Nanotechnology

"Safety for success"

Guidance in the medical area

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Outline

- EMEA in the EU Pharmaceutical Regulatory framework
- Medicines at nanometre scale: what is known and impact of new applications
- Scientific and Regulatory challenges

European Medicines Agency

- Established and governed since 1993 by dynamic EU pharmaceutical Regulation
- Designed to coordinate the existing scientific resources of EU Member States
- Providing scientific advice for development and scientific opinion on benefit/risk, vigilance and risk management of new medicines

CENTRALISED PROCEDURE: an attractive regulatory process

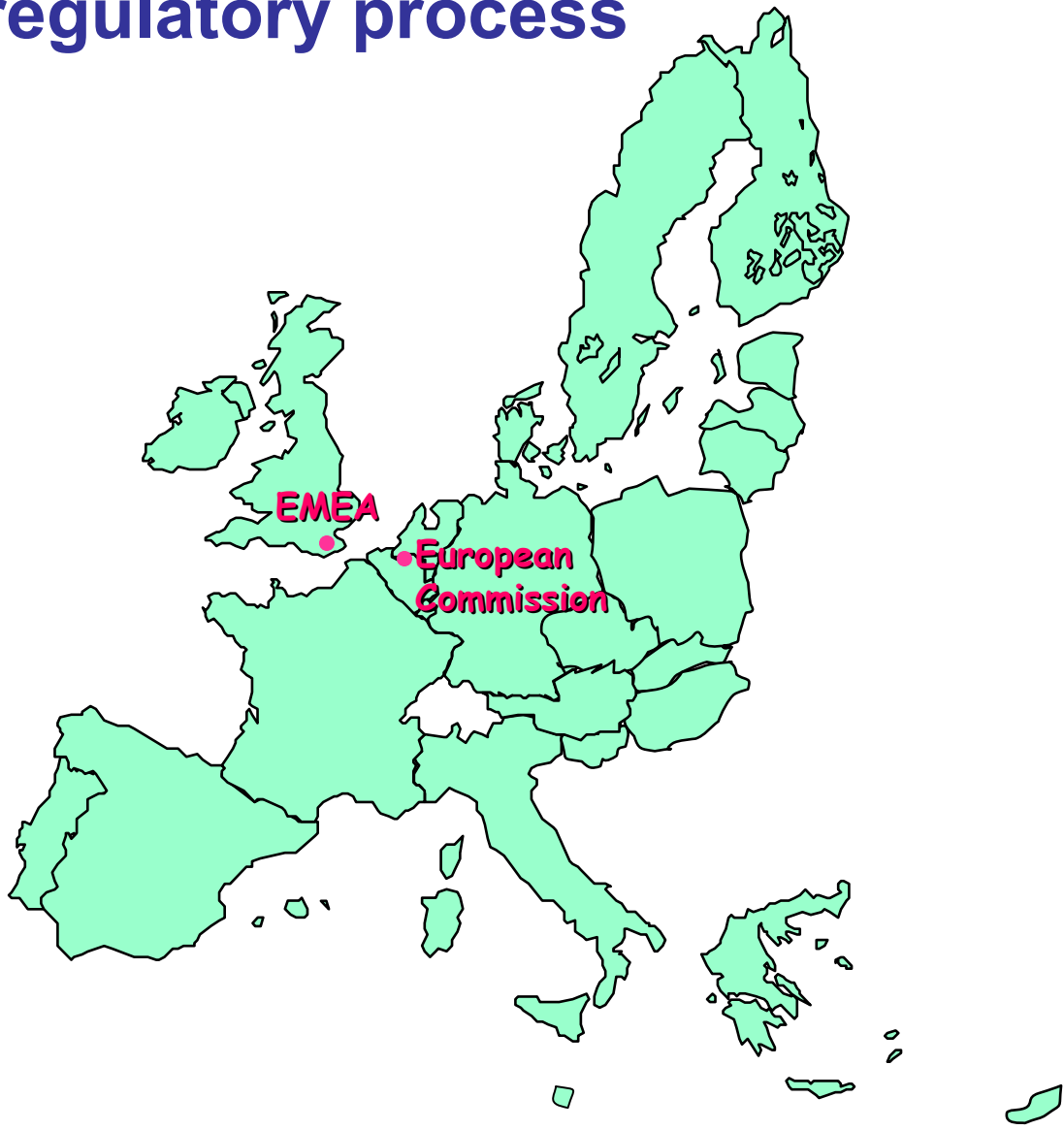
EU-wide

Fast (~ 180 - 210 days)

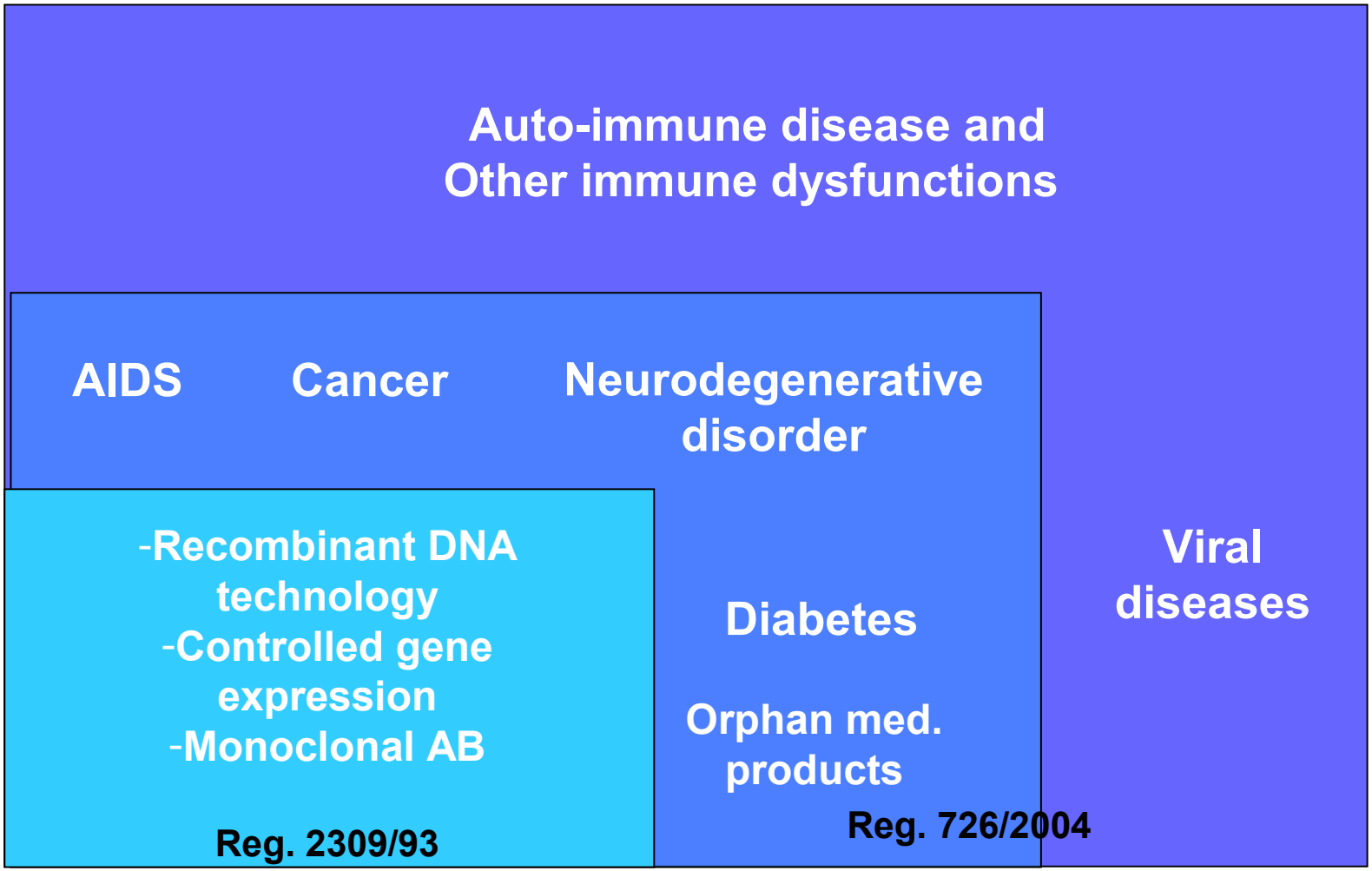
1 Dossier

1 EMEA Scientific Opinion

1 EC MA for the whole EU



Centralised procedure
Mandatory Scope



Centralised procedure
Optional Scope

Art. 3(2) of Regulation (EC) No 726/2004

Art. 3(2)(a)	Art. 3(2)(b)	
New Active Substances	Significant Innovation Therapeutic &/or **Scientific &/or Technical**	Interest of Patients at Community Level (IPCL)

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Nanotechnology

EMEA working definition[1,2,3]:

The design,characterisation, production and application of structures, devices and systems by controlling shape and size a the **nanometre scale** where **properties differ** significantly from those at larger scale

Nanotechnology is **not** viewed as **a single technology** but as a **multidisciplinary field** **integrating multiple technologies**

[1] UK Royal Society and Royal Academy of Engineering, (**2004**). Nanoscience and nanotechnologies: opportunities and uncertainties.
[2] European Science Foundation, (**2005**). Nanomedicine – An ESF –European Medical research Councils (EMRC) Forward Look report.
[3] European Technology Platform on Nanomedicine, (**2005**). Vision paper and Basis for a strategic research agenda for Nanomedicine.

Nanosize medicinal products

Not everything is new… Nano size alone does not imply novelty

Medicinal products containing nanoparticles have already been granted Marketing Authorisations, e.g.

- liposomes (i.e. Caelyx, Myocet),
- polymer protein conjugates (i.e. PegIntron, Somavert),
- polymeric substances (i.e. Copaxone),
- iron oxide particles for MRI imaging (Feridex)
- products using NanoCrystal technology (Rapamune, Emend)
- albumin-bound nanoparticles (Abraxane)

ICH M3; CPMP/ICH/286/95

- Safety pharmacology
- Local tolerance
- Genotoxicity *in vitro*
- Single dose
- Repeated dose tox. (2W)
  male reproductive organs

Phase I

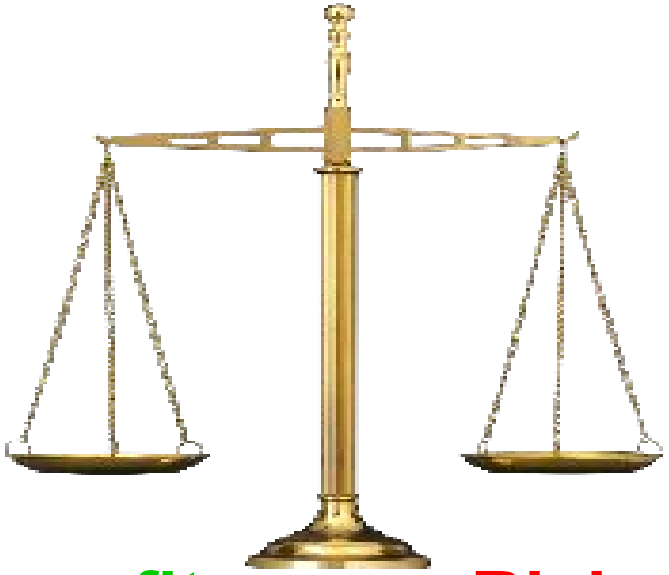
- Repeated dose tox. (2W-6M)
- Genotoxicity *in vivo*

Phase II

- Repeated dose tox. (1M – chronic)
- Reprotoxicity
  - male fertility
  - embryofetal
  - fertility
  - peri-post natal
- ADME

Phase III

Key elements in medicines evaluation
Benefit/risk balance in the lifecycle



- Quality and manufacturing
- Safety (including ERA)
- Efficacy
- Risks definition and Management Program

→ Product Information (SPC, Labelling, PL)
→ Information to the public (Q&A)
→ Conditions of MA
→ Educational material
→ Follow-up measures

~ 25% of MAA not approved; mostly due to lack of efficacy

Innovative nanotechnology in pharmaceuticals

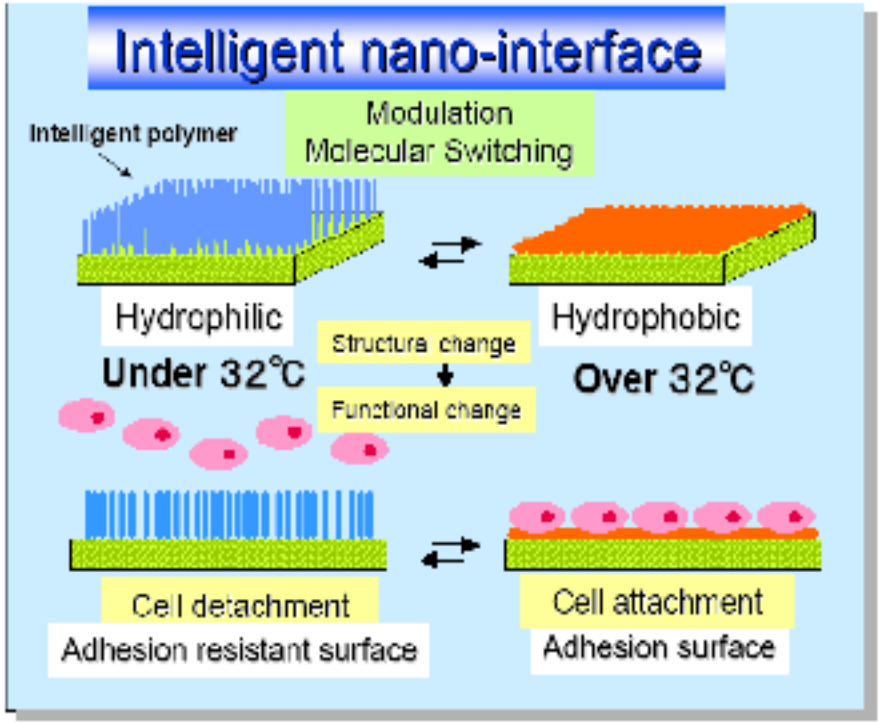
- **New manufacturing systems**

- **New drug delivery systems**

- Other **novel applications** of nanotechnology may include *(likely to be seen more in the future)*
  - Novel *in-vivo* diagnostics
  - Regenerative medicine (e.g. nanostructure scaffolds for tissue replacement)
  - Intelligent multifunctional platforms that can monitor the body and respond directly
  - In vivo theranostics

Nano-assisted manufacturing methods

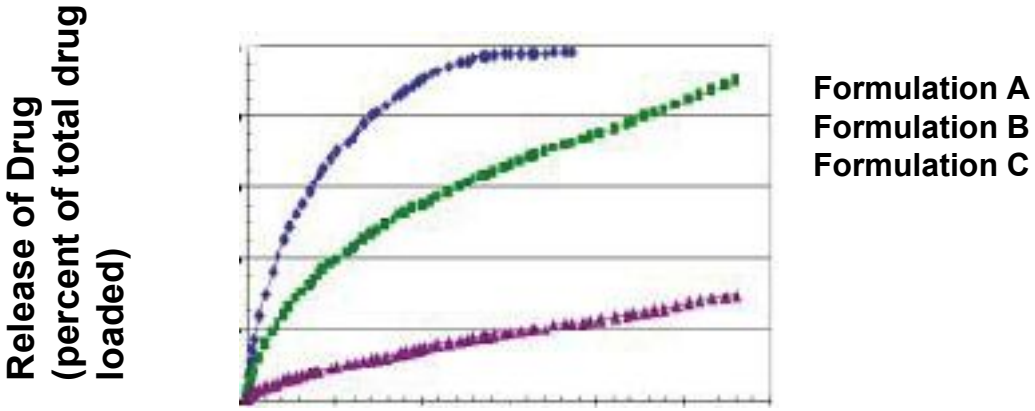
Principle of Cell Sheet Engineering



CellSeed

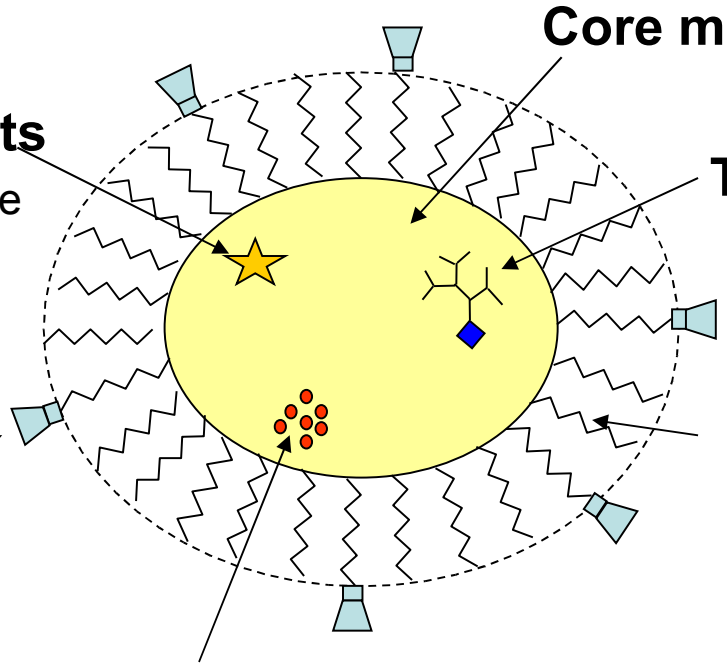
Innovative delivery systems

Figure 1. Microscopic image of an implant with a drug-eluting matrix coating. Note the uniformity of the coating on the complex geometry.



Data comparing the elution profiles of three coating formulations.

Example of a nanotechnology multifunctional platform



Core matrix

Imaging /Contrast agents

(e.g. MRI, ultrasound, radioactive marker)

Therapeutic agents

(e.g. small molecule, nucleic acid, protein)

PEG coating

Targeting agents

(e.g. monoclonal antibodies, receptor ligands)

Diagnostic molecules

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Quality

- A different approach might be needed compared to macro- molecules.
- Need for understanding the physical and chemical parameters that are crucial to product performance
- In addition to the usual parameters (e.g. size, size distribution, purity, chemical composition, stability, solubility) some other parameters might need to be considered, e.g.
  - surface characteristics –area, chemistry, porosity,
  - surface functionality
  - the possible aggregation in biologically relevant media
- There might also be a need to use different or additional characterization methods compared to the standard practice, e.g. microscopy, electrophoresis, zeta-sizer, fluorimetry etc.

Safety

- Particles behaviour in diverse biological systems at molecular and organ level
- Distribution, persistence (and its effects) of nanoparticles in humans and in the environment
- The existing methodologies seem to be able to address most, but not all the potential hazards

Adequacy of current toxicologic screens for nanoscale materials.

Potential for novel, unanticipated reactions.

New methods and models might need to be developed

Clinical requirements for Nanomedicines

As any other pharmaceuticals they should prove a positive benefit/risk balance with respect to

- Efficacy in the proposed indication
- Administration route
- Dose and method of administration
- ***Biodistribution***
- ***Safety profile in man***
- ***Risks management and minimization***

Regulatory challenges

- Complexity across regulatory boundaries
- Combining mechanical, chemical, pharmacological and immunological MOA
- Gaps in scientific knowledge
- Combining diagnostic and therapeutic functions
- Complex therapeutic environments

- Applicable Regulatory Framework (medicines, devices, combination products, advanced therapies)
- Requirements adaptation to reflect scientific progress
- Integration of appropriate scientific and regulatory expertise
- New and more complex risk communication issues

Regulatory challenges

- The mechanism of action defines the classification

Critical question:

- **What is the mechanism of action of the entity in question?**
  - Physical action → medical device,
  - Pharmacological, immunological or metabolic action → medicinal product.

- **Simplistic approach. Not clear sometimes !**
  - There are exceptions e.g. i.v. ultrasound diagnostic agents used in echocardiography

- **Nanomedicine often exhibit a complex mechanism of action**

Regulatory challenges

Applicable regulatory framework to be clarified early in the development since there are different regulatory requirements for the development of e.g. a medicinal product compared to a medical device

Conclusions

- Rapidly evolving field with a wide range of applications
- Borderline features require adaptation
- Essential to learn across frameworks not to reinvent the wheel
- Contact your regulators early in development

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THANKS

for your attention

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http://www.emea.europa.eu/htms/human/mes/itf.htm

http://www.emea.europa.eu/SME/SMEoverview.htm

http://www.emea.europa.eu/htms/human/sciadvice/Scientific.htm