Policy Issues in Nanotechnology and Oncology
National Cancer Policy Forum Workshop, Institute of Medicine, Washington DC, July 12–13, 2010

Nanomedicines Challenges and Opportunities in a Global Development Environment

iMed.UL
Research Institute for Medicines and Pharmaceutical Sciences

Rogério Sá Gaspar
Faculdade de Farmácia da Universidade de Lisboa e
iMed.UL (Research Institute for Medicines and Pharmaceutical Sciences, http://www.imed.ul.pt)

Current positions

- *Full Professor, Faculty of Pharmacy University of Lisbon - FFUL (Portugal)*
- *Coordinator of Nanomedicine & Drug Delivery Systems research group at the Research Institute for Medicines and Pharmaceutical Sciences (iMed.UL), since 2007*
- *Member of the General Council at the University of Lisbon (Portugal), since 2008*
- *Member of the Medicines Evaluation Committee at INFARMED and different positions in European regulatory affairs (1995-2002 and since September 2008,Portugal)*
- *Member of adhoc expert group in nanomedicines at European Medicines Agency (since April 2009)*
- *Member of the coordination of MSc_s in Regulatory Affairs (since 2001), in Advanced Pharmacotechnics (since 2006) and in Pharmaceutical Engineering (since 2007) at FFUL*
- *Doctoral Programme in BioNanotechnology (University Lisbon, approved 2009, to be started)*
- *Member of the Executive Committee of EUFEPS since 2009 (liaison with Network in Pharmacogenetics/Pharmacogenomics, chair of Network in Regulation & Science 2010, currently establishing Network in Nanomedicine)*
- *Controlled Release Society (CRS), Adhoc group in Regulatory Affairs, since 2010*
- *Member of Board, Portuguese Society for Pharmaceutical Sciences (SPCF) since 2005*

- The views and opinions hereby expressed reflect only my personal opinion and not the views of institutions or organisations with which I'm or have been affiliated in the past or present

Nanotechnology and Oncology

What policies support cooperative research internationally?

RESEARCH
- how to increase the probability of viable candidates for clinical evaluation

What lessons can US regulators learn from regulation of nanotechnology in other countries?

What policies support product development and regulation internationally?

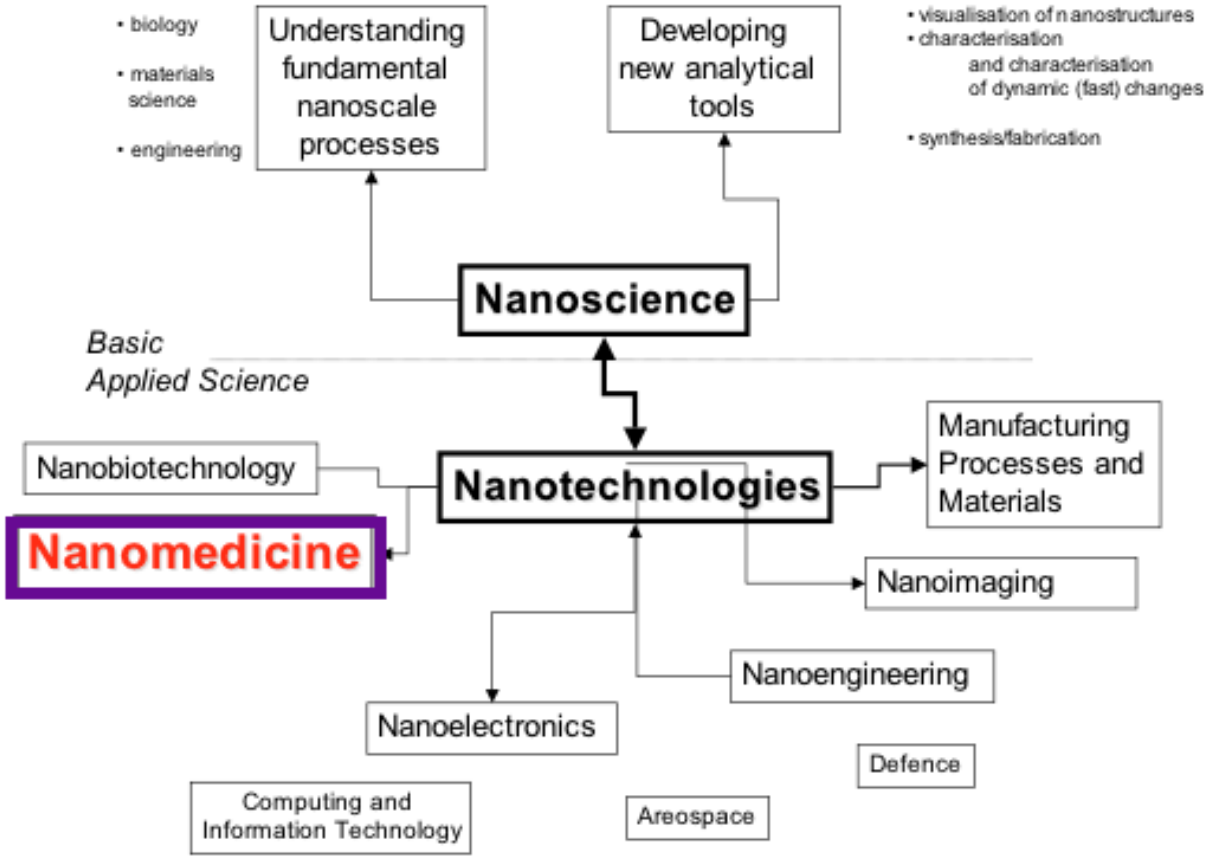
DEVELOPMENT
- how to increase the the probability of successful and timely product development

19-20 October 2006, Brussels

european nanosciences

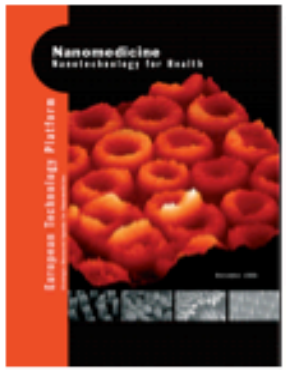
European Forum on Nanosciences: A Converging Approach Across Disciplines

A Converging Approach Across Disciplines.....



Build On Existing European Landscape ?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



nanomedicine
EUROPEAN TECHNOLOGY PLATFORM

October 2009

The **ETP Nanomedicine**, an initiative **led by industry** and set up together with the European Commission is addressing the **application of nanotechnology to achieve breakthroughs in healthcare**.

Diagnostics
- in vivo imaging
- In vitro diagnostics

Drug Delivery
- Nanopharmaceuticals
- Nanodevices

Regenerative Medicine
- Smart Biomaterials
- Cell Therapies

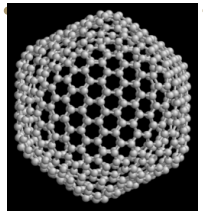
Evolution of Nanomedicines - drug targeting and controlled release

1970s | 1980s | 1990s | 2000s | 2009

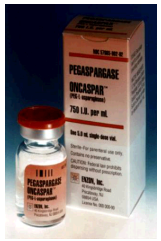
Liposomes

Doxil

nanocrystals for oral use

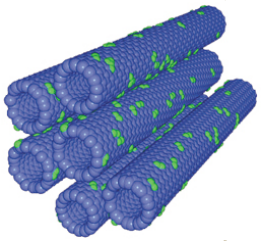


Polymer-protein and -drug conjugates



PEG-interferon α

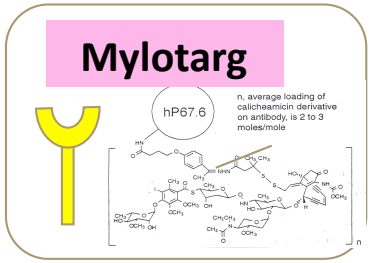
Neulasta

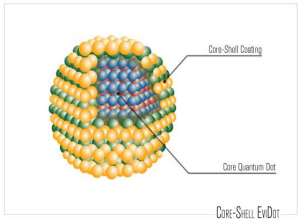


XYOTAX

Antibody conjugates

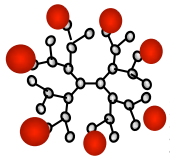
Mylotarg

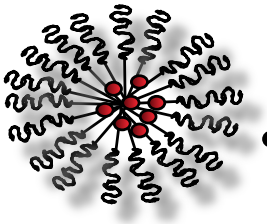




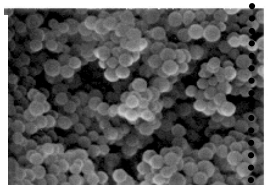
polymer micelles

dendrimers

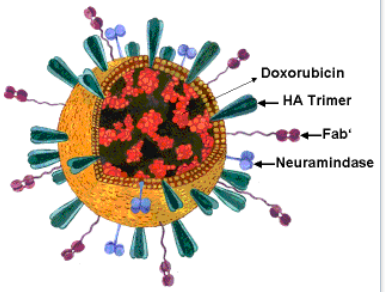




Nanoparticles



SP1049C



Abraxane

Controlled Release Depot Formulations

Zoladex
Leupron Depot

Gliadel

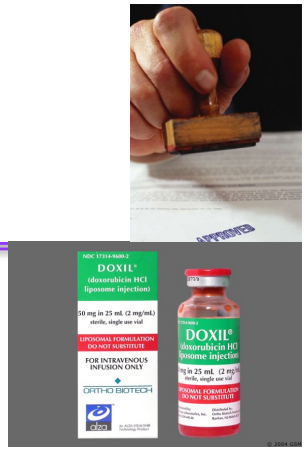
European regulatory scenario

- **Therapeutics**
  - Medicinal Products are covered by national and European agencies, within a networking system, under currently existing four procedures
    - national,
    - mutual recognition,
    - decentralised
    - and centralised (this one managed by EMA)
- **Imaging**
  - In vivo imaging agents are classified as medicinal products
- **Diagnostics**
  - Diagnostic agents have a different and complex regulatory frame, overlaping with a number of existing medical devices

Nanocrystals: Current Status

TRADENAME	DRUG	INDICATION	TECHNOLOGY	COMPANY	STATUS
Rapamune®	Rapamycin	Immunosuppressive	Nanocrystal® Elan	Wyeth	Marketed
Emend®	Aprepitant	Anti-emetic	Nanocrystal® Elan	Merck	Marketed
Tricor®	Fenofibrate	Hypercholesterolemia	Nanocrystal® Elan	Abbott	Marketed
Megace ES®	Megestrol	Anti-anoretic	Nanocrystal® Elan	Par Pharm.Co.	Marketed
Triglide®	Fenofibrate	Hypercholesterolemia	IDD-P® Skyepharma	Sciele Pharma Inc.	Marketed
Semapimod®	Guanylhydrazone	TNF-α inhibitor	own	Cytokine Pharmasciences	Phase II
Paxceed®	Paclitaxel	Anti-inflammatory	unknown	Angiotech	Phase III
Theralux®	Thymectacin	Anti-cancer	Nanocrystal® Elan	Celmed	Phase II
Nucryst®	Silver	Anti- bacterial	own	Nucryst Pharm.	Phase II

Doxil/Caelyx: Stealth® Liposomes



Caelyx is indicated:

- **As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.**
- **For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.**
- **For treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (< 200 CD4 lymphocytes/mm3) and extensive mucocutaneous or visceral disease.**
  - **Caelyx may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline).**

Myocet

Myocet, in combination with cyclophosphamide, is indicated for the first line treatment of metastatic breast cancer in women.

Antitumour efficacy summary for combination and single-agent studies

	Myocet/CPA (60/600 mg/m^2) (n=142)	Dox 60/CPA (60/600 mg/m^2) (n=155)	Myocet/CPA (75/600 mg/m^2) (n=80)	Epi/CPA (75/600 mg/m^2) (n=80)	Myocet (75 mg/m^2) (n=108)	Dox (75 mg/m^2) (n=116)
Tumour response rate	43%	43%	46%	39%	26%	26%
Relative Risk (95% C.I.)	1.01 (0.78-1.31)		1.19 (0.83-1.72)		1.00 (0.64-1.56)	
Median PFS (months)[a]	5.1	5.5	7.7	5.6	2.9	3.2
Risk Ratio (95% C.I.)	1.03 (0.80-1.34)		1.52 (1.06-2.20)		0.87 (0.66-1.16)	

Abbreviations: PFS, progression-free survival; Dox, doxorubicin; Epi, epirubicin; Relative Risk, comparator taken as reference; Risk Ratio, Myocet taken as reference

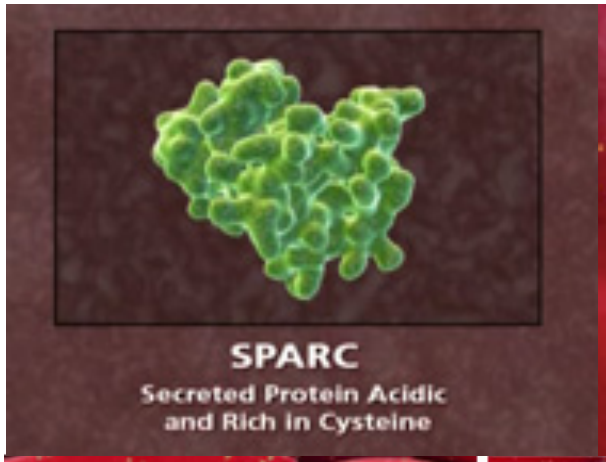
[a] Secondary endpoint

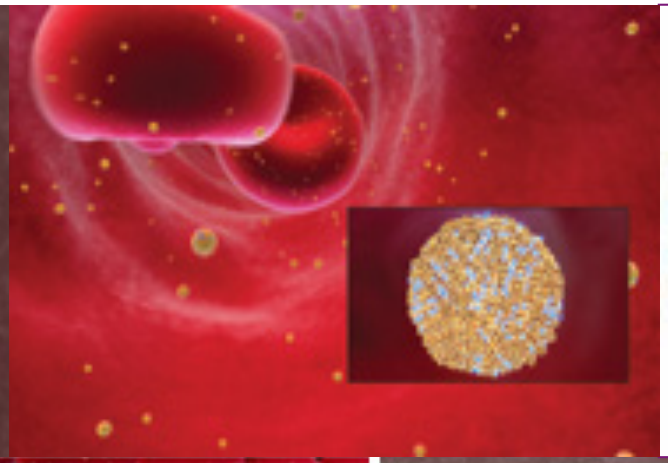
EMEA, European Public Assessment Report (EPAR), Summary of Product Characteristics (SmPC), 2007

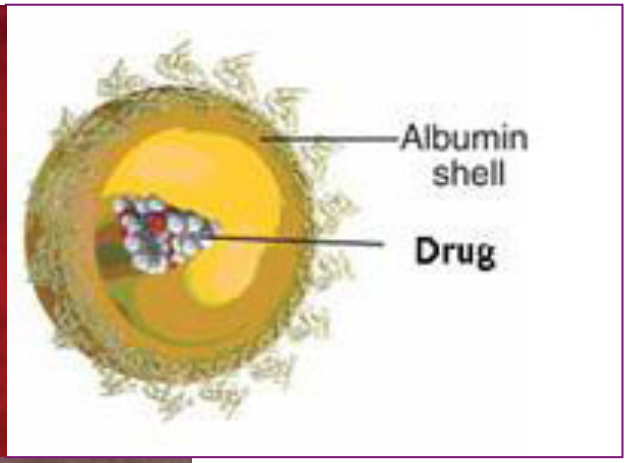
Liposomal and Lipidic Products (Many products in clinical development)

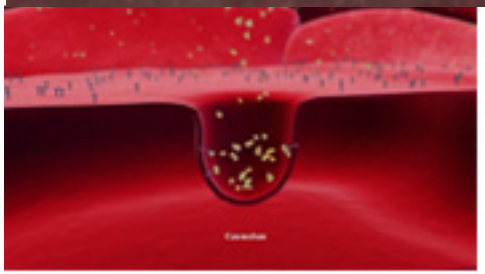
TRADENAME	DRUG	INDICATION	COMPANY	STATUS
AmBisome®	Amphotericin B	fungal infections	Astellas Pharma	Marketed
ABELCET®	Amphotericin B	fungal infections	Sigma-Tau Pharmaceutical	Marketed
DOXIL/Caelyx®	Doxorubicin	cancer	Schering-Plough	Marketed
Daunoxome®	Daunorubicin	cancer	Gilead Sciences	Marketed
MEPACT®	MTP	cancer	Takeda	Marketed
Visudyne	Verteporfrin	age related macular degeneration	Novartis	Marketed
Definity®	Octafluoropropane	Ultrasound imaging	Dupont Merck	Marketed
Myocet®	Doxorubicin	cancer	Cephalon	Marketed
Depocyt®	Cytarabine	cancer	Sigma-Tau Pharmaceutials	Marketed
DepoDur®	Morphine	pain relief	Flynn Pharma	Marketed
Octocog alfa®	Factor VIII	haemophilia	Bayer Schering	Marketed

Abraxane®

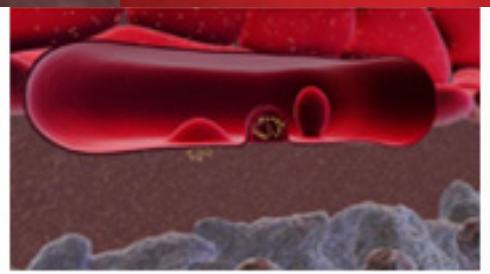






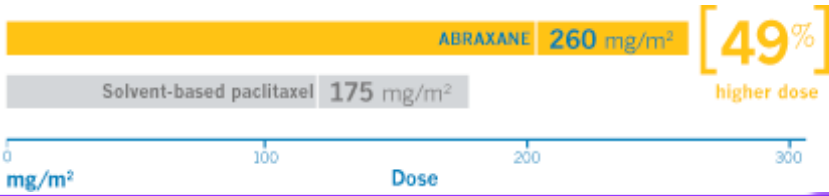


Albumin binds to caveolin-1 receptors and causes the formation of caveolae, to transport albumin across the endothelial membrane



Transcytosis is the transport of albumin across the endothelial barrier from within the blood vessel to the tumor's interstitium

SPARC is then secreted by the tumor to attract and retain albumin-bound nutrients within the tumor cell



Nanoparticles pipeline (overview)

Type of carrier and mean diameter (nm)	Drug entrapped or linked	Current stage of development	Type of cancer (for clinical trials)
Polymer–drug conjugates (6–15)	Doxorubicin, Paclitaxel, Camptothecin, Platinate, TNP-470	12 products under clinical trials (Phases I–III) and *in vivo*	Various tumours
Liposomes (both PEG and non-PEG coated) (85–100)	Lurtotecan, platinum compounds, Annamycin	Several products in clinical trials (Phases I–III) and *in vivo*	Solid tumours, renal cell carcinoma, mesothelioma, ovarian and acute lymphoblastic leukaemia
Polymeric nanoparticles (50–200)	Doxorubicin, Paclitaxel, platinum-based drugs, Docetaxel	Several products are in clinical trials (Phases I–III) and *in vivo*	Adenocarcinoma of the oesophagus, metastatic breast cancer and acute lymphoblastic leukemia
Polymersomes (~100)	Doxorubicin, Paclitaxel	*In vivo*	
Micelles (lipid based and polymeric) (5–100)	Doxorubicin	Clinical trials (Phase I)	Metastatic or recurrent solid tumours refractory to conventional chemotherapy
	Paclitaxel	Clinical trials (Phase I)	Pancreatic, bile duct, gastric and colonic cancers
	Platinum-based drugs (carboplatin/ cisplatin), Camptothecin, Tamoxifen, Epirubicin	*In vivo* and *in vitro*	
Nanoshells (Gold-silica) (~130)	No drug (for photothermal therapy)	*In vivo*	
Gold nanoparticles (10–40)	No drug (for photothermal ablation)	*In vivo*	
Nanocages (30–40)	No drug	Chemistry, structural analysis and *in vitro*	
Dendrimers (~ 5)	Methotrexate	*In vitro / in vivo*	
Immuno-PEG-liposomes (100)	Doxorubicin	Clinical trials (Phase I)	Metastatic stomach cancer
Immunoliposomes (100–150)	Doxorubicin, platinum-based drugs, Vinblastin, Vincristin, Topotecan, Paclitaxel	*In vivo*	
Immunotoxins, Immunopolymers, and fusion proteins (3–15)	Various drugs, toxins	Clinical trials (Phases I–III)	Various types of cancer

Nanocarriers as an emerging platform for cancer therapy,
D.Peer, J. M. Karp,S. Hong, O. C. Farokhzad,R. Margalit and Robert Langer, nature nanotechnology | VOL 2 | DECEMBER 2007 |

Anticancer Polymer Therapeutics – Since 1990

Product	Description	Application	Stage
Polymer-Protein Conjugates			
Zinostatin Stimalmer®	SMANCS	Hepatocellular carcinoma (local administration via hepatic artery infusion)	Market (Japan)
Oncaspar®	PEG-asparaginase	Acute lymphocytic leukaemia	Market
PEG-Intron®	PEG-Interferon alpha 2b	Hepatitis C	Market
PEG-Asys®	PEG-Interferon alpha 2a	Hepatitis C	Market
Neulasta™	PEG-Human-GCSF	Chemotherapy-induced neutropenia	Market
Polymer-drug Conjugates			
Xyotax™/Opaxio	PGA-paclitaxel	NSCLC and various others	Phase III
Prolindac®	HPMA copolymer-Pt	Melanoma, Ovarian	Phase II
CALLA01	polymer-cyclodextrin-siRNA		Phase I
NKTR-105	PEG-paclitaxel		Phase I
XMT 1001	polymer-CPT		Phase I

Superparamagnetic Iron Oxide Imaging Products

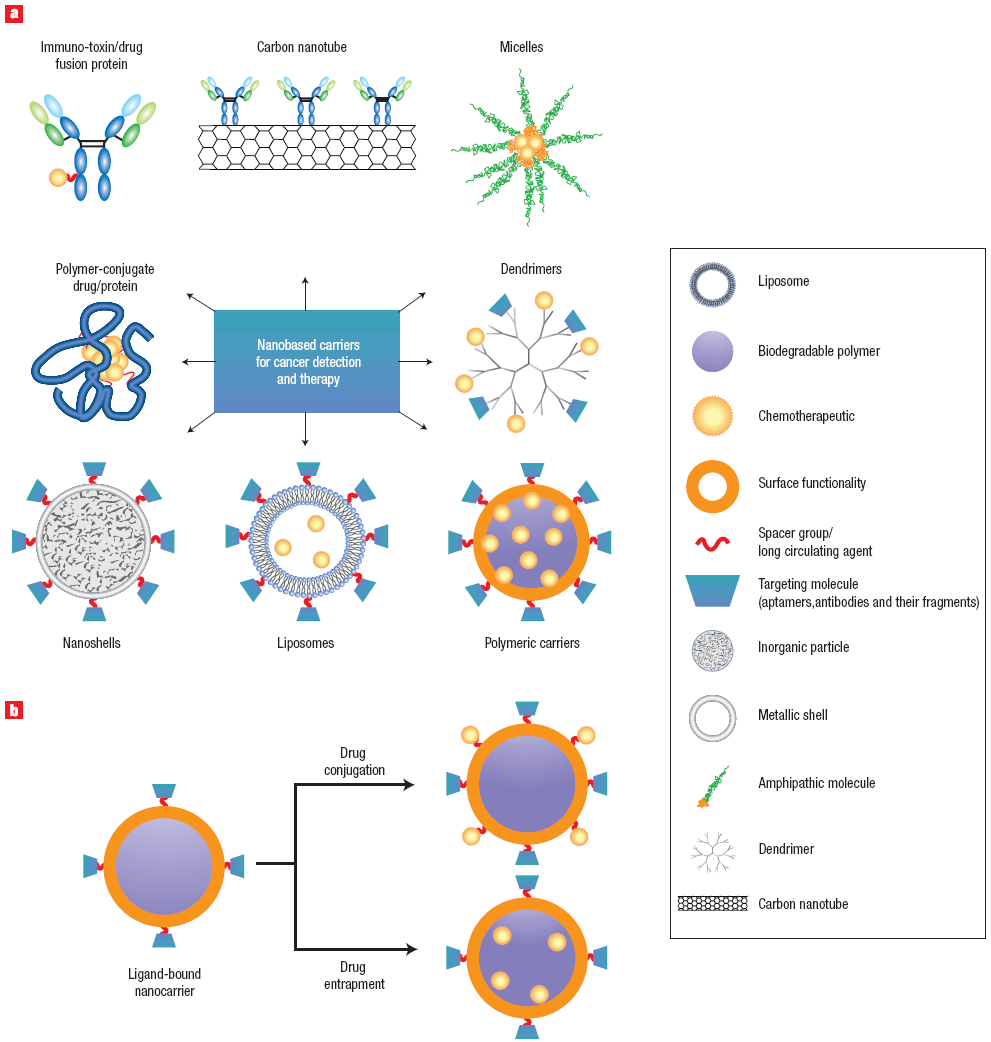
TRADENAME	INDICATION	COMPANY	STATUS
Feridex®	liver imaging i.v.	Bayer Healthcare Pharmaceuticals	Marketed
Endorem™	liver imaging i.v.	AMAG Pharmaceuticals Guerbet S.A.	Marketed
GastroMARK®	GI imaging oral	AMAG Pharmaceuticals	Marketed
Lumirem®	GI imaging oral	AMAG Pharmaceuticals	Marketed
Sinerem®	lymph node imaging - infusion	AMAG Pharmaceuticals	Phase III
Resovist®	small liver lesions iv	Bayer Healthcare Pharmaceuticals	Marketed

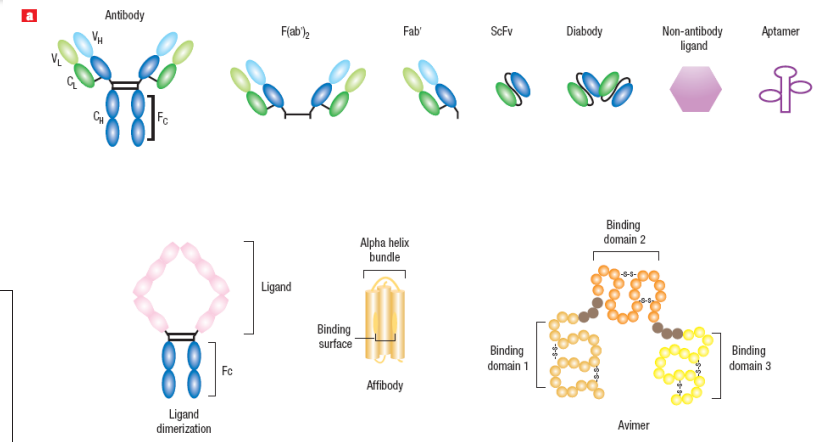
- (SPIO) Relatively new types of MRI contrast agents are superparamagnetic iron oxide-based colloids
- Median diameter > 50 nm
- Nonstoichiometric microcrystalline magnetite cores coated with
  - dextrans (in ferumoxide)
  - siloxanes (in ferumoxsil)

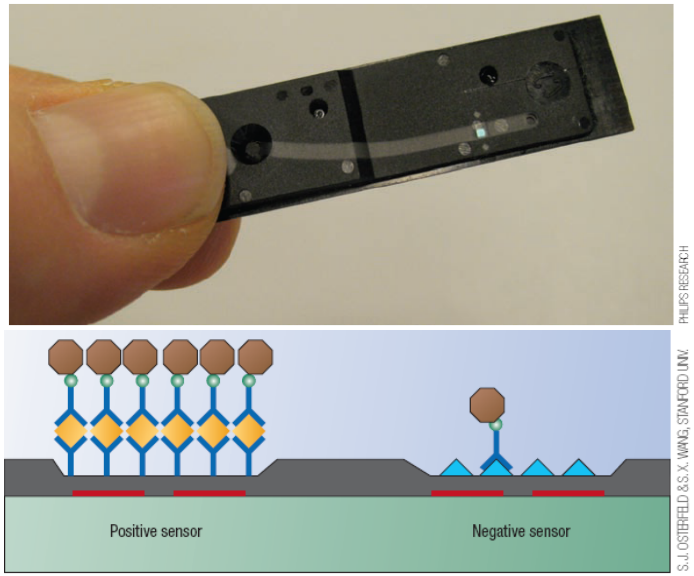
Regulation of Nanomedicines under appropriate control

- **Current regulation provided adequate frame for existing first generation of nanopharmaceuticals**

Diagnostics & Therapeutics







Personalized Medicine
& the integration of diagnostics and therapeutics

The Path to Personalized Medicine

Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.

The New England Journal of Medicine ***June 15, 2010.***

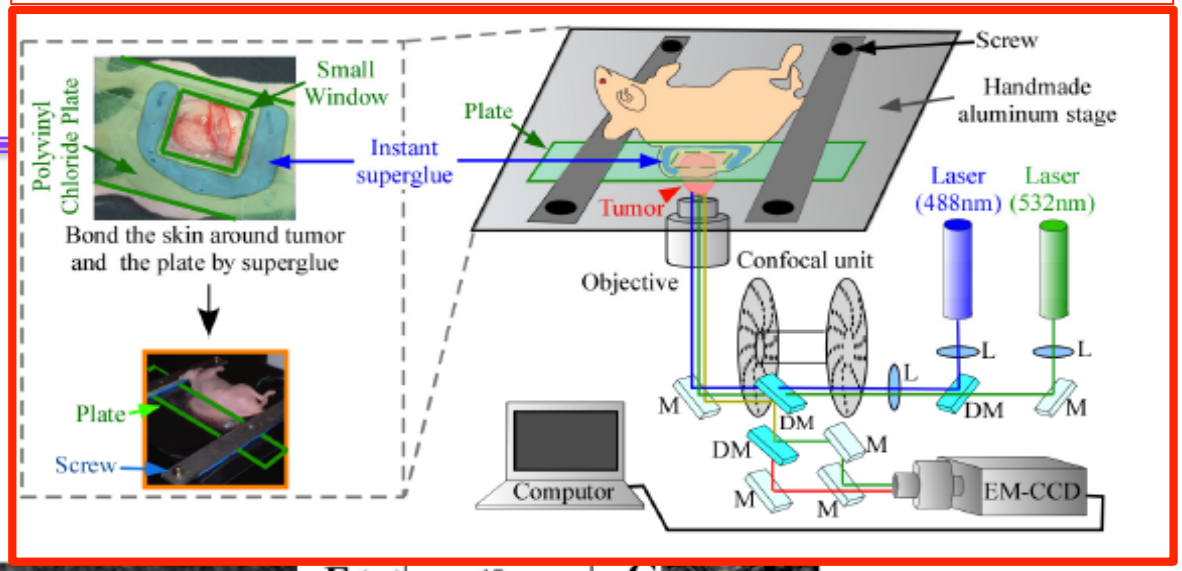
The success of personalized medicine depends on ***having accurate diagnostic tests*** *that identify patients who can benefit from targeted therapies.*
Increasingly, however, the use of therapeutic innovations for a specific patient is contingent on or guided by the results from a diagnostic test that has not been ***independently reviewed for accuracy and reliability by the FDA****.*

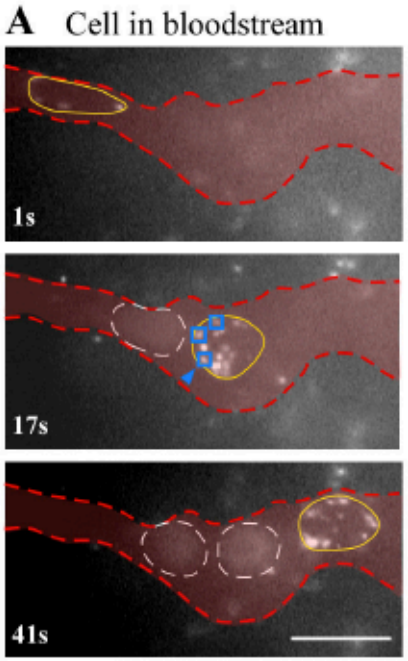
The agency's goal is an ***efficient review process that produces diagnostic–therapeutic approaches that clinicians can rely on*** *and allows companies that invest in establishing the validity and usefulness of tests to make specific, FDA-backed claims about benefits.*

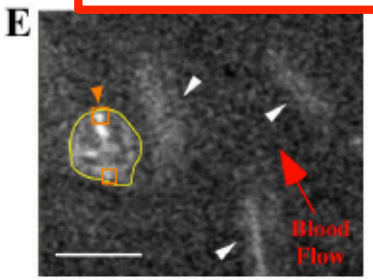
New England Journal of Medicine. The Path to Personalized Medicine.
http://content.nejm.org/cgi/content/full/NEJMp1006304

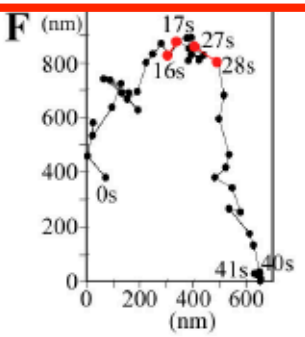
Future developments

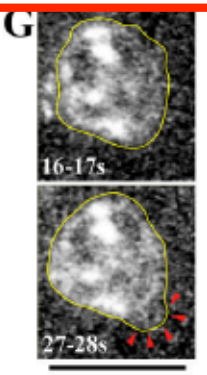
In vivo nano-imaging of membrane dynamics in metastatic tumor cells using quantum dots.
Gonda K, Watanabe TM, Ohuchi N, Higuchi H. (Tohoku University, Sendai, Japan) **J.Biol.Chem. Papers in Press.**
Published on November 16, 2009 as Manuscript http://, www.jbc.org/cgi/doi/10.1074/jbc.M109.075374

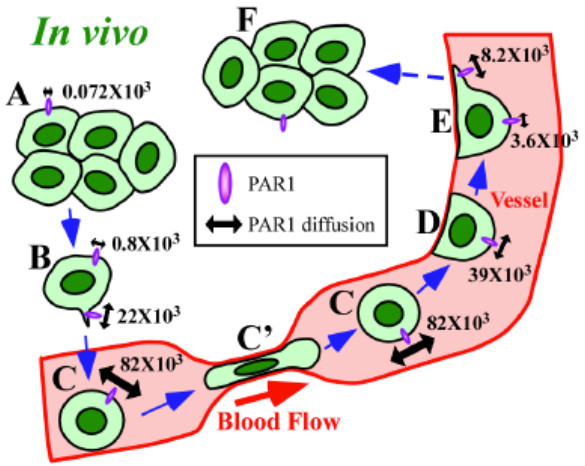


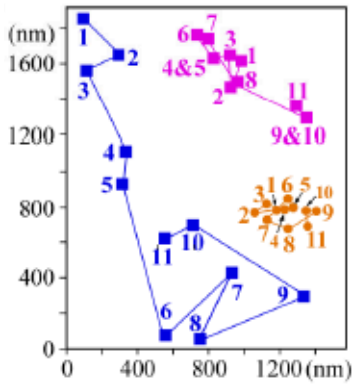


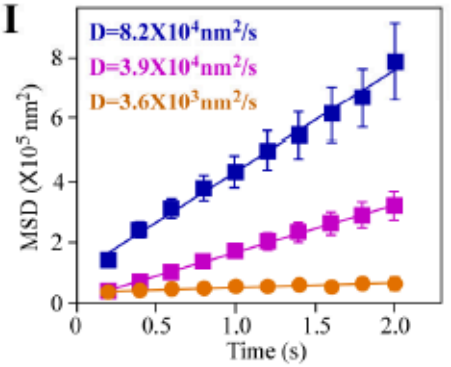




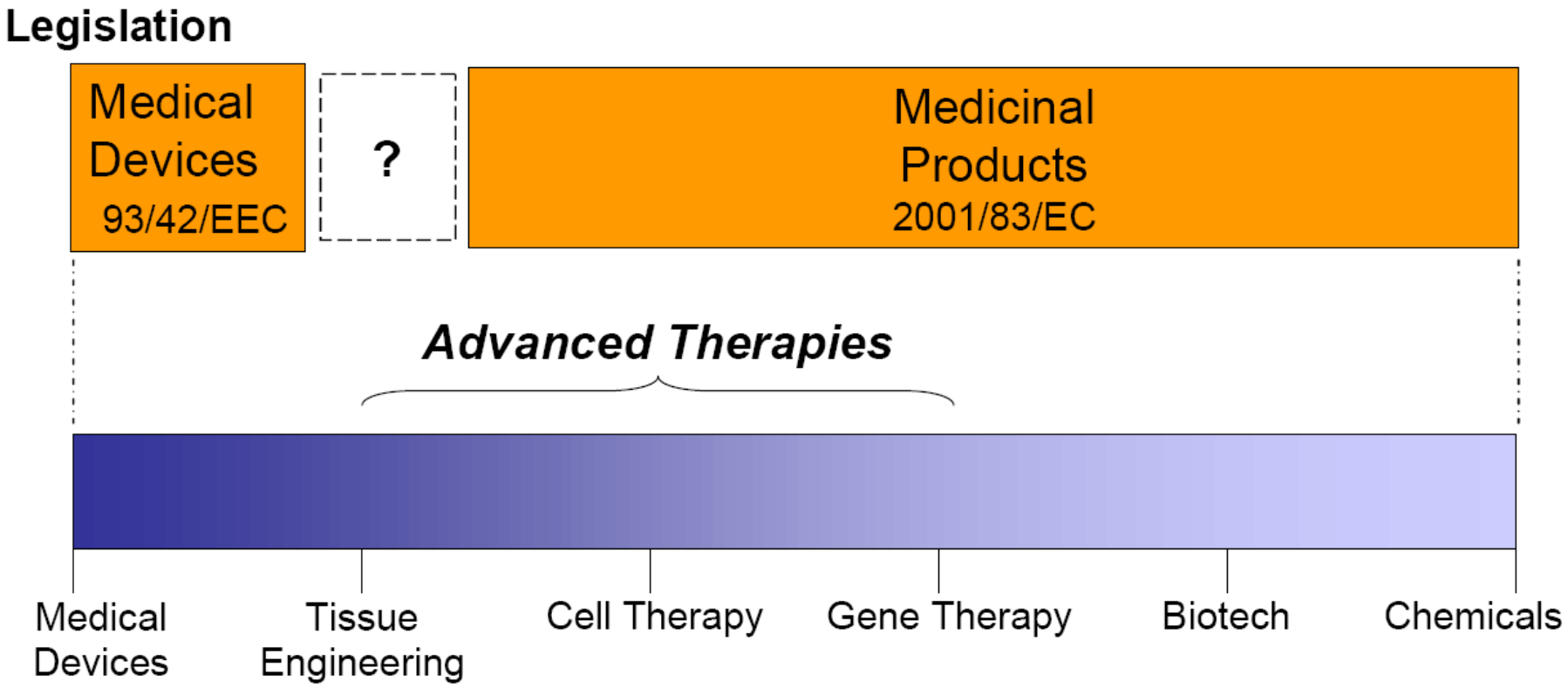








The Regulatory Gap



Key factors for design of new nanomedicines

(in respect of specific medical use)

- Materials Science and Formulation (Technology)
- Understanding underlying basic molecular mechanisms
- Integrating anatomo-physiological issues with pathology or disease state and its progression
- Changes in biological interactions
- Impact in toxicity and efficacy
- Relevance of animal models (In vitro ??! In vivo !!?)
- Differences both in Pharmacokinetics and Pharmacodynamics
- Translational models adapted to specific questions with “nano” (PK/PD versus specific organ toxicity and differential uptake of particles – translocation)
- Important issues in clinical development: How to move faster and safer? Comparability towards specific therapeutic indication?

Issues

- **Materials Science**
  - Challenges arising from new materials (inorganic nanoparticles, non-biodegradable/ non-biocompatible materials, quantum dots, cationic particles and dendrimeric structures, carbon nanotubes)
- **Formulation / Technologies**
  - Adapting existing technologies to new opportunities (e.g. Quality by Design, Process Analytical Technologies)
- **Translational Research**
  - Adequacy of non-clinical methodology before first in man use (relevance of, appropriate toxicityfficcacy biomarkers and barriers related to disease phase and different routes of administration)
- **Clinical development**
  - Comparability: non-inferiority versus superiority (risk-benefit management)
- **Market Access**
  - Comparative pharmacoeconomic assessment

Current and future regulatory challenges

- **combination therapy**
  - The trend for reformulation of old APIs, with advantages of combined administration on the same delivery system (issues on quality/stability, PK/PD, clinical, IP, market access)

- **potential theranostic approaches**
  - Combined system that is able to localize to the target pathophysiology and deliver an appropriate therapeutic agent (both diagnostic and therapeutic functions)

- **"follow-on" products**
  - A number of unresolved problems will arise if preventive action is not taken on matters related to old products, previously not classified as nanoparticles that are in fact colloidal nanoparticulate systems

Iron oxide similars / Iron nanoparticles

- **A number medicinal products contaning iron oxide nanoparticles have been approved as "follow on" products (controversial data published in the literature)**

Roth et al, Translational Research 2008;151:36-44 (BfArm)

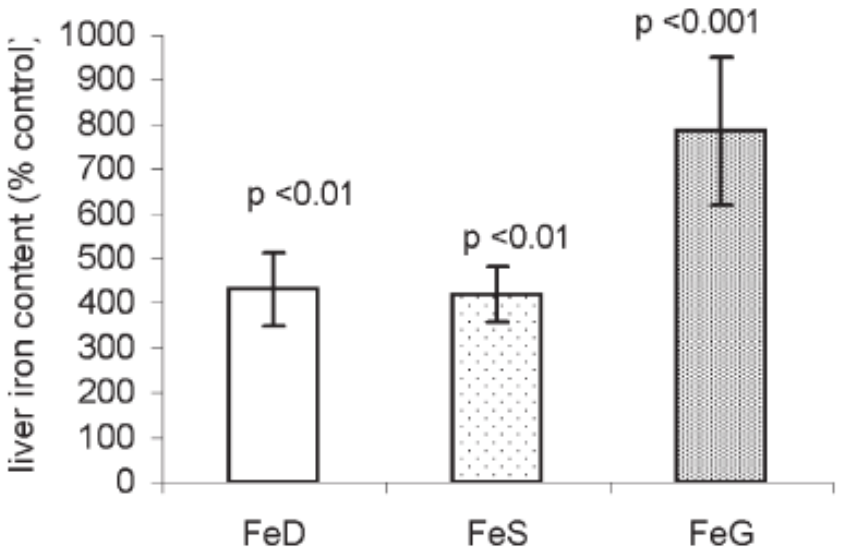


Fig 2. Mean liver iron content (in % of control ± SEM) after administration of FeD, FeS, and FeG that contains 8-mg Fe^{3+} to fertilized turkey eggs. Egg white injection, incubation time was 22 days. Statistical significance in comparison with control is shown.

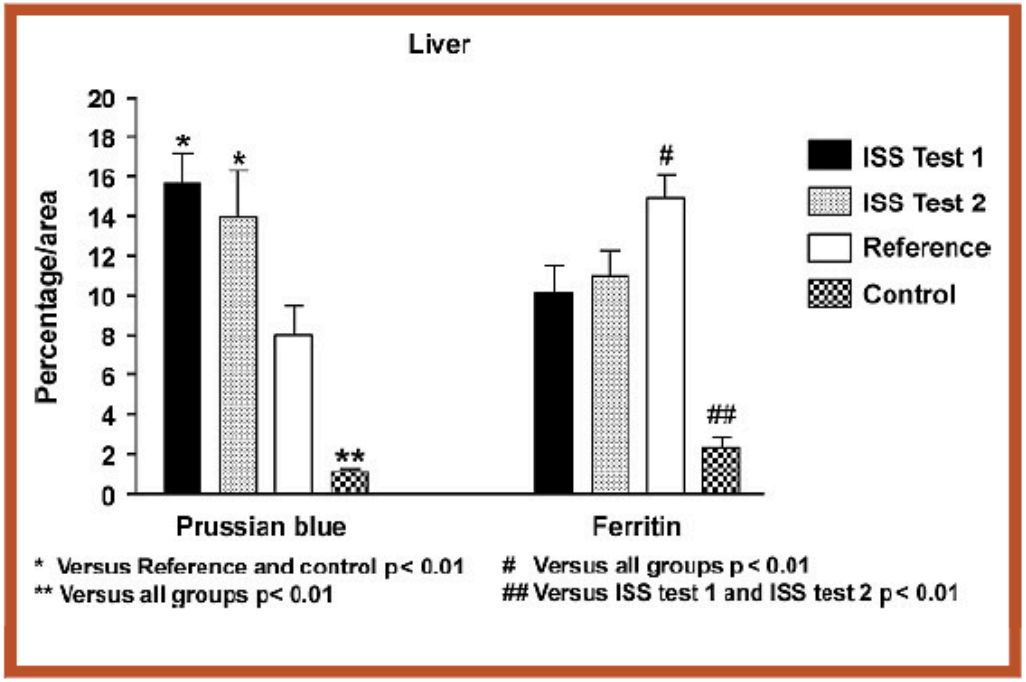


Fig. 6: Bar charts and micrographs showing Prussian blue staining for iron deposits and ferritin immunostaining for stored iron in liver samples taken from the ISS test 1, ISS test 2, reference and control groups on day 28.

Toblli et al, Arzneimittelforschung 2009;59(4):176–190

Risk management

(personal view presented previously during OECD Working Party in Nanotechnology, Vienna September 2009)

- ***What are the criteria used to decide that risk management actions are required?***
  - ***In the medicinal products sector well defined and implemented, not in the medical devices or other borderline areas…***
- ***How is scientific evidence and uncertainty reflected in subsequent risk management actions?***
  - ***In the medicinal products area integrated in the product life cycle permanent assessment***
- ***How are decisions taken? - and how transparent and predictable are they?***
  - ***Under established regulation framework for medicinal products, with well defined competences and enforcement modalities***
- ***To what extent is risk management science-based?***
  - ***Science-driven, based on data on medicinal products compiled with appropriate rules established under globally harmonized (USA, EU, Japan – ICH) guidelines; need care with situation regarding new engineered materials and combination products***

Biomarker Qualification

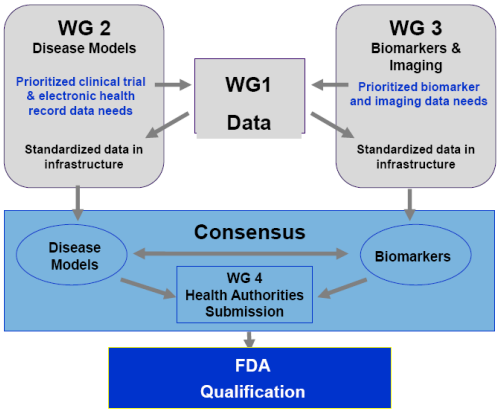
CRITICAL PATH INSTITUTE

Predictive Safety Testing Consortium

Planning Phase | **Execution Phase** | **FDA Review Phase**

Coordinating Committee Planning & Writing Groups → Work Scope Document → Working Groups
1. …
2. …
3. …
4. … → Methods & Results Sharing → FDA Submission → FDA Review → Qualified Preclinical Safety Tests → Greater Drug Safety

Workgroup Workflow



An International Endeavor

CRITICAL PATH INSTITUTE

PSTC Convenes 190 Scientists Monthly

EMEA Decision

CRITICAL PATH INSTITUTE

emea — European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 3 July 2008
Doc. Ref. EMEA/250885/2008 Rev. 1

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS

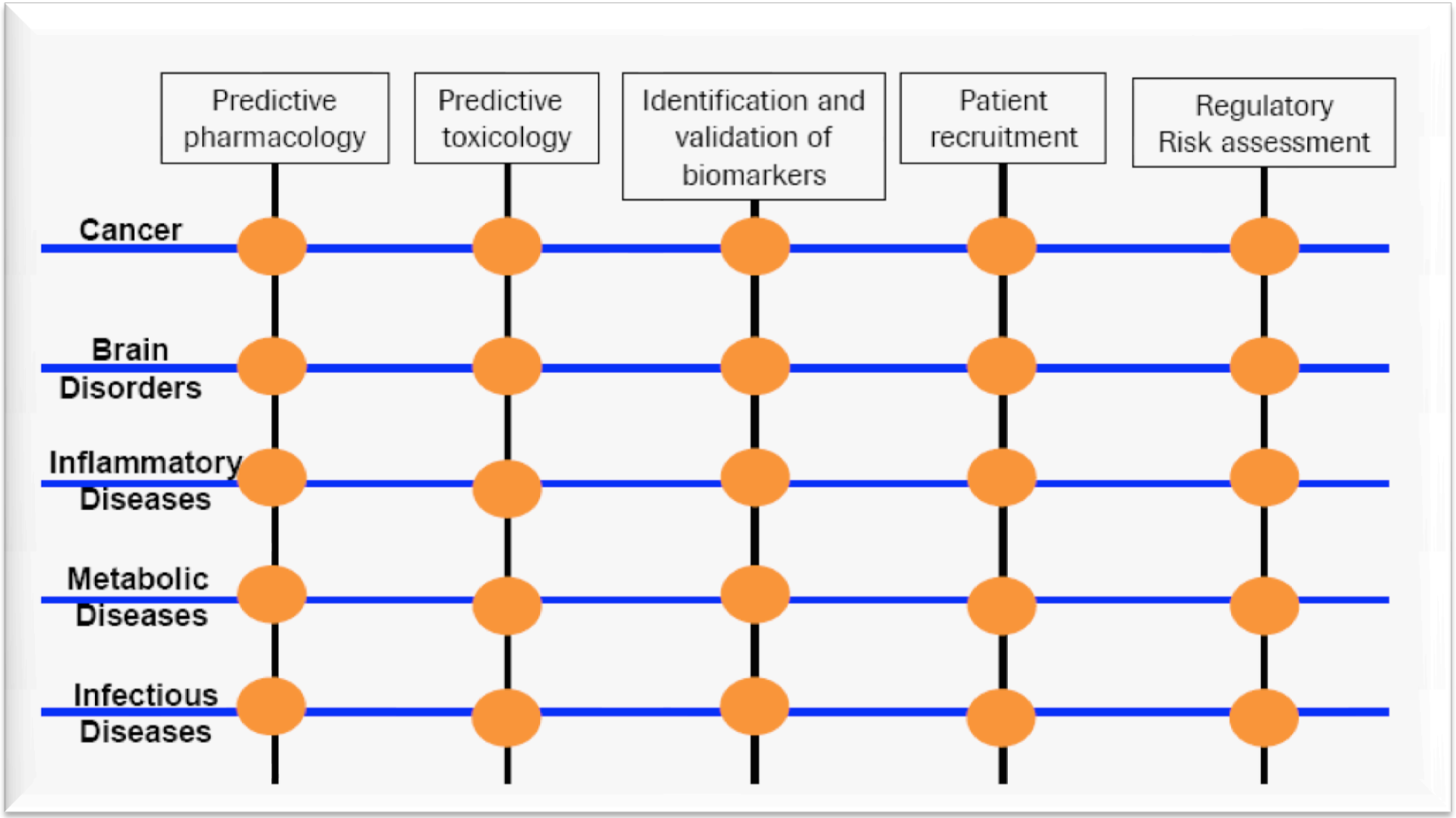
FINAL REPORT ON THE PILOT JOINT EMEA/FDA VXDS EXPERIENCE ON QUALIFICATION OF NEPHROTOXICITY BIOMARKERS.

ADOPTION BY CHMP	April 2008
FOR RELEASE FOR CONSULTATION	May 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	Extended to July 2008

Facul
iMed.UL (Resear

Current trends in the pharma/bio model for DDD

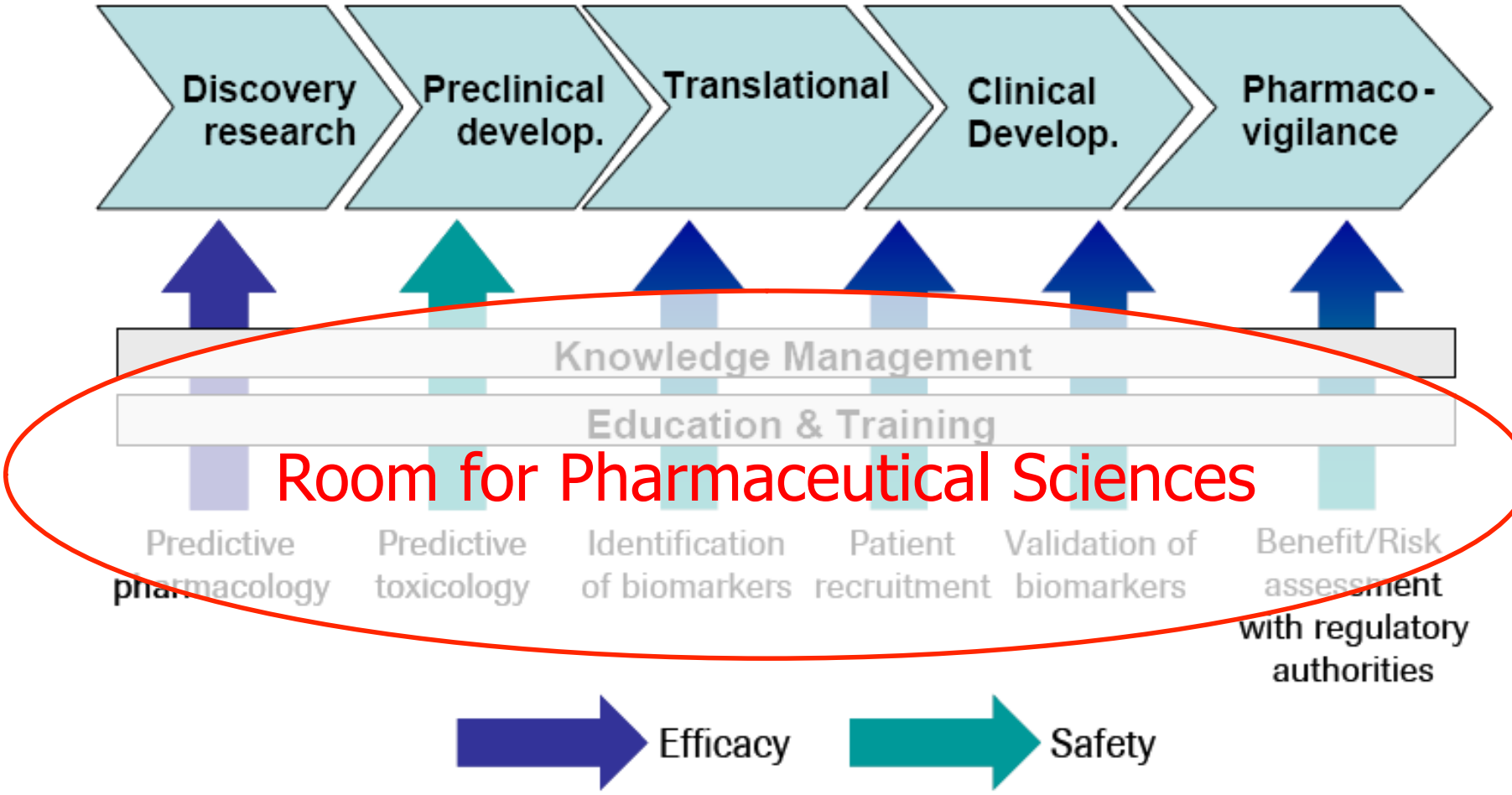
Innovative Medicines Initiative (IMI): addressing pre-competitive bottlenecks in pharmaceutical R&D



http://www.imi-europe.org/

Current trends in the pharma/bio model for DDD

Innovative Medicines Initiative (IMI): addressing pre-competitive bottlenecks in pharmaceutical R&D



http://www.imi-europe.org/

U.S.A. versus E.U. trends

FDA Critical Path

- Biomarkers & disease models
- Clinical trial streamlining
- Bioinformatics
- Manufacturing
- Develop products of urgent public health need (e.g., anthrax Rx)
- At risk populations-pediatrics

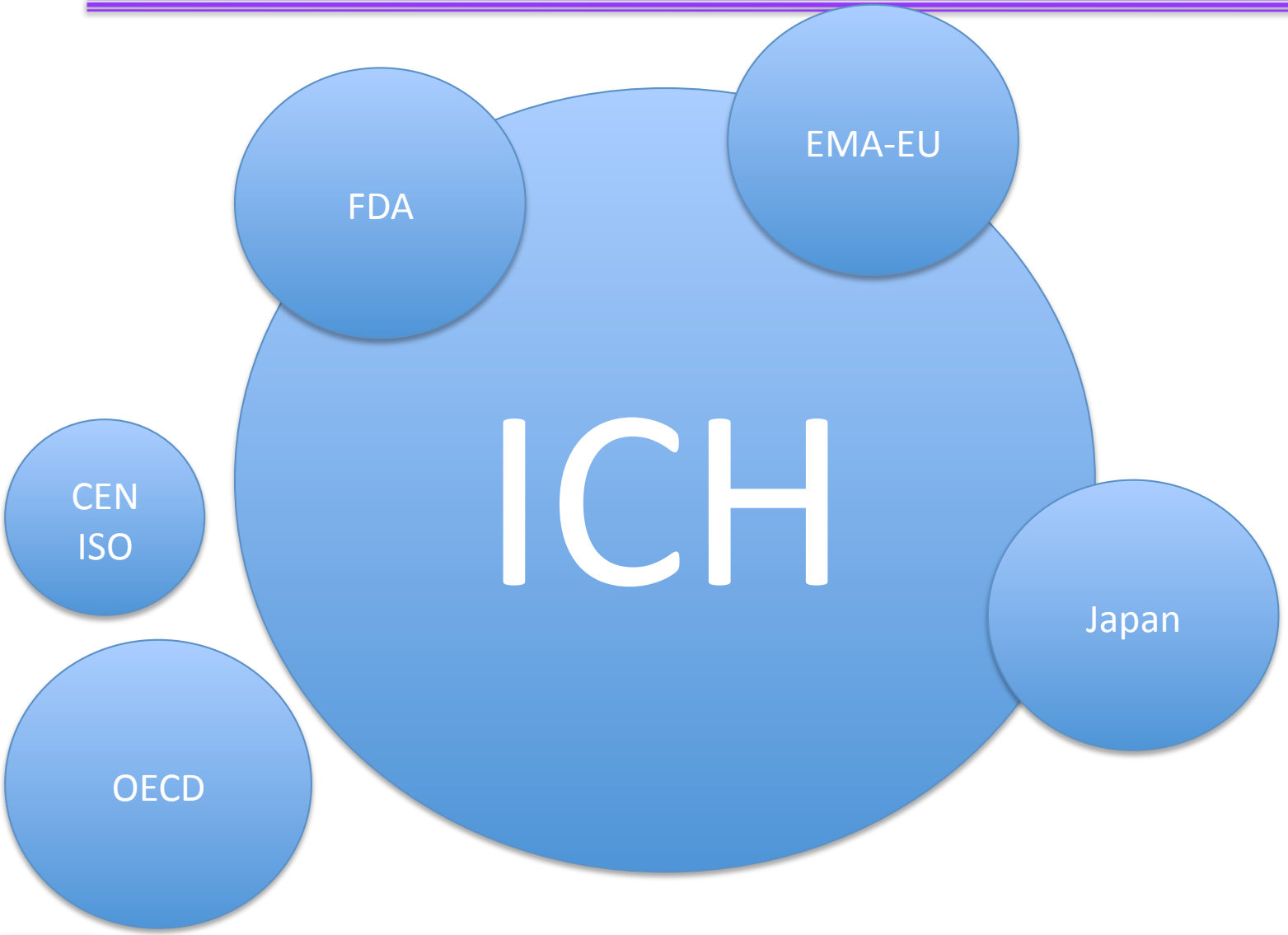
EU Innovative Medicines Initiative

- Prediction of Safety
- Early indication of Efficacy
- Knowledge Management
- Education & Training

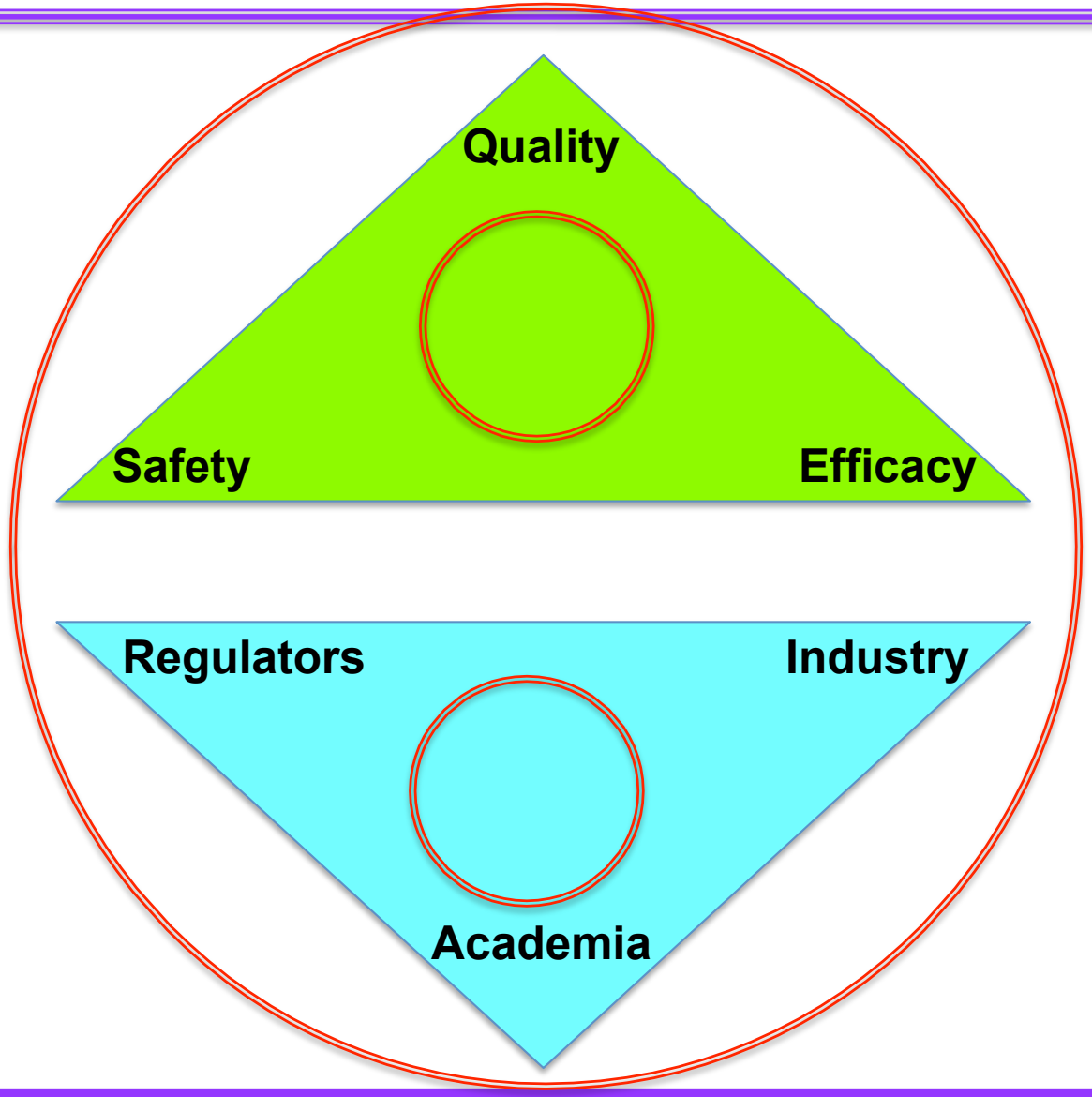
How to move in a global environment?

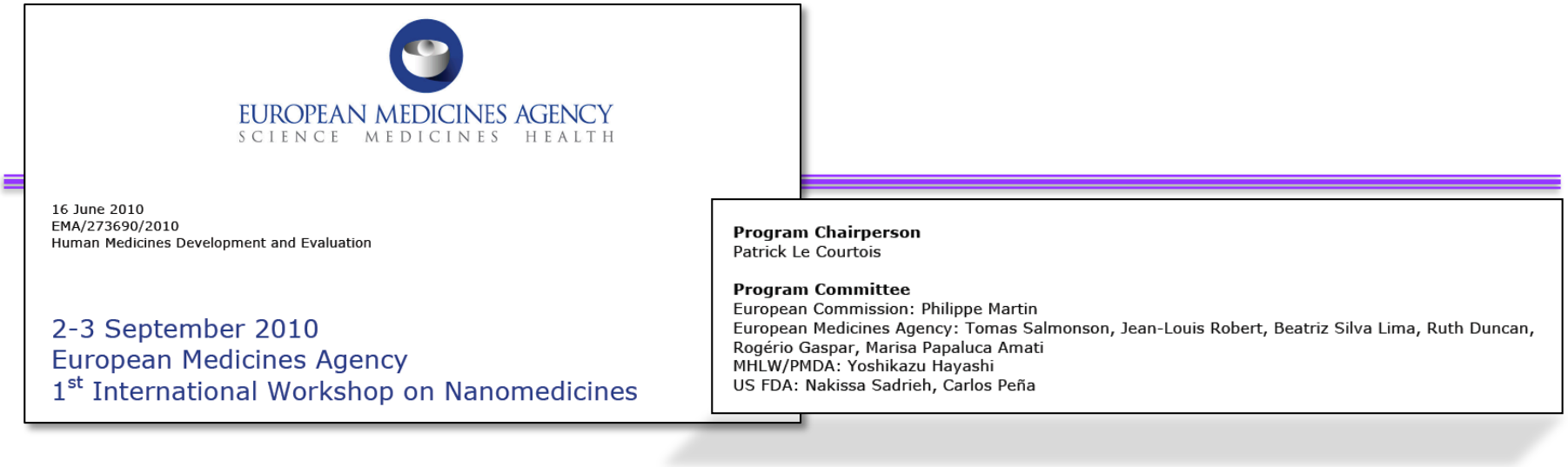
- **Learn with ICH cooperation**
  - Regulators and stakeholders, working groups, guidance documents and maintenance procedures
- **Improve efficiency of procedures**
  - Predictive Safety Testing Consortium (PTSC)
- **Establish institutional mechanisms for cooperation based on specific goals**
  - PPPs with limited and timed objectives (IMI-JTU)
- **Act global as soon as possible – R&D phase**
  - Scientific advise and increase cooperation between scientists and regulators

Need for global cooperation



Need for integrated routine collaboration





Scope:

The proposed workshop will focus on key features of nanomedicines1 and the emerging scientific knowledge in the field.

Objective:

Explore scientific aspects specific to nanomedicines and share experience at an international level, to anticipate future needs.

Outcome:

Report on identified issues and emerging science aspects, which may assist future developments in the
field and may be relevant to future regulatory considerations.