EU & FR MEDICAL DEVICES MARKET - ORIENTATION, CHALLENGES AND TRENDS : clinical tools

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CE Marking Director AB Certification – Associate SYNERGUS

Ph.D. in Biomedical Engineering, helps medical devices manufacturer direct their efforts in the European regulatory, reimbursement & pricing environment, particularly in France and provides assistance for managing compliance with assessment and certification procedures throughout Europe (CE marking, European National regulatory conformity, vigilance, post-marketing, etc.).
Skills/Special Qualifications
Ph.D. in Biomedical Engineering in Drug Delivery system including implantable pumps for pain control, chemotherapy, spasticity treatments with Baclofen, and diabetic treatments with insulin.
Master's Degree in Medical Imaging
Four years in Research Development for pharmaceutical laboratories;
Engineer in charge of French homologation, vigilance & post market surveillance on surgical devices (laser, lithotripter, HF, US) and Drug Delivery Systems;
Engineer in charge of relations with test laboratories at the French Ministry of Health;
Engineer in charge of official mission on behalf and on the name of the French Ministry of Health, and involved in a multiple expertise with French authorities and their partners (Social Security Organisation, Public Payers, Lab-test, etc) for reimbursement and health technology assessment;
Excellent knowledge of the European systems of healthcare and the disease management with technology assessment;
Good knowledge of the hospital environment, healthcare map, biomedical engineering, public tender rules, hospital medical project, etc…
International expert for the introduction of new biomedical technology through EU health systems

Presentation outline

- Introduction : **: need to clinical**
  - **Medicinal Product development & regulations**
  - **Medical Devices development & regulations**

- From Technology to medical device marketing
  Regulatory and challenges

- Conducting medical devices studies in EU (case of France) process and key steps

Produits de Santé - *Healthcare products*

- Médicaments et matières premières - *Drug*
- Dispositifs médicaux et de diagnostic in vitro – *MD-AIMD & IVD*
- Biomatériaux et produits d'origine humaine ou animale (organes, tissus, cellules, PTA, et dérivés) – *animal, human origin derivatives*
- Thérapie génique et cellulaire – *gene & cell therapy*
- Produits sanguins labiles – *Blood derivatives products*
- Préparations hospitalières – *patient customized preparation*
- Aliments diététiques destinés à des fins médicales spéciales - *nutricaments*
- Cosmétiques - *cosmetics*
- Insecticides et produits anti-parasitaires à usage humain - *biocides*
- Désinfectants – *disinfectants*
- Etc……

Medicinal Product Regulations : History

- EU: Thalidomide disaster in the early 1960s
- US: Tragic mistake in the formulation of a children's syrup in the 1930s and 260 childrens contract polio from 2 batches of polio vaccine that contained live polio virus in 1955

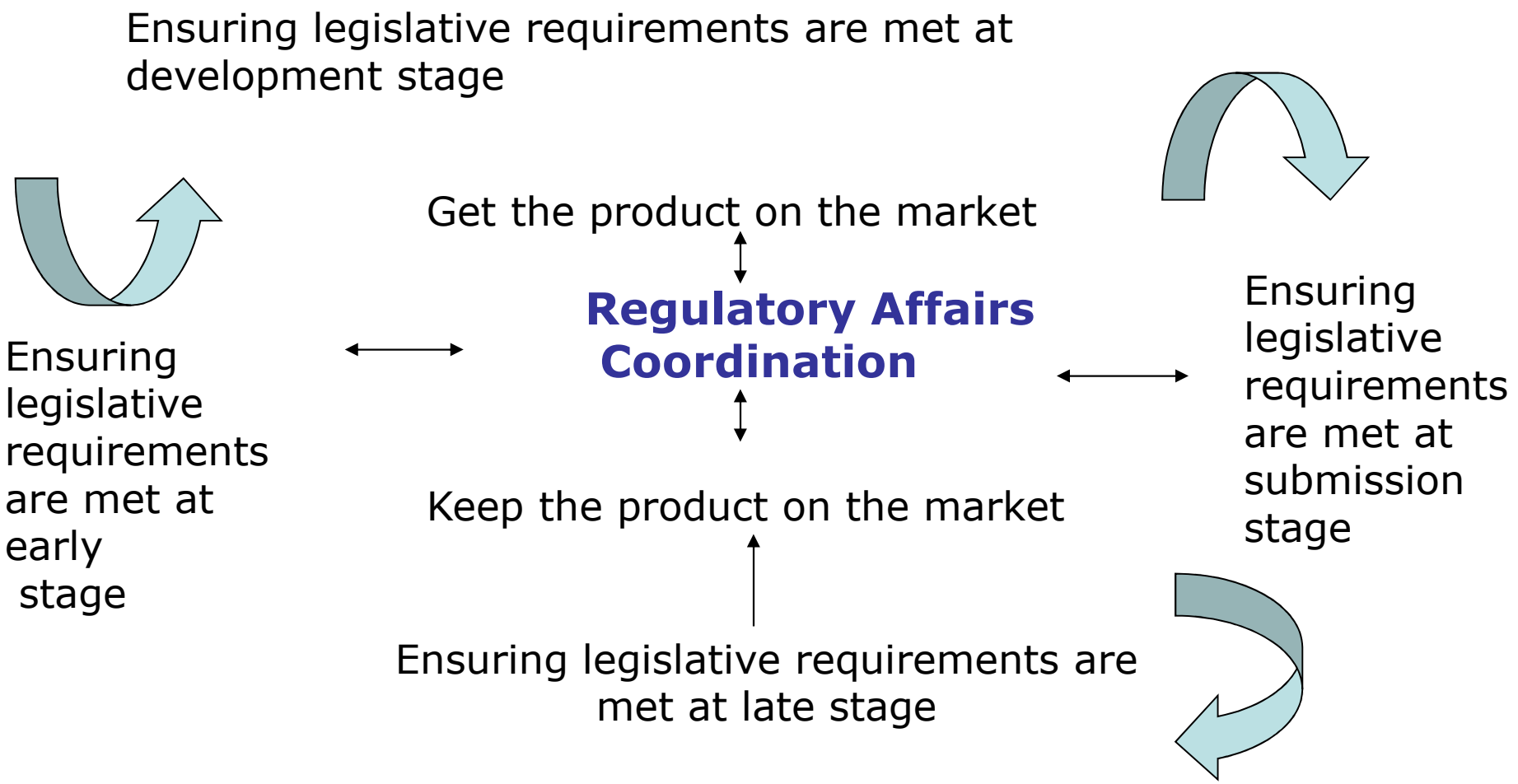
  - ✓ **Laws needed to <u>protect the public health</u> to prevent this type of disaster from occurring again**
  - ✓ **A regulation needs to ensure that pharmaceutical companies have standards to follow in the development, manufacture, control and marketing of medicinal products**
  - ✓ **Laws to assure "informed consent" of subjects participating in investigational drug studies**

Medicinal Product Regulations

Legally binding acts:

- EU:
  - ↘ Directives which require national implementation
  - ↘ Regulations (on all members states) which take prevalence on national law
  - ↘ Decisions (on individual MS)
- Non-legally binding acts:
  - Guidelines, guidance for industry, opinions, points to consider and communications
  - GxPs Guidelines (GMPs, GCPs, GLPs)
  - ICH Topics and Guidelines, CPMP, national guidelines
  - *Not law, but adherence is strongly recommended*

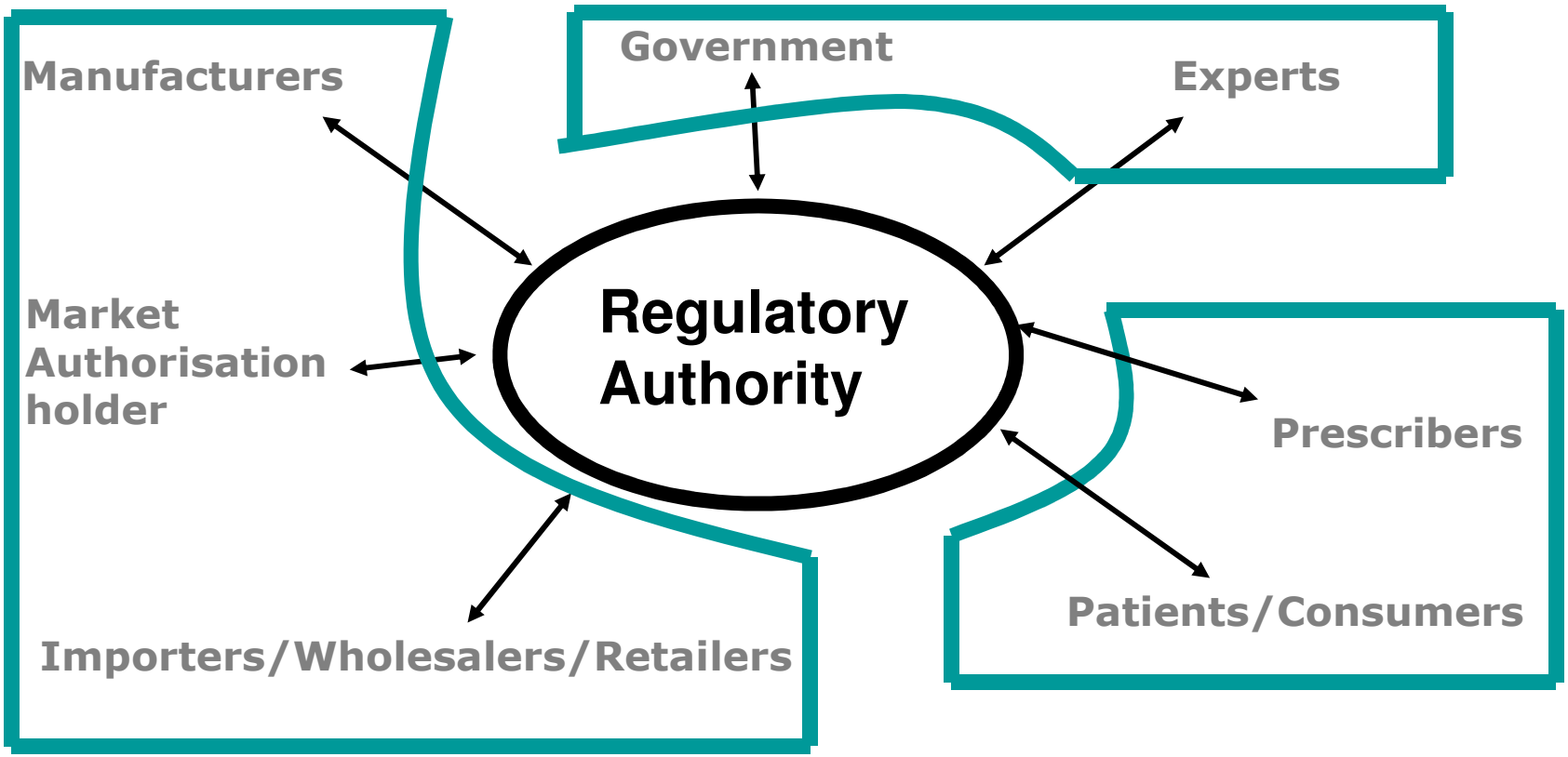
Medicinal Product Regulations



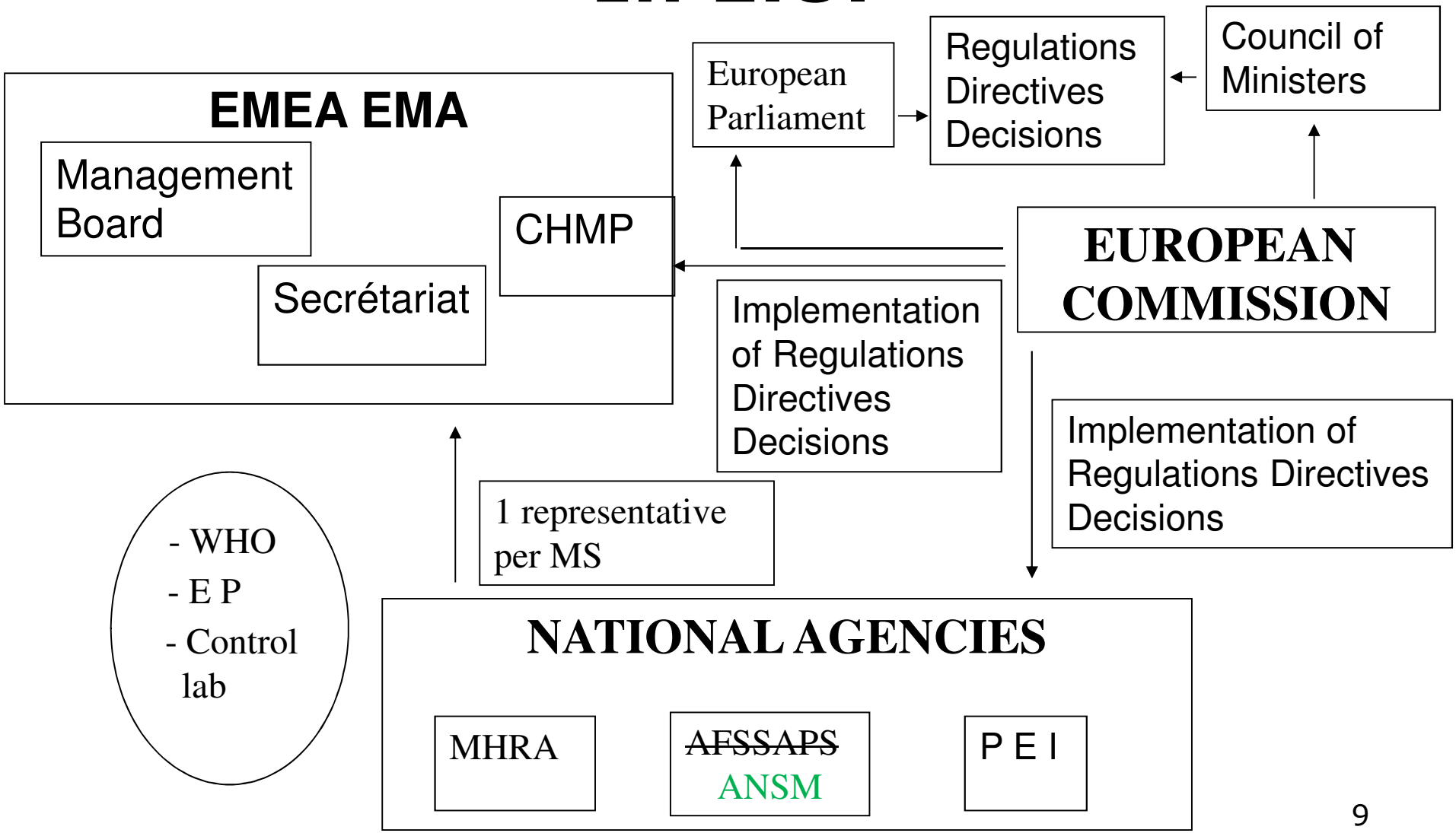
Medicinal regulatory Affairs questions

- Step of drug development
  - Successful transition from the science to a legal regulatory document (SPC/Labeling)
    - Balance between science and law
    - Risk/benefit balance (quality, safety and efficacy)
    - Support R-D process
    - Evolving area
- Step of clinical trials
  - Weighting the pros against cons
  - Approval from regulatory authorities following submission
  - Provides a scientific safety net for subjects

Role of the Regulatory Authorities



Role of the Regulatory Authorities In E.U.



Role of the Regulatory Authorities

To safeguard and protect the public health with regard of medicinal products

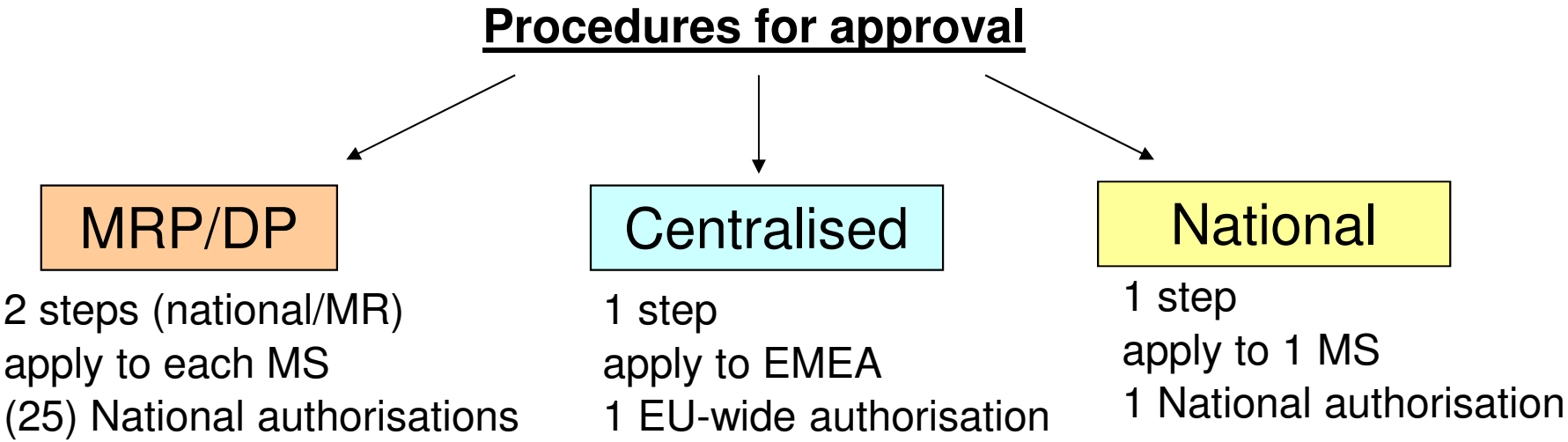
- Determine the risk/benefit ratio of the product by assessing its quality, safety, and efficacy
- Licensing of manufacturers, importers, distributors, wholesale and retail outlets
- Marketing authorization (product approval)
- Provision of medicinal products information and monitoring of the promotion and advertising

Role of the Regulatory Authorities

- Monitor the adverse drug reactions (pharmaco vigilance)
- Authorization of clinical trials
- Quality control laboratory testing and release
- Ensuring respect of legislation
- Development of new regulations and guidance documents for industry
- Development of standard / reference methods and products

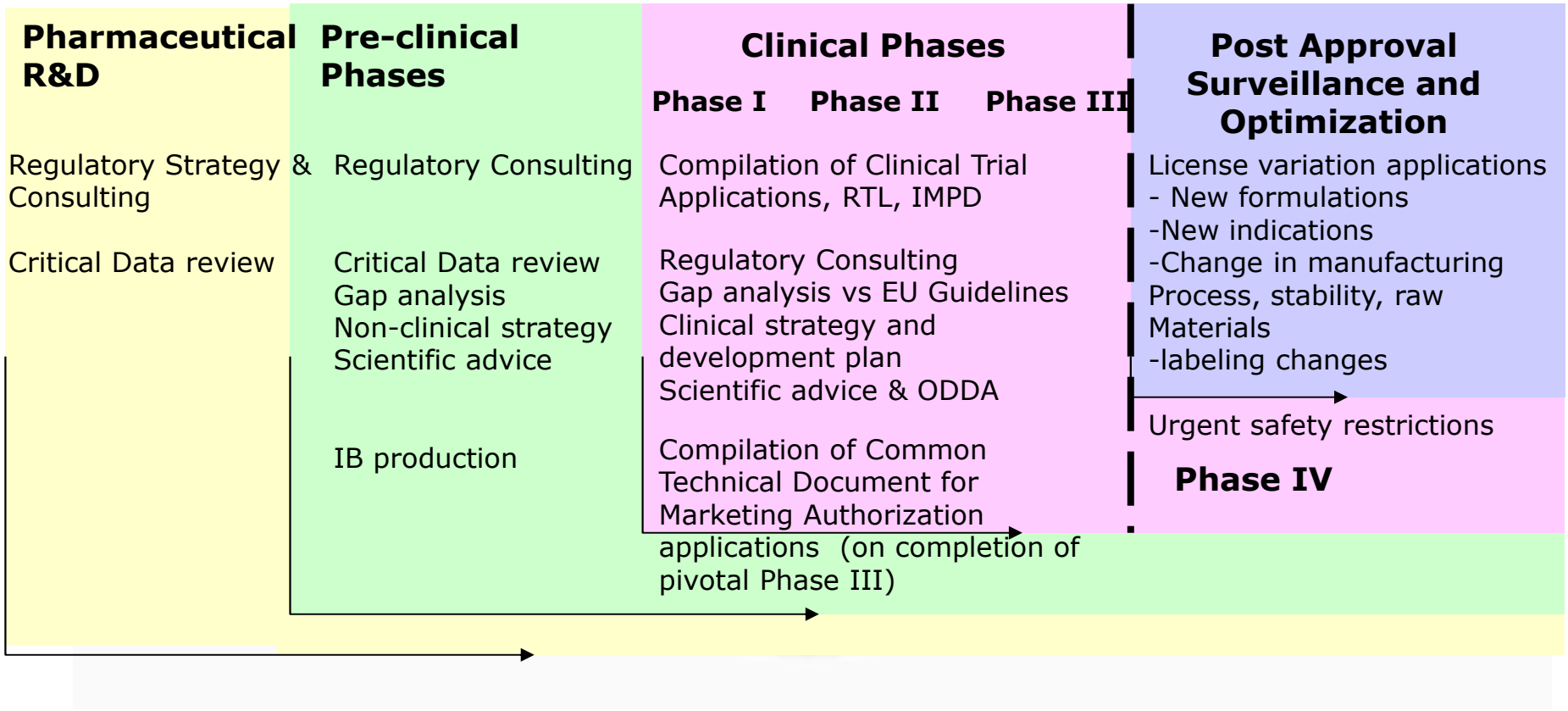
Medicinal Product Regulations

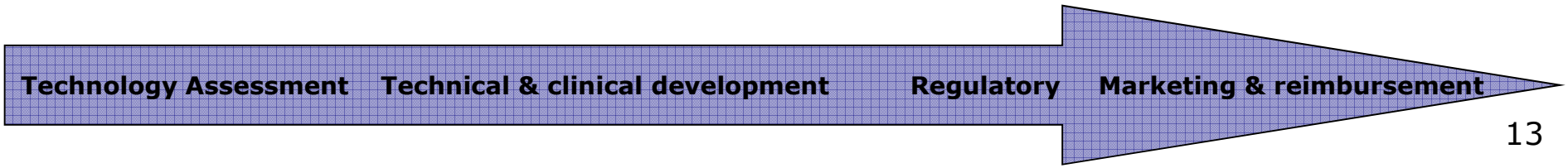
Every medicinal product which is promoted for sale in the EU must hold a marketing authorisation.



Medicinal Product Regulations

Regulatory Affairs & Product Development





Medical Device Sector

Potentially > 400,000 devices on the market (>10,000 families)

Contribution of Medical Technology to Life Expectancy

Infant mortality	***1960 - 2000***	***- 81 %***
Life expectancy at birth	***1960 - 2000***	***+ 13 %***

OECD Health Data 3rd Ed

Significant contribution in life expectancy of 8 years in Europe in last 30 years

Medical Device Sector

Potentially > 400,000 devices on the market (>10,000 families)

Vascular implants

Hearing Aids

Intra-Ocular Lenses

Dialysis Equipment

Imaging Equipment

Stimulators

Catheters

Wound Dressings

Tongue Depressors

Heart Valves

Physiological Monitors

Sutures

Orthopaedic Implants

Contact Lenses

Physiotherapy Equipment

Diagnostic Devices

Radiation Therapy Equipment

Radiation Therapy Simulators

Drug/nutrient Delivery

Cosmetic Prostheses

Contraceptives

Thermometers

Lancets

Endoscopes

Sterilisers

Filters

Surgical Instruments

Bone Cements

Spectacles

Operating Tables

Artificial Limbs

Stethoscopes

Surgical gloves

Defibrillators

Hospital Beds

Aspirators

Swabs

Medical Device Sector

Potentially > 400,000 devices on the market (>10,000 families)

Contribution to Healthcare

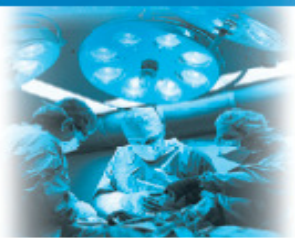
- Prevention
- Screening
- Diagnosis
- Treatment
- Rehabilitation
- Improvement of Quality of Life
- Reducing the Cost of Healthcare

Differences between drugs and medical devices

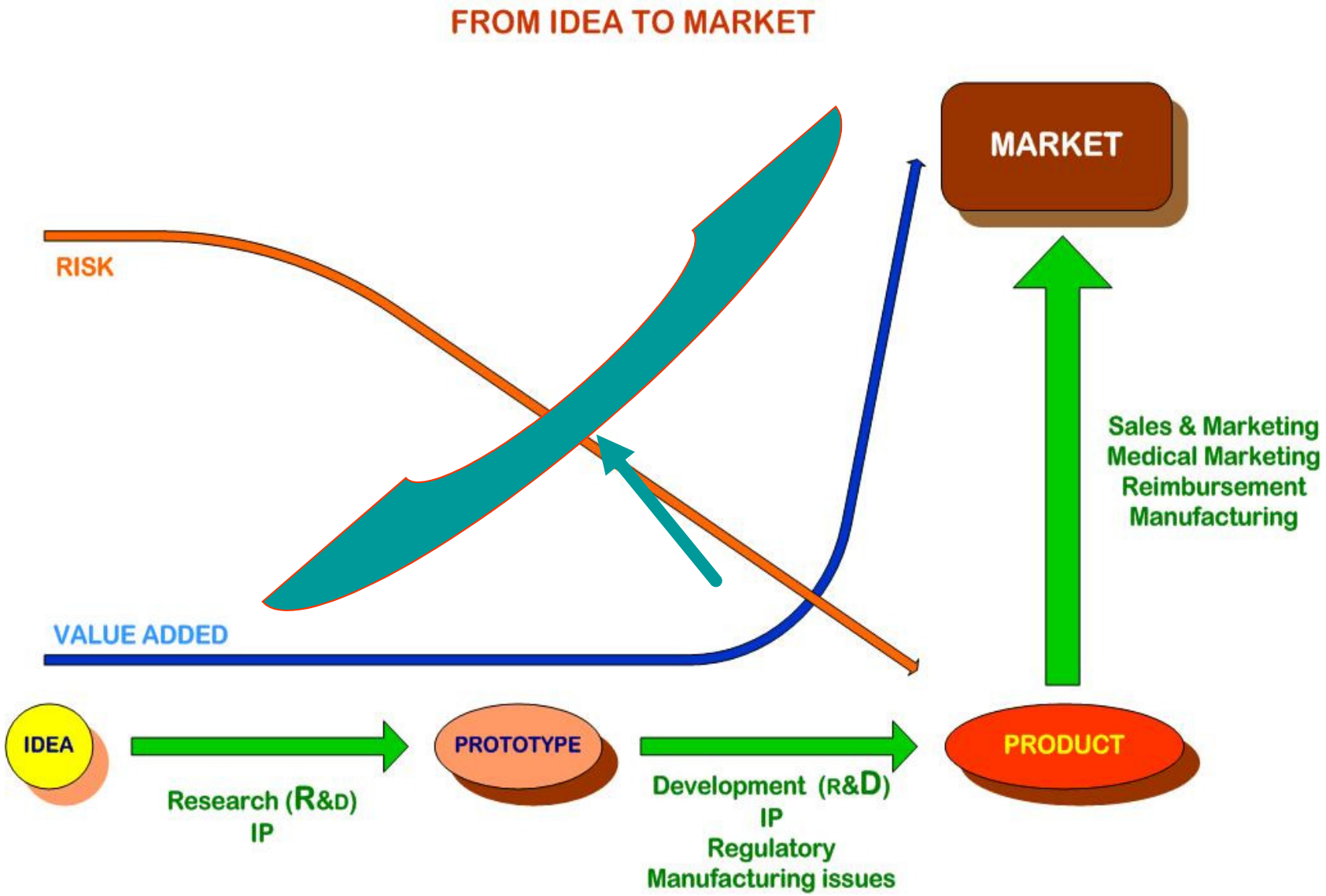
PRODUCTS

more than 10.000		limited number
designed to perform certain functions based on quality, safety and performance		development by trial and selection on basis of quality, safety and efficacy
generally based on mechanical, electrical and/ or materials engineering		based on pharmacology and chemistry now encompassing biotechnology and genetic engineering
generally act by physical means		biologically active: effective when absorbed into the human body
continuous innovation and iterative improvements based on new science, technology and available materials		continuous innovation and some improvements based on new science and technology
short product lifecycle and investment recovery period (typically 18 months on the market) the majority of new products typically bring added functions and clinical value based on incremental improvements		extensive product lifecycle and long investment recovery period
high cost of distribution high cost of user training and education provision of service and maintenance for high tech devices		low distribution cost in most cases, no service and maintenance
often integral to clinical procedure, so user education and training are essential for safe and effective use		training required for use much less intensive than for high tech medical devices

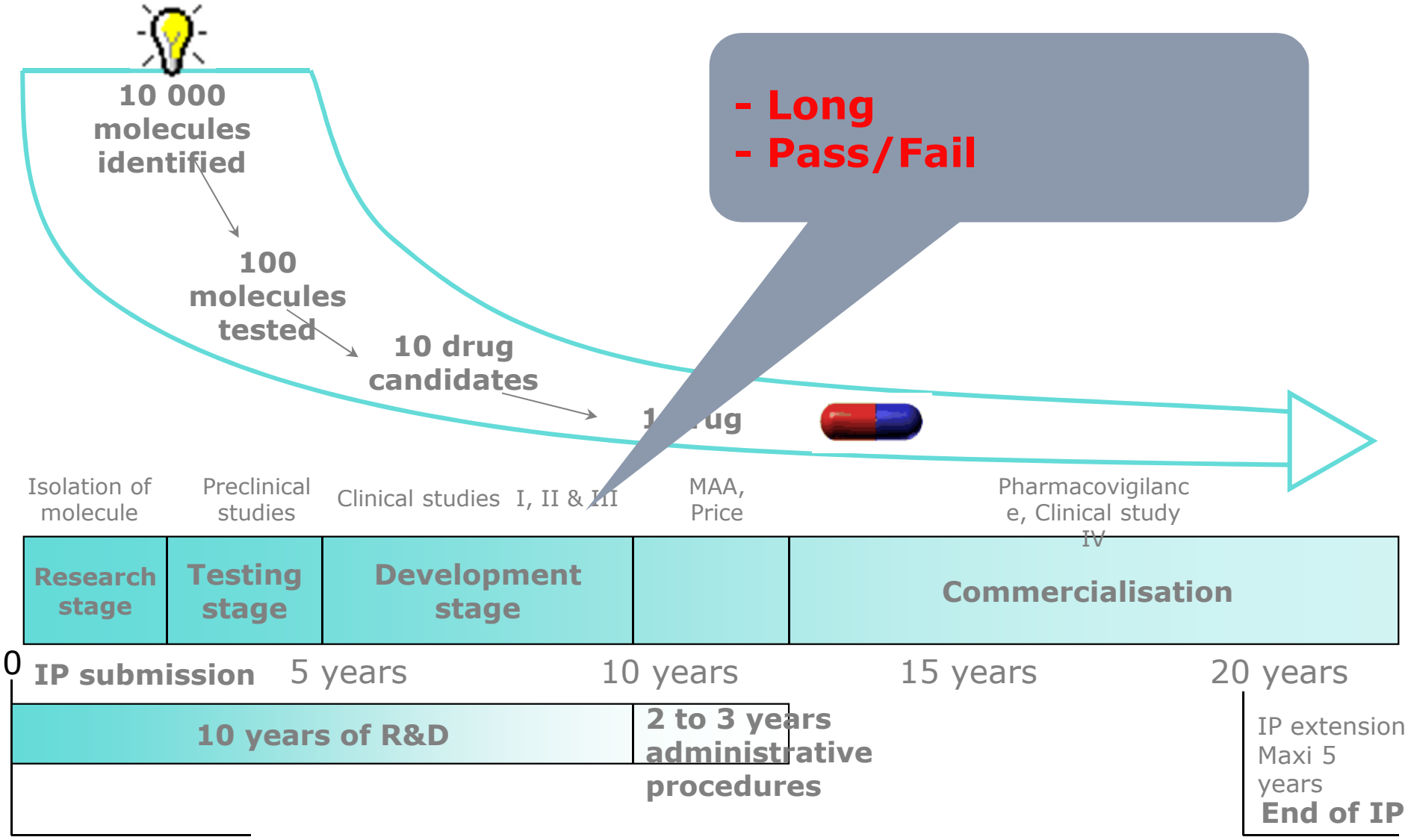
EU REGULATION

based on the "New Approach" (CE marking) applicable processes depend on risk-category government-appointed Notified Bodies certify the conformity assessment procedures improvements often result from user feedback		prescriptive approach: pre-market approval/ licensing of individual product

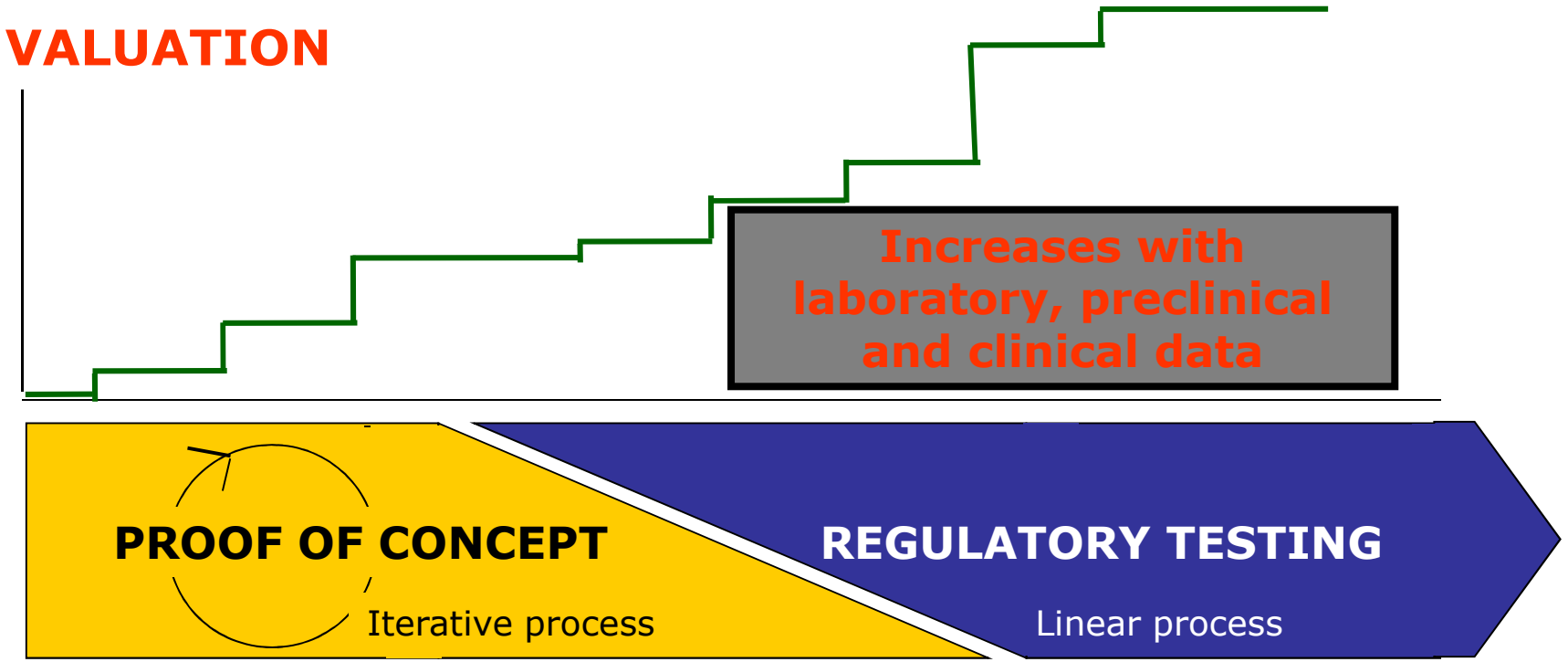
Valuation

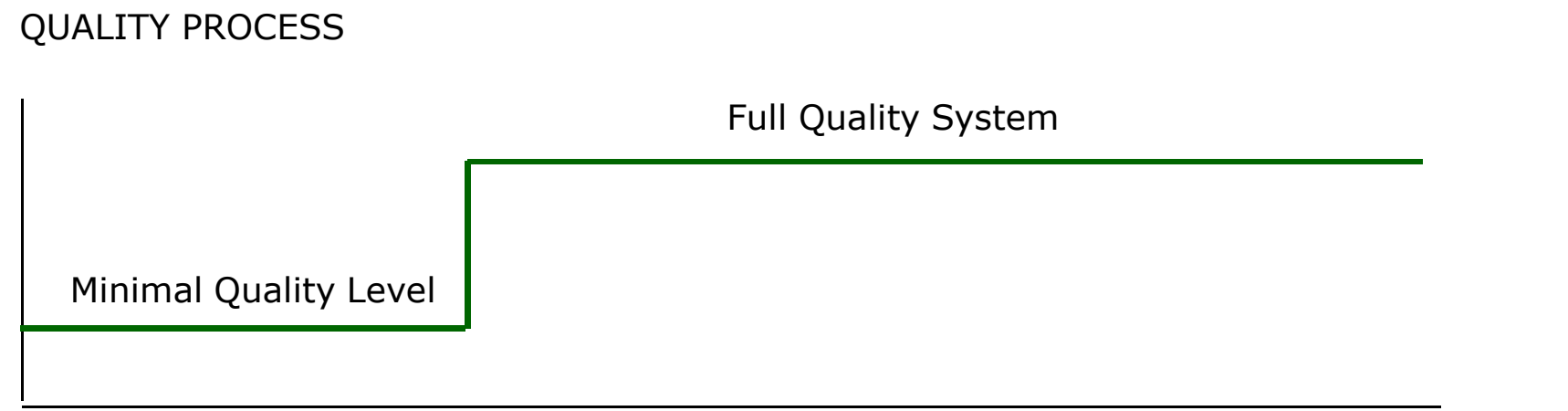

FROM IDEA TO MARKET
MARKET
RISK
VALUE ADDED
Sales & Marketing
Medical Marketing
Reimbursement
Manufacturing
IDEA
PROTOTYPE
PRODUCT
Research (R&D)
IP
Development (R&D)
IP
Regulatory
Manufacturing issues

From Idea to Drug



Evolution of MD Development Process



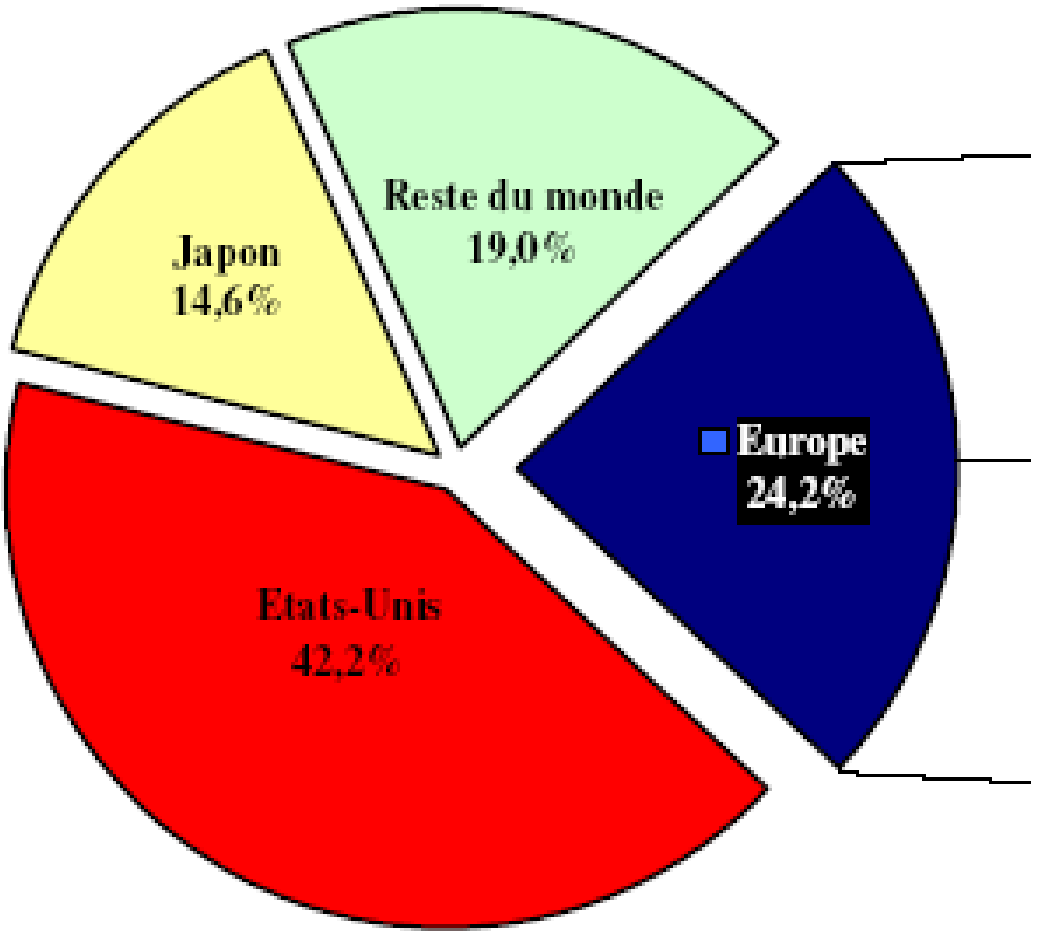


Medical Devices

European and Worldwide Growth

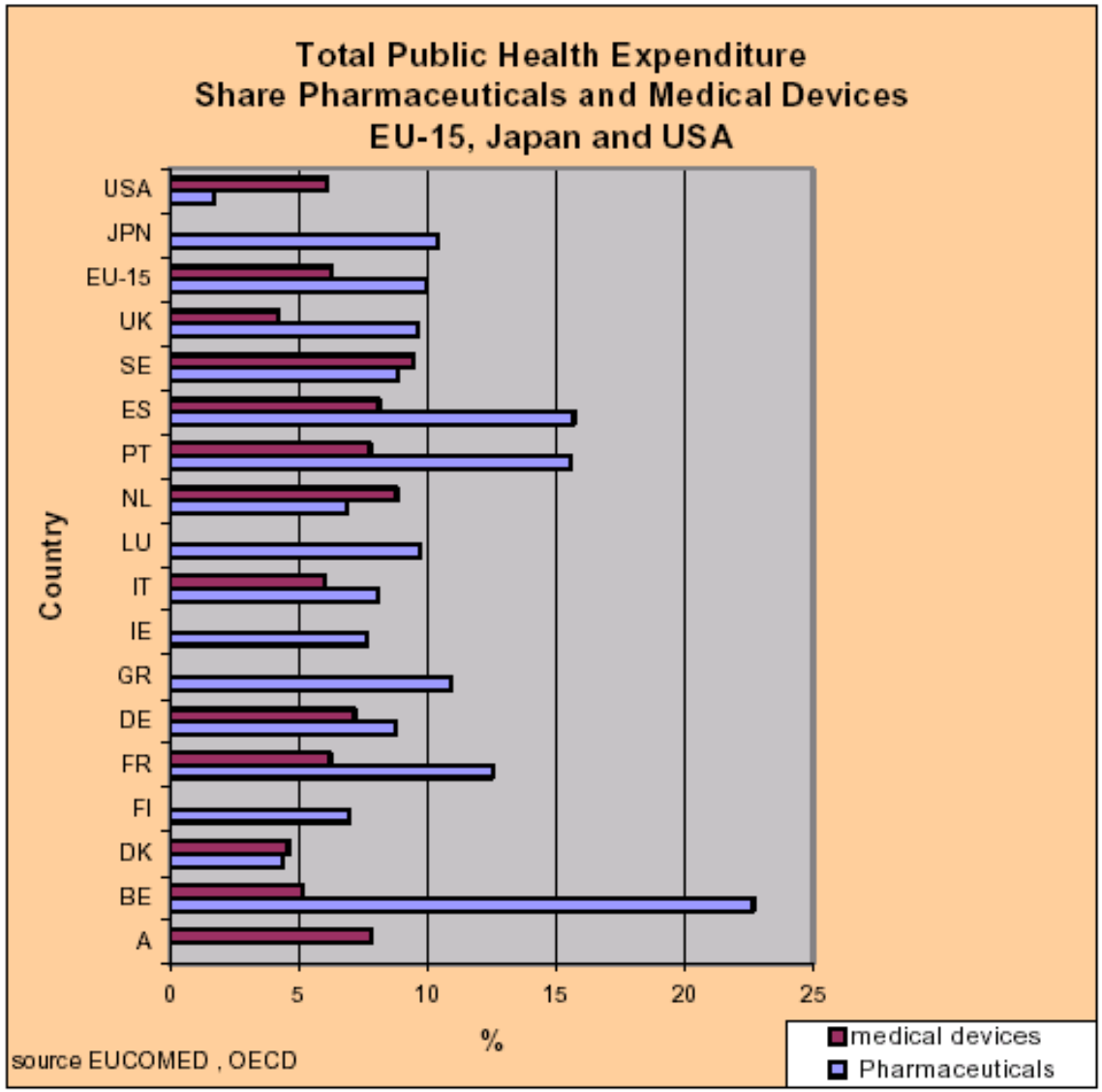
Trends and Niche Products

Medical Devices Market



Données EUCOMED

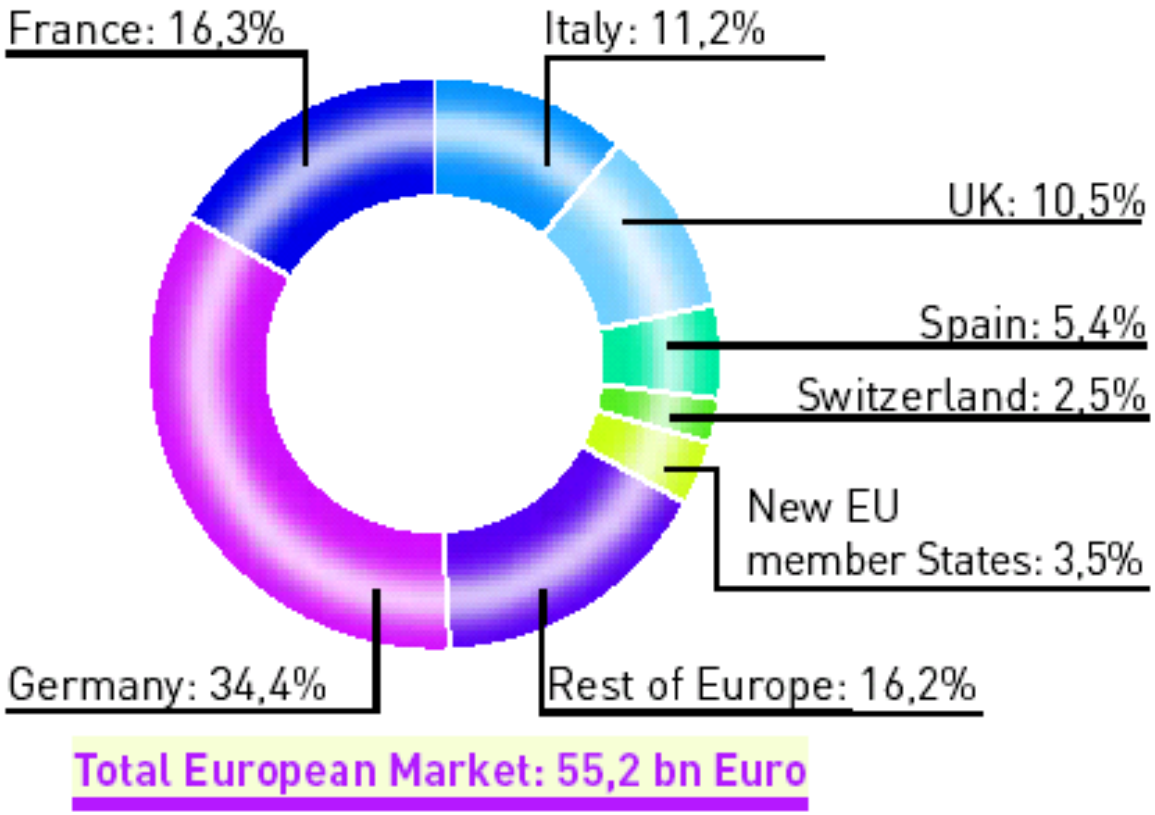
European Medical Technology Market Position



Commission Communication on Medical Devices

- **Europe 2nd largest market after USA, followed by Japan**
- **Devices no longer overshadowed by pharmaceuticals - some countries devices outstrip pharma**
- **Public expenditure believed increasing - offset against benefits - net effects positive**
- **Highly innovative**
- **Last Commission EU competitiveness study 2003 - next report expected July 15**

European Medical Technology Market Split %



	Bn Euro
World Market	**184**
• **Europe**	**55.2**
• **USA**	**79.3**
• **Japan**	**20.0**
=	**154.5 (or 83%)**

Source: Eucomed Member Associations, Medistat and Eucomed calculation

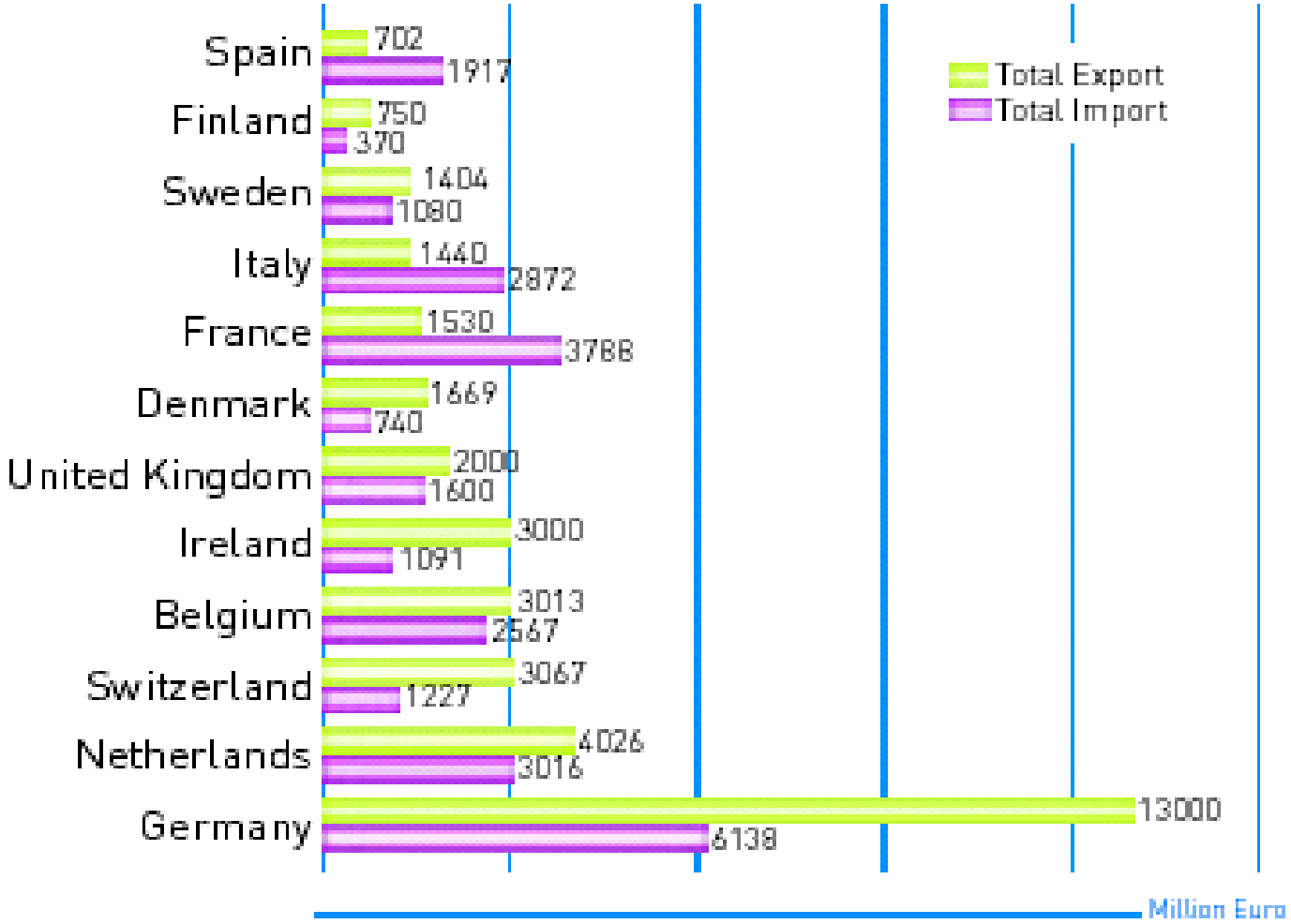
Expenditure in Medical Technology and Total Healthcare Expenditure

Country	Population 1000	THE in Bn Euro	THE/GDP in %	EMT in Bn Euro	EMT/THE in %
Austria	8.092	16,9	7,9	0,73	4,3
Belgium	10.397	22,7	9,0	0,82	3,6
Cyprus	728	0,6	6,1	0,03	4,5
Czech Republic	10.211	4,7	7,3	0,37	7,9
Denmark	5.398	15,2	8,6	0,87	5,7
Estonia	1.351	0,4	5,8	0,04	10,8
Finland	5.220	9,4	7,0	0,45	4,8
France	59.896	139,0	9,5	9,00	6,5
Germany	82.545	221,2	10,7	19,00	8,6
Greece	11.047	12,2	9,4	0,54	4,4
Hungary	10.115	3,9	6,8	0,36	9,2
Ireland	4.025	7,4	6,5	0,36	4,9
Italy	57.482	106,7	8,6	6,16	5,8
Latvia	2.319	0,5	5,8	0,06	11,5
Lithuania	3.447	0,8	5,7	0,06	8,3
Luxembourg	451	1,2	5,6	0,05	4,1
Malta	400	0,9	8,8	0,02	1,7
Netherlands	16.258	38,2	8,9	2,50	6,5
Norway	4.514	15,0	8,0	0,93	6,2
Poland	38.194	12,5	6,3	0,77	6,1
Portugal	10.480	11,3	9,2	0,60	5,3
Slovak Republic	5.381	1,3	5,7	0,11	8,6
Slovenia	1.997	1,9	8,0	0,13	7,1
Spain	40.978	48,8	7,5	3,00	6,1
Sweden	8.975	21,3	8,7	1,08	5,1
Switzerland	7.233	30,5	11,1	1,36	4,5
United Kingdom	59.518	121,3	7,6	5,80	4,8
Europe Total/average	466.652	865,8	8,6	55,20	6,4
United States	284.797	1553,3	13,9	79,281	5,1

40%

Source: OECD, European Commission, Eucomed Member Associations and Medistat

Import and Exports of Medical Technology



Source: Eucomed Member Associations and Medistat

Medical Technology Market Examples 1/2

Orthopedics market :

Reconstructive joint replacement: 27%
Spinal implants : 26%
Bone Graft : 10%
Arthroscopy : 9%
Trauma : 7%
Bone growth stimulators : 2%
Powered instruments : 2%
Soft goods : 6%
CMF: 3%

Other : 7%

Medical Technology Market Examples 2/2

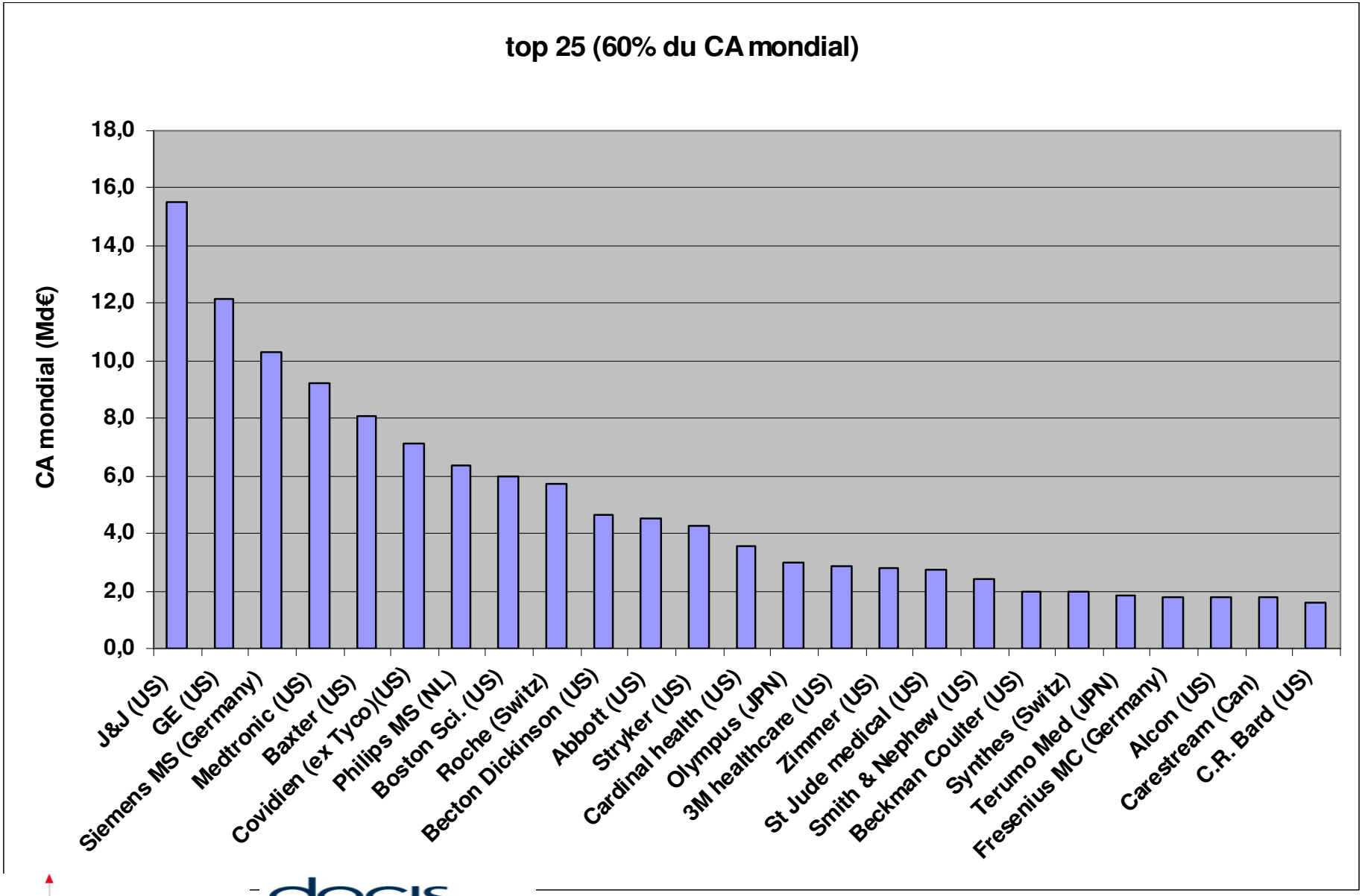
Orthopedics market (2010) :

Germany : 25% EU = 632 M$
France : 20% EU = 499 M$
UK : 15% EU = 372 M$
Italy : 14% EU = 349 M$
Spain : 10% EU = 236 M$
Scandinavia : 4% EU = 120 M$

US : 58% = 7.1 B$
Europe : 20% = 2.45 B$
Asia : 15% = 1.9 B$
Amaricas: 7% = 0.9 B$

Surgical Dynamics (Tyco)
Zimmer (BMS)
Depuy (J&J)
Stryker
Sulzer Medical
Synthes – Stratec
Medtronic Sofamor Danek
Biomet
Smith & Nephew
Hanger
Orthofix International
OrthoLogic
Osteotech
Advanced Tissue Sciences
Integra
Interporre Cross International
Bionx
Corin
Raymedica
Wright Medical Thechnology

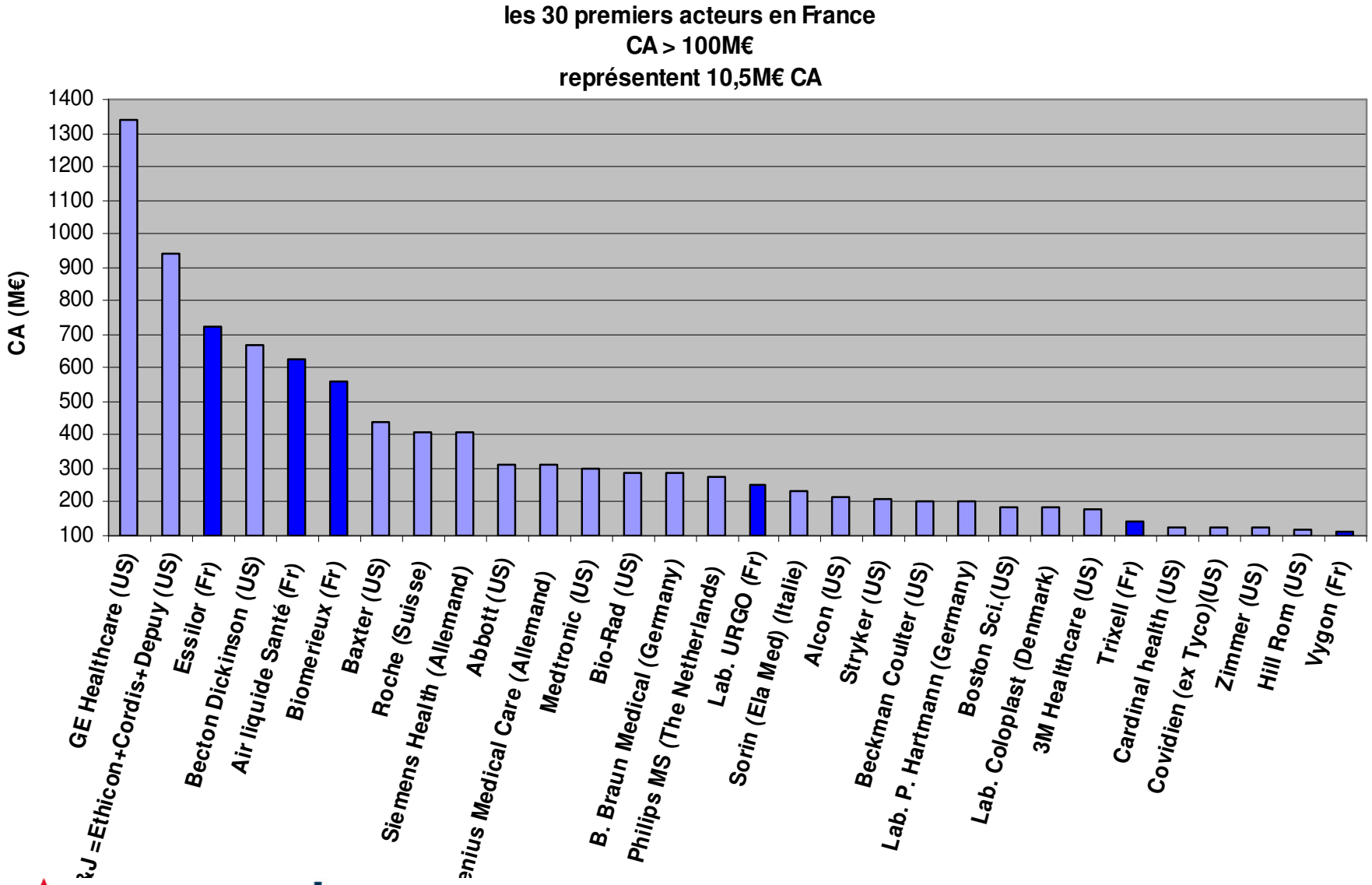
Les 25 acteurs industriels mondiaux



PIPAME
Pôle interministériel de prospective et d'anticipation des mutations économiques

dgcis
direction générale de la compétitivité de l'industrie et des services

Les 30 premiers acteurs en France : une entreprise sur cinq est nationale



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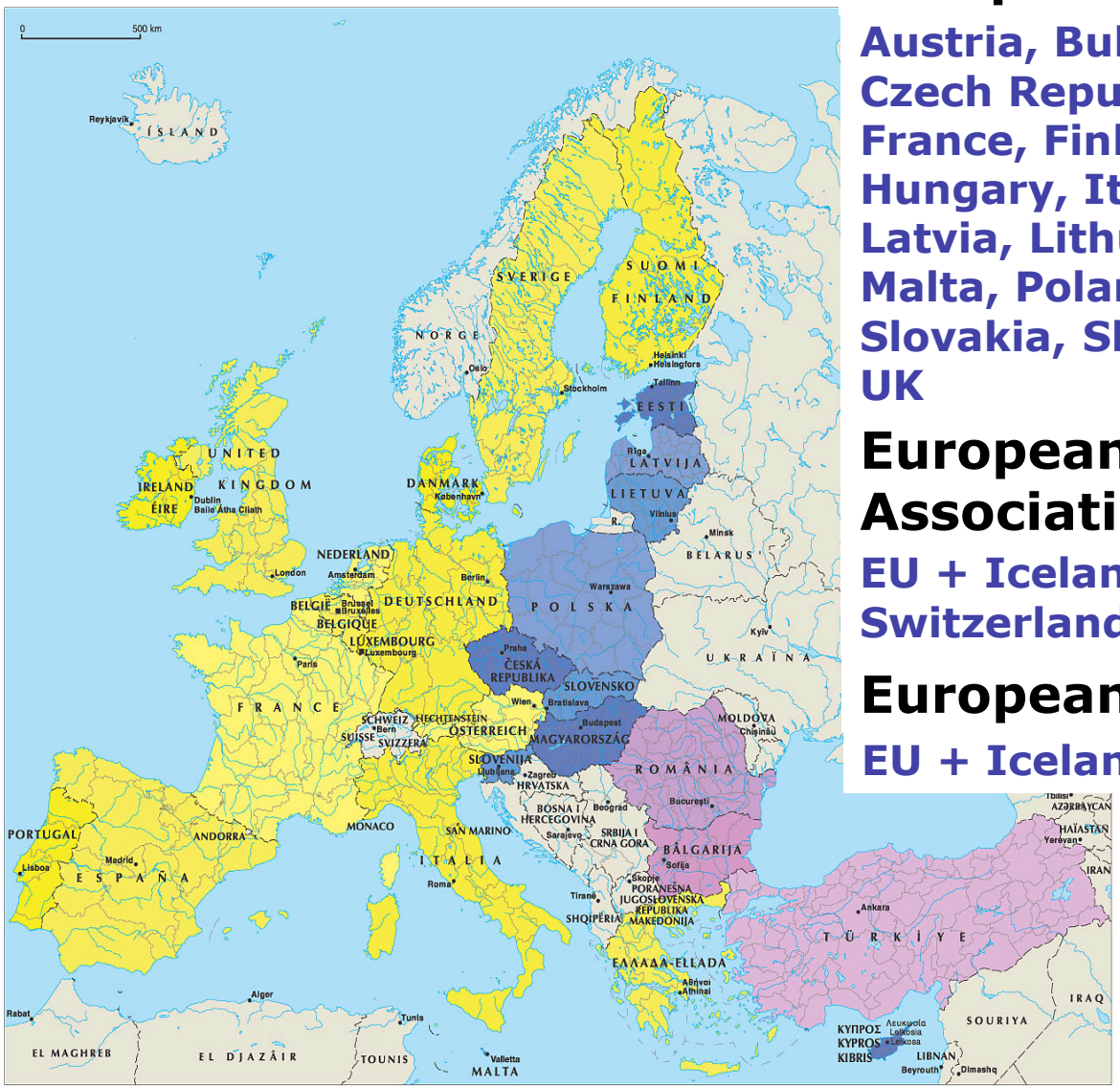
European Contracting Member States



European Union (EU) - 27

Austria, Bulgaria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, France, Finland, Germany, Greece, Hungary, Italy, Ireland, Netherlands, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK

European Free Trade Area Association (EFTA) - 4

EU + Iceland, Liechtenstein, Norway, Switzerland

European Economic Area (EEA)

EU + Iceland, Liechtenstein, Norway

EU Candidates + 2

Turkey, Croatia

EC Medical Devices Directives

To mitigate in part the **RISKS** posed by **MEDICAL DEVICES** we have devised **PRE / POST-MARKET CONTROLS:**

- **90/385/EEC Active Implantable Medical Devices**
- **93/42/EEC Medical Devices**
- **98/79/EC In Vitro Diagnostic Medical Devices**
- **2000/70/EC Devices Incorporating Human Blood Derivatives**
- **2003/12/EC Reclassification of Breast Implants**
- **2003/32/EC Tissues of Animal Origin**
- **2005/50/EC Reclassification of orthopaedic articulation devices**
- **2007/47/EC Amendments of 90/385 & 93/42**

http://europa.eu.int/comm/enterprise/medical_devices/index_en.htm

Medical Devices Directive 93/42/EEC

Scope and Definitions

Medical Device: Any instrument, apparatus, appliance, material software or other article, including software required for its proper functioning, whether used alone or in combination, ***intended by the manufacturer*** to be used solely or principally for the purpose of:

- diagnosis, prevention, monitoring, treatment, alleviation of disease
- diagnosis, monitoring, treatment or alleviation of injury or handicap
- investigation, replacement or modification of the anatomy or of a physiological process
- control of conception

and does not achieve its ***principal intended action*** in or on the human body by pharmacological, immunological or metabolic means but which may be assisted in its function by such means

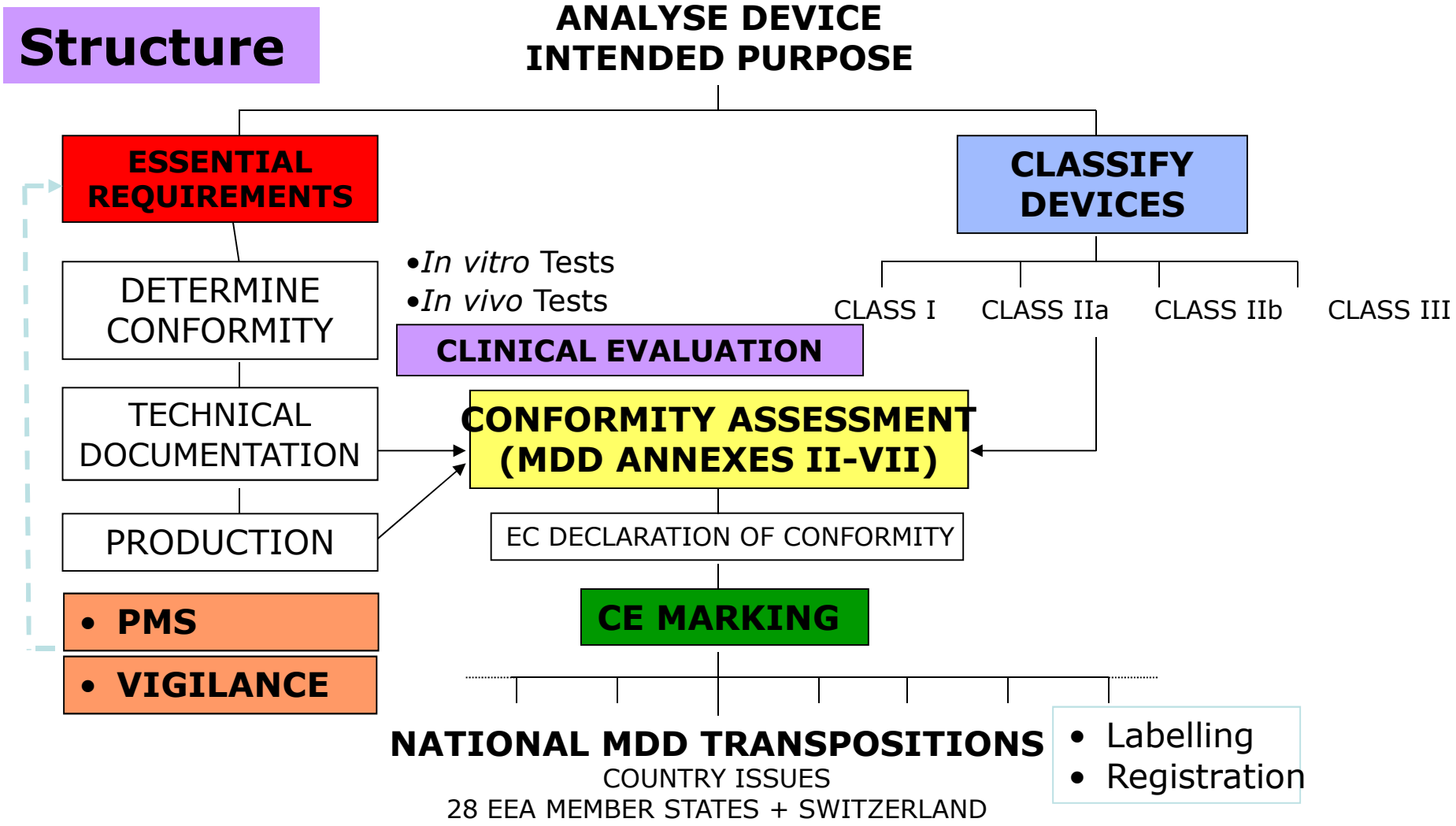
MDD Article 1.2(a)

Medical Devices Directive 93/42/EEC

Scope and Definitions

- Medical devices and their accessories
- MDD excludes:
  - AIMDs, IVDs covered by own Directives
  - medicinal and cosmetic products
  - human blood, blood products, plasma, or cells, or devices incorporating them (but not HBD)
  - human transplants, tissues or cells
  - animal tissues or cells unless rendered non-viable
  - personal protective equipment

Medical Devices Directive 93/42/EEC



Medical Devices Directive 93/42/EEC

Single European Market

27 Different Versions

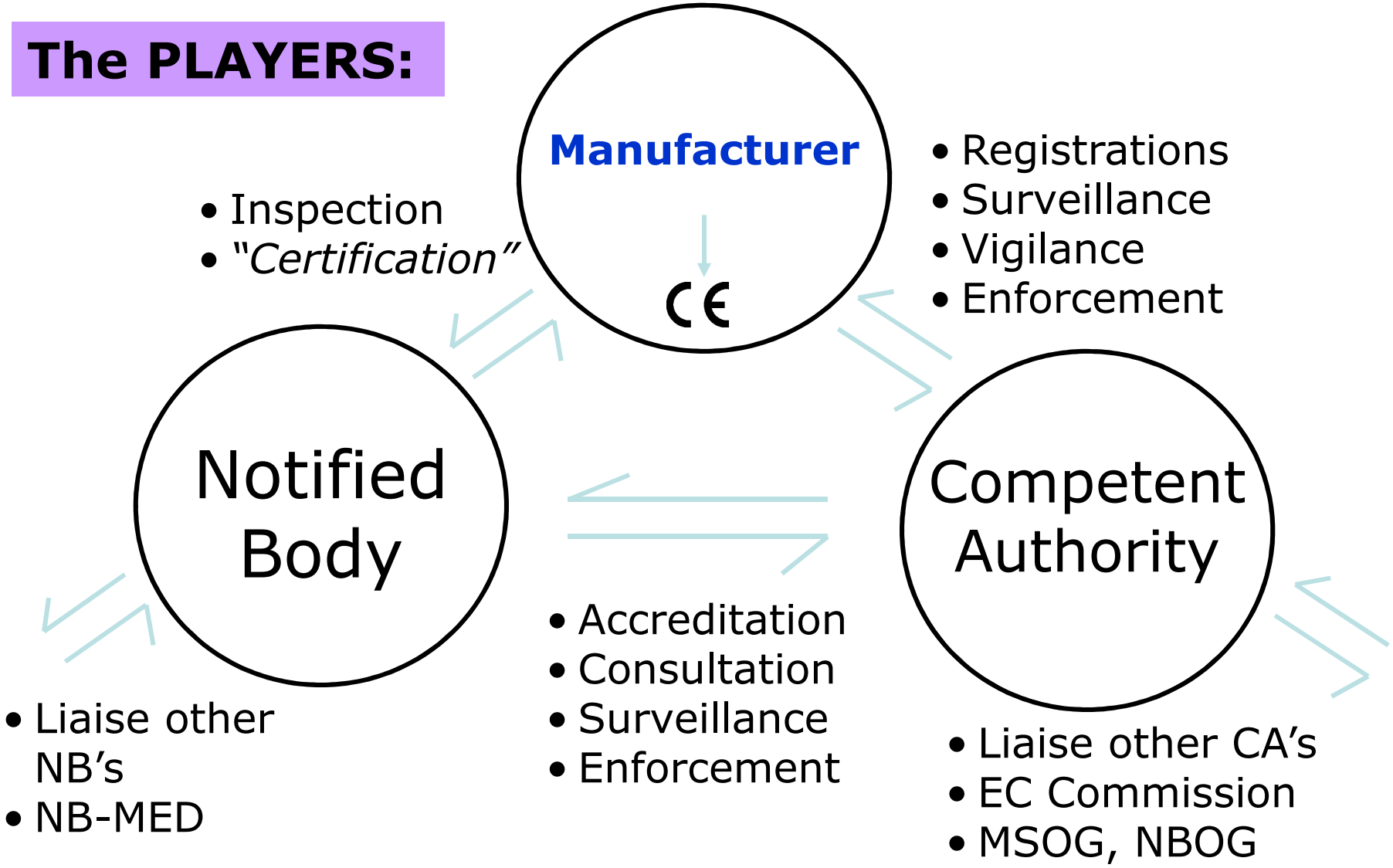
29 with EEA + Switzerland

29 Competent Authority Interpretations (note + 90 counting State authorities)

+ 75 Notified Bodies

Medical Devices Directive 93/42/EEC

The PLAYERS:



Comparison Regulations:

	EEA		USA		JAPAN
Regulator (enforcement)	CA's		FDA		Prefecture
Authorisation	NB's		FDA Centre		MHLW
Definitions, Classification	✓	≠	✓	≠	✓
General Requirement	Safety and Performance		Safety and Effectiveness		Safety and Effectiveness
Specific Criteria	Essential Requirements		X		X
Conformity Assessment	Options		Prescribed		Prescribed
Emphasis	Self-regulation		510K, PMA		Notification and Licensing,
Full Quality System (design and production)	Optional (but not available for Class I)		Mandatory Class II+III (some Class I)		Mandatory (but excludes most Class I)

Impact of MDD Revisions

(as defined by **2007/47/EC** amending **93/42/EEC**)

Conducting Medical Device Studies

Impact of MDD Revisions

Setting the Scene:

Timelines MDD Revision (as defined by 2007/47/EC amending 93/42/EEC)

- **05 September 2007**: Date of Directive 2007/47/EC
- **21 September 2007**: Date of Publication in the OJEU
- **11 October 2007**: Date that Directive enters into force (ref. *Article 5)*
- **21 December 2008**: Final Date by which EU Member States need to have transposed the Directive into corresponding National Legislation (ref. *Article 4*, 1st paragraph)
- **21 March 2010**: Directive becomes mandatory throughout EU; "old MDD" no longer applicable (ref. *Article 4*, 2nd paragraph)

Impact of MDD Revisions

(as defined by **2007/47/EC** amending **93/42/EEC**)

Assess Relevant Changes to MDD Impacting manufacturer

Clinical Data

&

Conformity Assessment Procedures,

Device –Drug Combinations,

Labelling,

PMS,

Miscellaneous

Impact of MDD Revisions

(as defined by **2007/47/EC** amending **93/42/EEC**)

Changes to MDD Impacting manufacturer : Clinical Data

1. **Added Definition** [ref. Article 1(k)]
2. **Additional Requirements** [ref. Art. 15 and Annex]
3. **Significant Amendment** [ref. Annex X]
4. **More Explicit Essential** [ref. Annex I, ER 6bis]
5. **More Explicit reference** [ref. Annex II, 3.2(c)]

Impact of MDD Revisions

(as defined by **2007/47/EC** amending **93/42/EEC**)

Changes to MDD Impacting manufacturer : Clinical Data

1.Added Definition [ref. Article 1(k)]

k) “données cliniques”:

informations relatives à la sécurité et aux performances obtenues dans le cadre de l'utilisation d'un dispositif. Les données cliniques proviennent:

- des investigation(s) clinique(s) du dispositif concerné, ou

- des investigation(s) clinique(s), ou d'autres études citées dans la littérature scientifique, d'un dispositif similaire pour lequel l'équivalence avec le dispositif concerné peut être démontrée, ou

- des rapports, publiés ou non, relatifs à une autre expérience clinique acquise sur le dispositif ou un dispositif similaire pour lequel l'équivalence avec le dispositif concerné peut être démontrée.»

Impact of MDD Revisions

(as defined by **2007/47/EC** amending **93/42/EEC**)

Changes to MDD Impacting manufacturer : Clinical Data

2. Additional Requirements [ref. Art. 15 and Annex]

.....

7. Le fabricant ou son mandataire notifie aux autorités compétentes des États membres concernés la fin de l'investigation clinique, en justifiant, le cas échéant, l'arrêt prématuré de l'investigation. Si l'investigation clinique a été interrompue prématurément pour des raisons de sécurité, la notification est adressée à tous les États membres et à la Commission. Le fabricant ou son mandataire tient le rapport visé à l'annexe X, point 2.3.7, à la disposition des autorités compétentes.»

More Transparency across EU / Status Clinical Investigations no longer Confidential

Impact of MDD Revisions

(as defined by **2007/47/EC** amending **93/42/EEC**)

Changes to MDD Impacting manufacturer : Clinical Data

3. Significant Amendment [ref. Annex X]

Annex X, pt. 1.1 amended

Section 6 of Annex I, must be based on clinical data.

For High Class Devices clinical study becomes Default. Rigorous Justification required if alternative

Annex X, new pt. 1.1

More Rigorous Substantiation expected if clinical data are not used …but remains possible.

Annex X, pt. 2.3.5 amended

Will require additional and prompt SAE reporting (also non-device related) to additional CA's on top of the CA of the country where the SAE occurred

Impact of MDD Revisions

(as defined by **2007/47/EC** amending **93/42/EEC**)

Changes to MDD Impacting manufacturer : Clinical Data

4. More Explicit Essential [ref. Annex I, ER 6bis]

"Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X."

Question if the "must" is not in contradiction with quoted statement in Annex X, pt. 1.1d (previous slide !)

Manufacturers need to Update their Essential Requirements Checklist (Note: ER 14 needs to be deleted at same time and other ER's updated as needed).

Impact of MDD Revisions

(as defined by **2007/47/EC** amending **93/42/EEC**)

Changes to MDD Impacting manufacturer : Clinical Data

5. **More Explicit reference** [ref. Annex II, 3.2(c)]

> "*The procedures for monitoring and verifying the design of the products,* ***including the corresponding documentation****, and in particular:[…] the* ***clinical evaluation*** *referred to in Annex X*".

Take into account when compiling Design Dossier / Technical File.

Impact of MDD Revisions

(as defined by **2007/47/EC** amending **93/42/EEC**)

Changes to MDD Impacting manufacturer : Clinical Data

5. More Explicit reference [ref. Annex II, 3.2(c)]

"*The procedures for monitoring and verifying the design of the products,* ***including the corresponding documentation****, and in particular:[…] the* ***clinical evaluation*** *referred to in Annex X*".

- **Take into account when compiling Design Dossier / Technical File.**

Impact of MDD Revisions

(as defined by **2007/47/EC** amending **93/42/EEC**)

Take home message

Relevant Changes to MDD Impacting manufacturer

The need of Clinical Data

Clinical Investigations are needed

Status Clinical Investigations no longer "Confidential"

More Transparency across EU

Directive 2007/47/CE (4/11) : réglementation applicable

- **La conformité aux EE doit inclure une évaluation clinique (EE 6bis)**
- **DMIA et DM de classes III doivent faire l'objet d'investigations cliniques sauf si le recours aux données existantes peut être dûment justifié**
- **Mise à jour de l'évaluation clinique avec les données obtenues par la surveillance après commercialisation**
- **Si pas de suivi clinique post-commercialisation : justification nécessaire**

Directive 2007/47/CE (6/11) : REGLEMENTS

- **Propositions publiées le 26 septembre 2012**
  (2012/0266 relatif aux DMs et DMIAs) et
  (2012/0267 relatif aux DMDIV)
- **Pourraient être adoptées en 2014 ?**
- **Applicable 3 ans après publication au JO**
  (dès 2017?)
- **Règlement ≠ Directive :**
  - **Pas de transposition, donc pas d'interprétation possible!**

Directive 2007/47/CE (7/11) :

- **Chapitre VI : Articles 49 à 60**
  - **Evaluation clinique & investigation clinique**
    - **+ détaillé que dans les directives actuelles**
    - **Enregistrement électronique des investigations cliniques**
    - **Délai soumission : max 35 jours + 6 jours**
    - **Si plusieurs soumissions en UE : possibilité d'une soumission unique à l'échelle Européenne**

Directive 2007/47/CE (10/11) :

- **Annexe XIII:**
  - **Evaluation clinique et suivi clinique post-commercialisation**
  - **Exigences mieux détaillées que dans les directives**
- **Annexe XIV:**
  - **Investigations cliniques**
    - **Description des méthodes**
    - **Documentation**
    - **Contenu IB / Protocole**

New System – ANSM Authorisation

Insurance

(CPH Art. R. 1121-7)

Minimum:

1,000,000 €	per victim
6,000,000 €	per research protocol
10,000,000 €	for total claims during one insurance year for several research protocols

New System – ANSM Authorisation

Main issues to consider

- **According to a ANSM presentation, based on experience**

- Incomplete data on the MD;
- Inadequate patient selection criteria;
- Duration of patient follow-up : not adequate for the study objectives;
- Patient information regarding the risks

New System – ANSM Authorisation

Experience from pilot phase

Based on ANSM experience :

Of 346 declarations made, 83 were done according to the pilot phase:

- **76% were given a favourable opinion at the first round;**
- **22% of cases:**
  - protocol changes suggested or
  - changes to the patient information
  - or supplementary information requested.
- **Only 2% non-authorisation issued**

The future

- New EU regulation for drug clinical trials coming into publication : changes within the existing system
- The new regulation regarding MD/AIMD & IVD will for sure make some changes within the present law and mainly for observational (non interventional) studies ?

Thanks for attention

Questions?

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NL ISO
14155-1

Première édition
First edition
2008

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Investigation clinique des dispositifs médicaux pour sujets humains – partie 1: Exigences générales

Clinical investigation of medical devices for human subjects – Part 1: General requirements

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Investigation clinique des dispositifs médicaux pour sujets humains – Partie 2 : Plans d'investigation clinique

Clinical investigation of medical devices for human subjects – Part 2: Clinical investigation plans

May 9, 2006

July 2, 2006

Nov 9, 2011