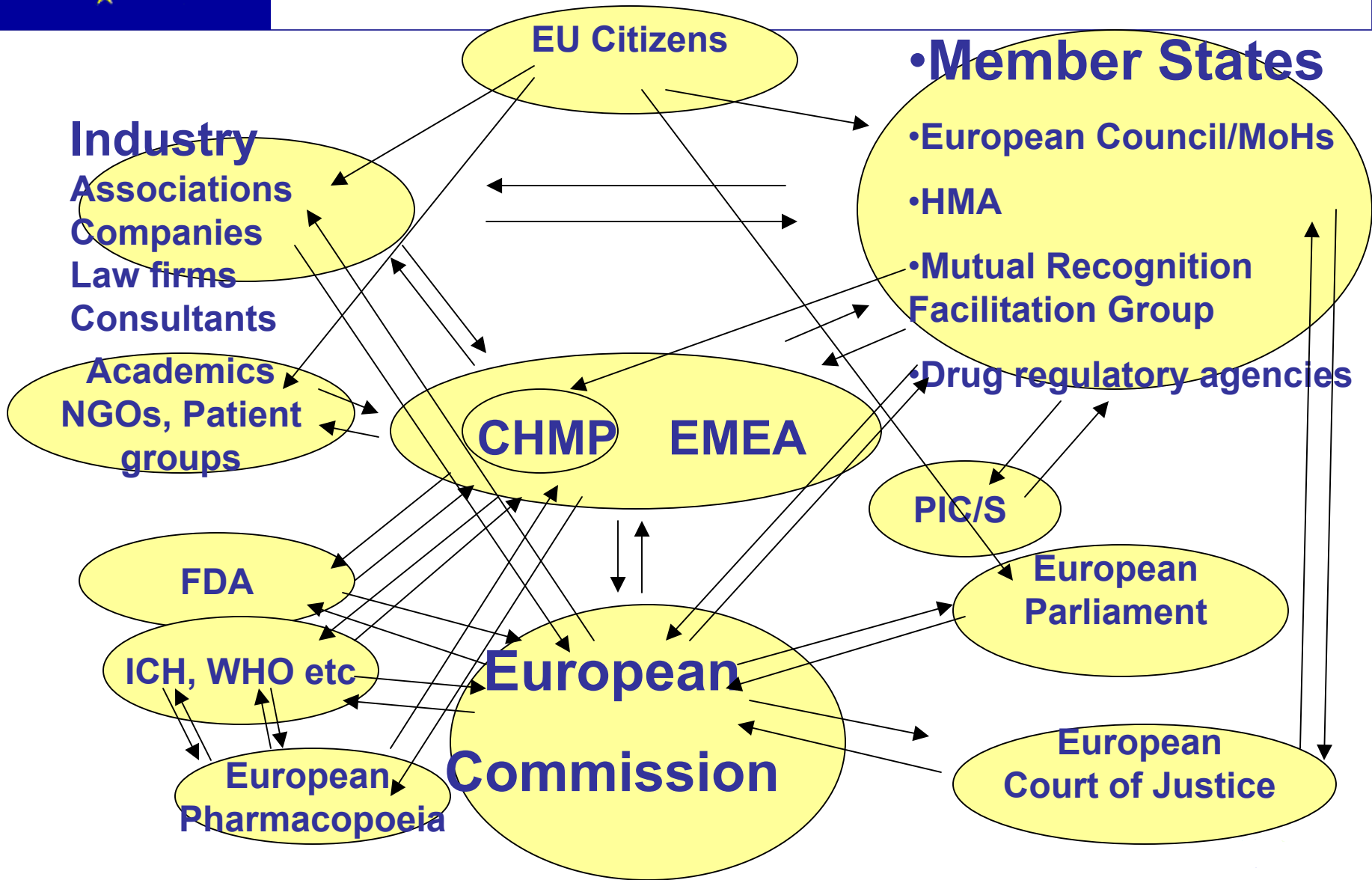
EU Pharma: Key Players



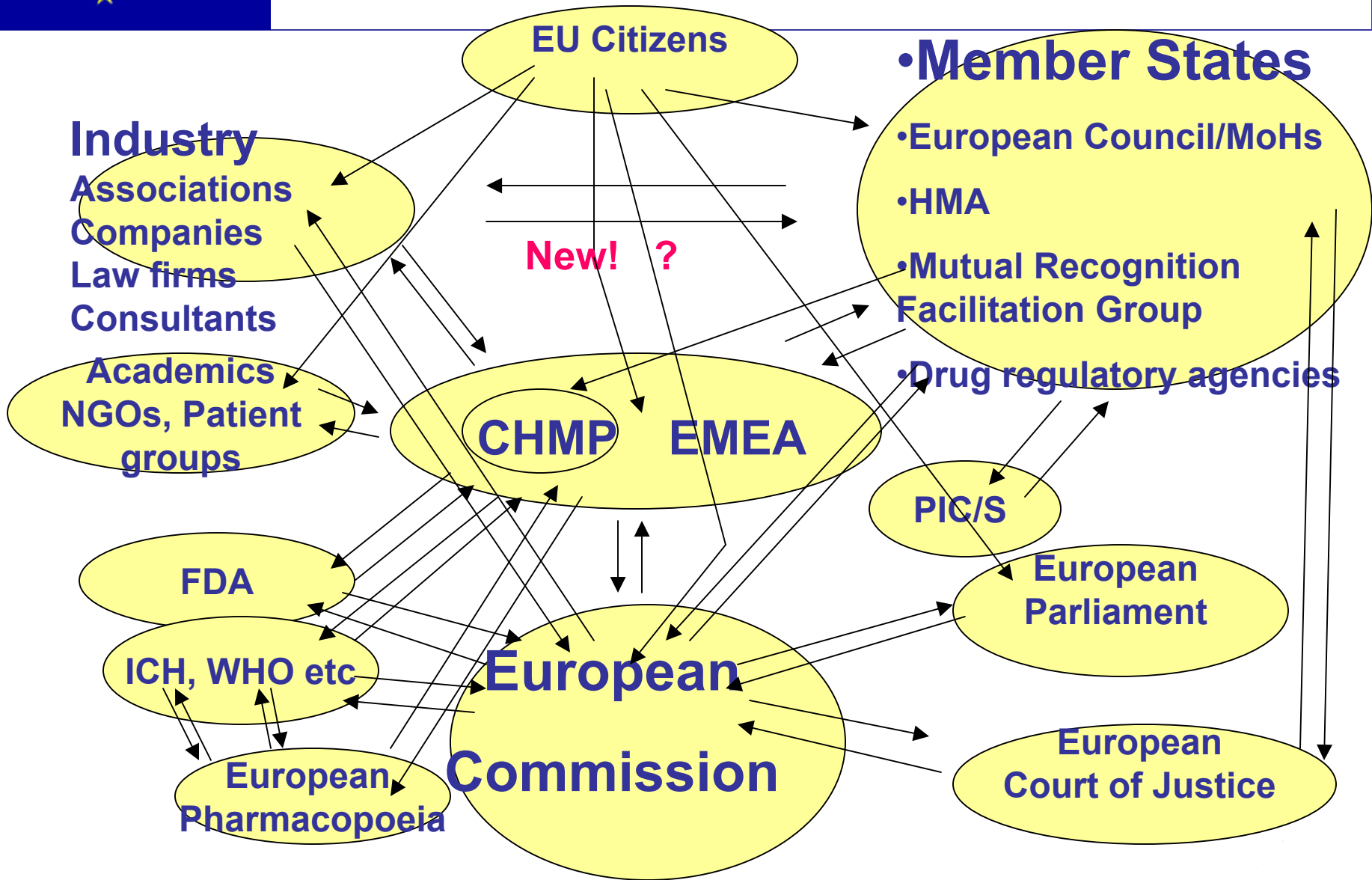
EU Pharma: Key Players



EU Pharma: Key Players



Pharma: Key Players



Recent regulatory changes

Landmarks in EU Pharma Law

Pharmaceutical Review Legislation

Landmarks in Development of EU Medicinal Products Law

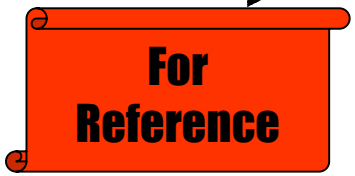
1965 

- Thalidomide→Directive 65/65, which launched European Community harmonization of regulation of medicinal products

For Reference

Landmarks in Development of EU Medicinal Products Law

2001



- Clinical Trials Directive—2001/20
- Community Code on Medicinal Products--2001/83: the Human Use Directive
  - codifying 65/65, 78/318, 75/319, 89/342, 89/341, 89/381, 92/25, 92/26, 92/27, 92/28, etc.
  - July 2001: Start of Review Process that→ legislation published April 30, 2004

Landmarks in Development of EU Medicinal Products Law

2003

- 2003/63: New Annex 1 to Directive 2001/83
  - ICH Common Technical Document is implemented
  - additional requirements for biological medicinal products
  - “clarifying” coverage of gene therapy and somatic cell therapy
- Commission Regulations on Variations, (EC) No 1084/2003 of 3 June 2003 and Commission Regulation (EC) No 1085/2003 of 3 June 2003

For Reference

Pharmaceutical Review Legislation

For Reference

2004

- **"EMEA Regulation" (EC) 726/2004**: authorisation and supervision of medicinal products for human and veterinary use and on the European Medicines Agency (EMEA) (replacing Regulation (EC) 2309/93)

- **Directive 2004/27/EC** amending the Community code on medicinal products for human use (Directive 2001/83/EC)

- **Directive 2004/24/EC** on traditional herbal medicinal products (also amending Directive 2001/83/EC)

- **Directive 2004/28/EC** amending the Community code on medicinal products for veterinary use (Directive 2001/82/EC)

Timeframe for implementing laws published April 30, 2004

Amendments to Community code directive:

Entry into force: April 30, 2004

Implementation by Member States by October 30, 2005

EMEA regulation:

Entry into force May 20, 2004

Application by November 20, 2005

Decentralized Procedure vs Centralized : Scope

Decentralized

- **Mandatory for"variation"and line extension of products approved through this procedure**
- **All products are eligible for this procedure except:**

  -Biotech products and biotech biosimilars

  -Orphan products

  -Other products subject to mandatory procedure

Centralized

- **Mandatory EMEA review for biotech products;** until Nov. 20, optional for other innovative products(lists A/B)
- **Nov. 20, 2005 :centralized review mandatory for**
  - **Biotech drugs & biosimilars**
  - **Orphan drugs**
  - **Innovative drugs for certain diseases (expanding list)**
- **New optional review**: applicant justifies EMEA review (Art.3)

Comparison Centralized vs Decentralized

Decentralized

- several MAs
- several tradenames
- free choice of the RMS
- free choice of the market
- divergent opinion possible
- final MA may take time

Centralized

- 1 MA
- 1 tradename
- 1 opinion
- 1 decision
- 1 MA directly in the whole EU

Decentralized Procedure
= Mutual Recognition Procedure

Recognition of an original national Marketing Authorization (MA) granted by the Reference Member State (RMS) by one or a few MS (Concerned MSs)

If not: arbitration by the CHMP followed by a binding decision

First original MA in the RMS -->one or a few national MA in the CMSs

Decentralized Procedure vs Centralized : Result of the 2001 Review

Decentralized

- Ability to pick markets
- Familiar procedure
- More access and flexibility

BUT

- Review periods can be long
- Lack of consensus among MSs
- Problem with mutual recognition
- Industry avoidance of arbitration procedure (prefer to withdraw)
- NO single market

Centralized

- 25+3 country market
- High level of satisfaction
- Very efficient

BUT

- Process viewed as rather heavy and bureaucratic
- Review periods can be long
- Restricted scope
- Big reward-- but big risk if you don't get authorization

Coming soon:

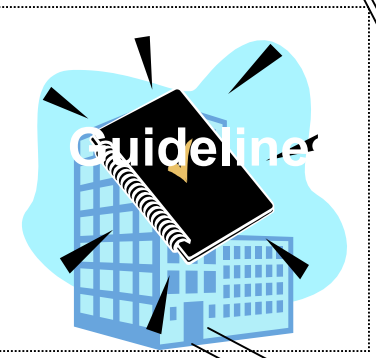
Decentralized

- Tighter deadlines for reviews
- Definition of risk to public health, to limit MS objections to mutual recognition
- Formal and legal status for the MRFG
- Improvement of the arbitration phase

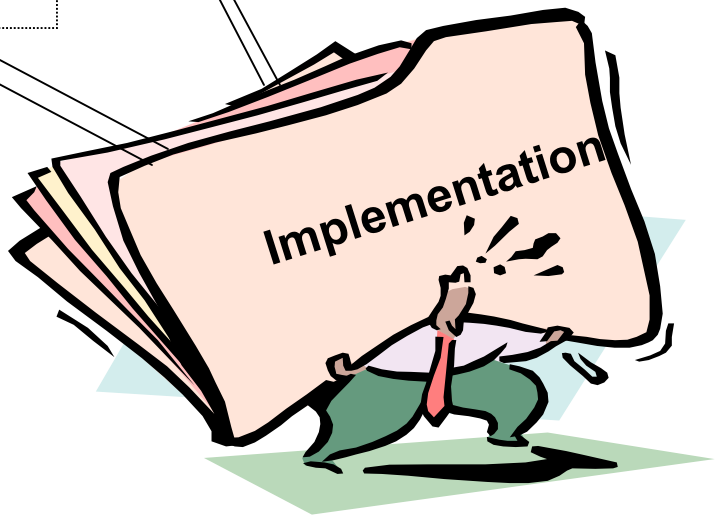
Centralized

- Broader scope
- Tighter deadlines for reviews
- Creation of a fast track procedure
- Authorization valid for unlimited duration after first 5-year term
- Already EMEA has more powers,modified structure

COMMISSION: BRUSSELS



EMEA/
LONDON



Member State Role

Impact of EU Laws on Members

- Heavy load of legislation to implement
- Increased informatics requirements (clinical trial database, pharmacovigilance, website updates, etc.)
- More interaction with patients and industry expected
- Resource shortfalls can be expected:
  - New responsibilities at Member State level
  - Committee participation responsibilities at EU level
  - Fewer fees when more products are approved centrally and national authorisations don't need renewal every 5 years

Member States' Duties: EU Level

- Supply of experts
- Rapporteurs and co-rapporteurs of centralised applications through the CHMP
- Other committees and working parties
- Notice to Applicants Working Group (guidelines for centralized & decentralized procedures)
- **ICH/EP/WHO working groups**

Key Member State Duties

- Clinical trial approvals and oversight
- National authorizations and maintenance
- Licensing of establishments within territory
- Importation licenses, including parallel imports
- Licensing of wholesalers and distributors
- Surveillance, inspections and enforcement.
- Sales and promotional activities (relations with doctors and hospitals) - much recent enforcement activity

EU regulation of drug safety and quality in a product's life cycle

- Which laws, when
- Overview of regulatory life cycle
- Preclinical
- Clinical
- Marketing Authorization
- Postmarket/Pharmacovigilance
- Quality (throughout life cycle)

Which laws, when

1.Preclinical*	Good Laboratory Practice Directive
2. Clinical*	Clinical Trials Directive/ICH GCPs
3. Marketing Authorization	a. Community code on medicinal products (for decentralized process; some provisions are referenced in EMEA regulation and thus apply to centralized processes); guidelines including Notice to Applicants are key here b.EMEA Regulation (centralized plus some supervision of MSs); Decisions; guidelines
4. Postmarket	Community code; referrals to EMEA possible (centralized/decentralized)
5. Quality	Community code & 2003 Commission directive on GMPs, guidelines, PIC/S, EP.

*** Data are generated in accordance with laws and guidelines in bloc 3.**

Drug safety/pharmacovigilance (PVG) life cycle

EMEA or
Member Agency

ICH "S"
Preclinical Testing

ICH "E"
Clinical Testing

ICH "M"
Market Authoriz-ation/MAA

ICH "E"
Postmarket Surveillance

Renewal in 5 years
BENEFIT RISK?
Commission
Withdrawal?

GCPs

MS
Ethics Committees

Clinical trial application

Scientific advice

MAA (includes risk mgmt. plan); CHMP/rapporteur

Comments/clockstop/reply

CHMP meeting & opinion
EMEA→Comm'n→Journal

Periodic Safety Update Reports (PSUR) to EMEA or MS agency

EMEA→ PVG cmtee>CHMP

Member state referral to CHMP (re central or decentralized)

Quality committee->CHMP

Good laboratory practices

ICH "Q" CMC/GMP: chemistry and manufacturing controls; variations

Clinical testing

- Scientific advice given new emphasis
- Clinical Trials Directive, Commission GCP Directive, MS laws, ICH GCPs
- Database of clinical trials (EUDRACT)
- Ethics Committees (ECs) given new duties
- Suspected unexpected serious adverse reactions (SUSARs)→EC, MSs, EMEA
- Member States implementing GCP audits, with EMEA coordinating (esp.re centralized)

EU Market Authorization Stage

- Criterion for authorization favorable benefit/risk
- MAA contains full reports on safety, efficacy, quality (abridged for generics)
- ICH has harmonized many requirements
- MAA to include risk management plan
- Safety issues are scrutinized
- Conditional approvals possible under new law
- Post-market studies are being ordered already
- New EU penalty regulation will add teeth to enforce commitments for centralized approvals

Postmarket: Pharmacovigilance

- Pharmacovigilance planning, per ICH
- Adverse events→ Eudravigilance
- Reforms underway

Quality throughout life cycle

- Chemistry & manufacturing controls (CMC) similar to U.S.
- Key players PIC/S; FDA via foreign inspections; European Pharmacopoeia and its European Directorate Quality Management; WHO certification scheme
- Manufacturers of finished drugs must be licensed
- GMPs recently extended to clinical stage (w/ flexibility)
- **Qualified person must release product**:trials &marketing
- ICH Q7: GMPs apply to Active Pharmaceutical Ingredients
- After Eprex and Chiron, expect even more attention to GMPs, especially for biologicals

Changes in EU CMC system

- Like FDA, the EMEA and MS agencies are moving to a quality risk management process in the GMP area (ICH Q9)

Key Elements of Laws Published 4/30/04

- Improved marketing authorisation process
  - *Streamlining centralised procedures*
  - *Expanding EMEA jurisdiction*
  - *Tackling "non-recognition" problem in decentralized/mutual recognition procedures*
- Accelerated access to medicines & compassionate use
- Greater transparency, patient information
- Generics and biosimilars defined; Bolar
- Harmonized data exclusivity ("8+2+1)

Where is drug safety?

- This was not a prominent issue during the 2001-2004 consideration of the pharmaceutical review legislation.
- We will discuss a few features of the new laws that are relevant to drug safety.
- However, there have been other steps recently to tighten drug safety regulation, as we shall see.

Validity of Marketing Authorization (MA)

- Valid for an initial five-year period (Article 24)
- Thereafter: unlimited, unless pharmacovigilance finding leads approval authority to proceed with 5-year renewal

Access to Medicines

- Accelerated procedure for products of significant therapeutic interest (210 → 150 days)
- Conditional marketing authorisation possible in certain cases for important therapies
- Provision on situation where a medicine is authorised in another EU Member State ("Cyprus clause," new Article 126a)

Access to Medicines

- EU-wide system to make medicines available in advance of authorisation for "compassionate use," provided:
  - application for MA has been filed
  - clinical trial underway

Transparency/Patient Information

New provisions on:

- Reason for withdrawal of a drug
- Refusals of drugs
- European Product Evaluation Reports (EPARs)
- Rules of Procedure
- Database on drugs, MAHs, etc. is underway
- Database on clinical trials (accessible only by Member States)
- Pharmacovigilance opinions of the CHMP

Transparency/Patient Information

- Broader patient information issue was controversial - opposed by many consumer groups and parliamentarians
- European Commission approach was rejected …. for now
  - Commission is to report within three years concerning information practices (Internet)
  - Commission is to make proposals
- European Commission officials and industry continue to argue for more information, but not U.S.-style DTC ads

EU response to “drug safety crisis”

- EMEA head criticizes industry
- Actions on COX II inhibitors, SSRIs
- European Risk Management Strategy Action Plan

"Europe regulator attacks drug groups over disclosure of side effects," FT, Oct. 20, 2004

- Thomas Lönngren: "Once again, history has shown that we do not have a sufficient system in place."
- "More and better communication on the safety of medicines is the key, and here we are a little disappointed in the pharmaceutical industry….they are focused more on the stock market sometimes.
- "We are very concerned that, because we want the company to communicate with the regulator and not to bother about the stock market first."
- EMEA officials are angry because they did not have time to prepare advice for doctors and patients before the Vioxx withdrawal was announced.

- **Financial Times: London, Oct.20, 2004**

Member State angst

- “The Vioxx withdrawal caused an ‘earthquake’ in the pharmaceutical sector.”

French regulator and industry reply on drug safety, Scrip, Feb. 25, 2005

- “…Vioxx was associated with only a handful of reports of myocardial infarction in the UK yellow card ADR scheme over the last few years…”

Few clues from UK yellow card scheme about Vioxx ADRs, Scrip, March 2, 2005

European Risk Management Strategy (ERMS), 2003

Action Plan to further progress the ERMS, May 2005

Aims of the ERMS

1. Build on MSs' resources and expertise, while enhancing EMEA coordinating role
2. Support consistent, robust decisionmaking
3. Ensure accessible information on safety
4. Reduce duplication of work
5. "Be demonstrably effective in protecting public health"

Five key priorities of ERMS

1. Review mandate of EMEA's PhVWP (Pharmacovigilance Working Party)
2. Conduct survey of EU pharmacovigilance resources
3. Propose ways to strengthen communication
4. Secure best use of scarce resources for pharmacovigilance, and
5. Provide guidance on Risk Management Plans

May 2005 Action Plan: EU Toolkit

1. Risk management plans in MAAs
2. Post-authorization collection of pharmaco-vigilance data from targeted patient groups
3. Provisional vigilance measures, if indicated
4. Reinforce benefit/risk balance concept
5. Change timing of Periodic Safety Update Reports (PSURs)
6. Mandate e-reporting of adverse events
7. Strengthen enforcement; penalize violations

Moving toward EU "Intensive Drug Monitoring System"

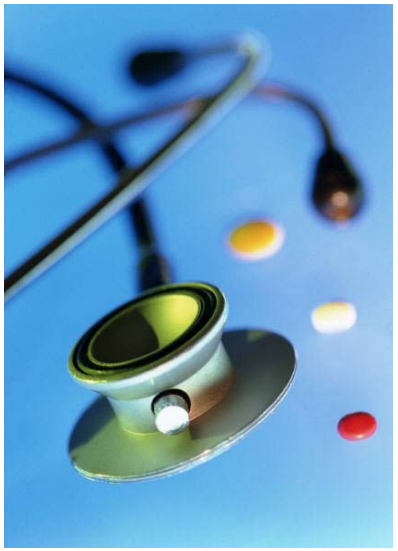
- Risk detection: increase ADRs but explore new ways to increase safety signals
- Risk assessment: review the PhVWP; introduce concept of risk minimization
- Risk communication enhancements
- Improve reporting re pediatric use, vaccines
- Enhance overall quality of EU regulatory system (benchmarking, peer reviews)
- Heads of Medicines Agencies play key role

What to expect?

- Increased referral of safety reviews from local to EMEA
  - Increased publicity
  - More rigorous scientific standards
  - More “Phase IV” studies
- More uniformity across countries
  - Labeling changes

What to do?

- Implement crisis management plan
- Increase understanding of EMEA



Contact details

- Counsels clients in the food, pharmaceuticals, medical devices, animal health and cosmetics industries on regulatory requirements of the European Union, the U.S. Food and Drug Administration (FDA) and the requirements of the agency's counterparts elsewhere.
- Recommended in the *European Legal 500* for EU regulatory work in the areas of pharma & biotech and food & drug.
- Focuses on regulatory pathways, EU, FDA and global
- Served as FDA's Director of International Policy; Deputy Chief Counsel for Regulations; Legislative Director
- Extensive experience worldwide and contacts with regulatory and parliamentary officials.

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