Nanomedicines: Regulatory Aspects

Joan-Albert Vericat
Neuropharma SA

jvericat@neuropharma.es
• Company belonging to the Spanish Zeltia group.
• Searching for Alzheimer’s disease treatments (1 in Phase 1; 1 to initiate Phase 1 in winter 2006-7).
• Cell therapy approach to treat spinal cord injury (Phase 1 foreseen in 2008).
• Searching for active compounds in sea organisms.
What is a “Nanomedicine”?

Concept as in the NANOMEDICINES EU platform:

New tools for diagnosis
New tools to improve delivery
New approaches for regeneration

The dream of the “lab in a chip”

What is a "Nanomedicine"?

Proteus
Products being impacted by nanotechnology

1. Drugs (nanomedicines or delivery systems)
2. Medical devices
3. Biotechnology derivatives
4. Tissue engineering products
5. Vaccines
6. Cosmetics
7. Combination products
Examples of current situation

- **Nano-enabled tools**
  - Atomic force microscopy
  - Nano-mass spectroscopy
  - Dip-pen nanolithography
  - Nano-arrays

- **Nano particles/materials**
  - Quantum dots
  - Shells
  - Bars
  - Dendrimers

- **Nano-enabled drugs**
  - (improved delivery):
    1. Abraxane
    2. RenaZorb
    3. Paclitaxel
    4. Nanofarma project
Nanomedicines and “nano-tools” are combinations of ingredients, either with or without therapeutic potential, possessing both individual and combined properties.
Nanotechnology & Nanomedicines: Drug Discovery

- Improved understanding of chemicals at cellular / molecular levels
- Improved visualisation of drug interactions
- Improved identification and validation of target proteins and drug levels
- Reduced time to identify new drugs
- Reduction on reagents

Nanotechnology
• Authorities regulate products in a product-by-product basis:
  - Pre-marketing authorisations and approvals
  - Post-marketing control

• Authorities do not regulate “technologies”.

• The review process evolves with knowledge and time.
Main Concepts to Consider in Combination Products

• **Primary Mode of Action:**
  - The most important therapeutic action of the combination product or device (may not be possible in early phases!).

• **Ingredients (or parts):**
  - Individual constituents are subjected to regulation.

• **The combination is a new product:**
  - Interactions (“additive” effects).
**Question:** Are nanomedicines out of current regulation?

**No!** (existing regulation covers an important part of “nanomedicines”).

- “Nano” applies to the cellular and molecular size.

- Since...
  - (Classical) drugs are metabolised
  - Devices degrade
  - Diagnostic agents are considered as drugs

- Everything becomes “nano”.
• Nanomedicines are covered by the existing regulation(s):
  - 21CFR3.2(e): A combination product is “a product of two or more regulated components that are physically, chemically or otherwise combined or mixed as a single entity;...”
    ➢ This is a nanomedicine!

• Where are the open aspects in the current regulation?
## Classical vs. Nanomedicines

### Standard Drugs
1. Single chemical entity
2. Well known
3. \(<24\text{-h half life (in general)}\)
4. Historical data base for comparative purposes
5. Regulatory approaches well defined
6. Human safety “established”

### Nanomedicines
1. (Complex) mixtures
2. Mainly unknown
3. (Very) long half life and stability
4. Absence of historical data (something with particles)
5. Regulatory approaches not well defined
6. Human safety “unknown”
Biodevices vs. Nano-tools

**Biodevices**

1. "Big" size
2. Well known
3. Long life
4. Historical data-base for comparative purposes
5. Regulatory approaches well defined
6. Human safety "established"

**Nano-tools**

1. (Very) "small" size
2. Mainly unknown
3. Long life
4. Absence of historical data (something with particles)
5. Regulatory approaches not well defined
6. Human safety "unknown"
Differential aspects of nanomedicines and nano-tools

1. Size
   - They are smaller than existing biodevices, but bigger than molecules: PARTICLES.

2. Time stability
   - Tendency to (very) long half life, allowing slow release of active ingredients.

3. Complexity
   - Tendency to more complex structures or combination of materials
Mesa Redonda: Nanodiagnóstico *in vivo*, 17 Agosto 06

--- Regulatory concept

1. Drugs (nanomedicines or delivery systems)
2. Medical devices
3. Biotechnology derivatives
4. Tissue engineering products
5. Vaccines
6. Cosmetics
7. Combination products
The ICH CTD is designed to facilitate registration of a new pharmaceutical for human use:

- Module 1: Region specific
- Module 2: Summary
- Module 3: Quality or CMC
- Module 4: Non clinical study reports
- Module 5: Clinical study reports
Let’s imagine the CTD applied to a nanomedicine...

- **Quality or CMC:**
  1. Form(s)? How particles are presented to host, cells, organelles?
  2. Tools for characterization and their validation?
  3. Critical chemical and physical properties? Limits?
  4. Critical steps in scaling up and production?
Let’s imagine the CTD applied to a nanomedicine...

- **Safety (human health):**
  1. Aspects associated to route of administration?
  2. ADME?
  3. Bioanalysis?
  4. Mass balance?
  5. Combination product, ingredients, degradation products, metabolites, ...?
  6. Distribution and clearance?
  7. Immunotoxocoly
Let’s imagine the CTD applied to a nanomedicine...

- **Safety (environment):**
  1. Release and estability in the environment?
  2. Methodological considerations for monitoring?
  3. Ecotoxicology?
Conclusions (1)

- Existing pharm-tox approaches are valid for most nano-products.
- Open questions regarding impact of size in safety evaluation.
- Open questions regarding long half-life
- Open questions regarding complexity and interactions.
- New tools might be required.
Conclusions (2)

• “These are the tasks at hand: Do the science. Gather information. Revisit the issue of regulation”

Report from the Conference:

Health and Nanotechnology: The Promise and Challenges of Nanomedicines.

The United States Department of State & the European Commission
January 22-24, 2006

Further reading:
“The appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies”
European Commission
Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)
(Adopted in 7th plenary meeting, 28-19th September 2005)
¡Gracias!

jvericat@neuropharma.es

Mesa Redonda:
Nanodiagnóstico *in vivo*, 17 Agosto 06