



## **PREAMBLE**

This statement was prepared by the Nanomedicines Alliance, a consortium of research-based pharmaceutical, biotechnology and medical device companies interested in appropriate and scientifically based regulatory approaches to nanomaterials and nanotechnologies used in the research, development and manufacturing of pharmaceutical and biotechnology products and medical devices and diagnostics.

## **BACKGROUND**

Nanoscale materials could be described as particles (of various shape and composition) with at least one dimension on the nanometer scale (i.e.,  $10^{-9}$  m). Due to their small size, nanomaterials usually exhibit some properties not observed in the same material at a larger scale. These properties have spurred the development of nano-applications in almost all sectors of industry and technology.

The use of nanotechnology and nanomaterials in medicine holds great promise for patients and society. The unique properties of medicinal nanomaterials are being harnessed to improve targeting and effectiveness of drugs, to reduce drug exposure and toxicity, to reduce environmental burden, and to diagnose pathological conditions at an earlier stage to facilitate successful treatment.

At the same time, several studies have raised concerns about potential risks that nanoscale materials may pose for the human and environmental safety. Such concerns should be taken seriously and should be discussed in the context of particular types of products. The level of risk varies considerably depending on the type of the nanomaterial and on the level of scientific and regulatory scrutiny that a product is subjected to before becoming widely available. This paper provides an appropriate context for discussion of nanoscale materials used for medicinal products and devices.

## **CURRENT REGULATORY APPROACHES FOR MEDICINAL PRODUCTS AND DEVICES ARE ADEQUATE**

Currently, pharmaceutical and biological products – including those employing nanoscale materials – must undergo a series of rigorous studies before commercialization, in order to characterize a product's physical and chemical properties, safety and effectiveness, and to assess a product's potential environmental impact. In the US, all pharmaceutical and biological products and medical devices are regulated, respectively, by the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research, or Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) under the U.S. Department of Health and Human Services (DHHS). In other countries, similar government bodies oversee the approval and licensing of medical products and devices.

The terminology and specific requirements may vary from one country to another but the overall process for a new product typically involves the following steps, each often lasting several years:

- **Drug Discovery.**
  - Based on the knowledge about the target disease, develop a hypothesis for a mechanism of treatment and evaluate it using modeling software; determine feasibility of producing and evaluating the selected compound.
- **Screening and Lead Optimization.**
  - Synthesize as many plausible drug candidates as possible and screen them for biological activity. Identify candidates that are likely to be able to:
    - reach the target site in the body,
    - elicit the desired action at the site,
    - be eliminated from the body, and
    - have a suitable safety profile.
  - Optimize the structure of lead compounds to make them safer, more effective, more stable.
  - Begin developing a process to manufacture the experimental drug.
- **Pre-Clinical Testing.**
  - Evaluate toxicity in animals and assess how the drug is absorbed, distributed, metabolized, and excreted in animals.
- **IND Application.**
  - Assemble all relevant information about the drug candidate into an Investigational Drug Application (or equivalent, if outside of the US) and submit it to the U.S. FDA (or other appropriate regulatory body) to obtain permission for human exposure to the experimental drug.
  - Continue developing a process to manufacture the experimental drug.
- **Phase 1 Clinical Trials.**
  - Determine safety and dosage of the experimental drug in 20-80 subjects.
  - Continue development of a manufacturing process.
- **Phase 2 Clinical Trials.**
  - Evaluate effectiveness and side effects of the experimental drug in 100-300 patient volunteers.
  - Continue development and evaluation of the manufacturing process.
  - In the U.S., at the end of Phase 2, discuss all findings to date with FDA before starting Phase 3 trials. (Similar meetings may occur in other countries).
- **Phase 3 Clinical Trials.**
  - Confirm effectiveness, assess adverse reactions from long-term use in 1000-3000 patient volunteers.
  - Finalize the proposed manufacturing process.
  - Have the FDA (or appropriate national authority) conduct a Pre-Approval Inspection (PAI) of the manufacturing facilities. During a PAI, the regulators assess compliance with the

current Good Manufacturing Practices (cGMPs), Quality Systems (QS) requirements (or similar national requirements) and other applicable regulations. As part of the inspection, regulators also review clinical batch records; development report; equipment and process validation; stability protocols; stability data; analytical methods; Standard Operating Procedures (SOPs); the chain of quality control/quality assurance measures from the receipt of raw materials through processing, packaging, storage and distribution.

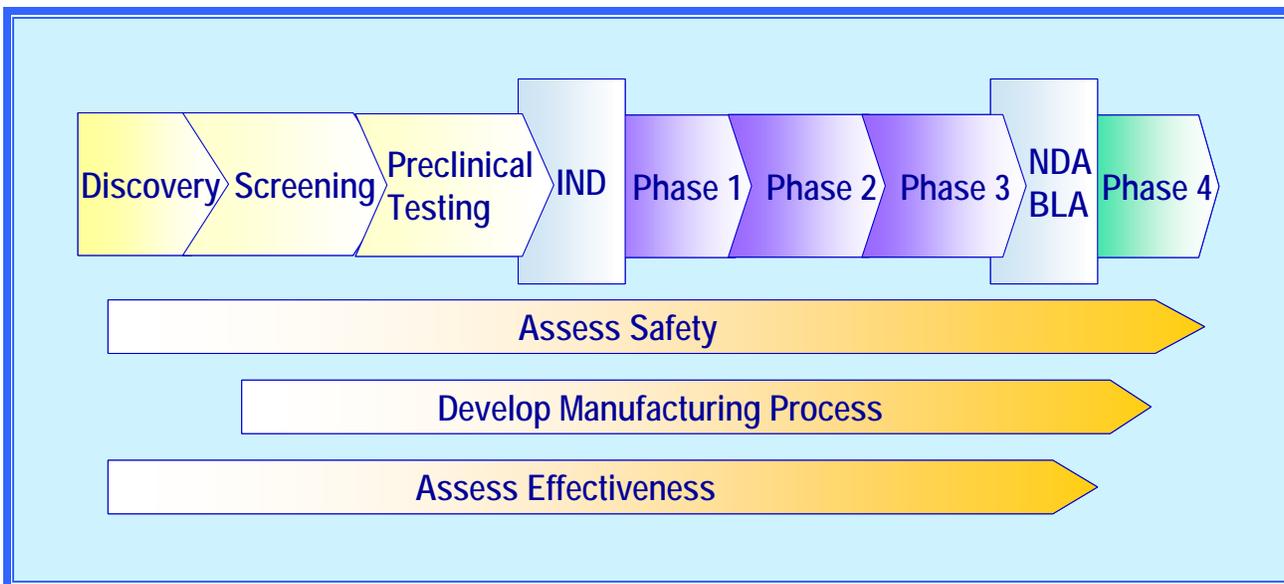
- **New Drug Application (NDA) or Biologic License Application (BLA).**

- Assemble all relevant information about the experimental drug into a New Drug Application (NDA) or Biologic License Application (BLA) and submit it to FDA for review and approval to enter the market (or similar applications in other countries). The application must provide sufficient evidence for the FDA to conduct medical, biopharmaceutical, pharmacology, chemistry, microbiology and statistical review and to determine whether:
  - The proposed drug is safe and effective.
  - Benefits outweigh the risks.
  - Proposed labeling is appropriate.
  - Manufacturing methods and controls ensure the drug's identity, strength, quality and purity.
  - Potential environmental impact is negligible and is justified by the public health considerations.

- **Phase IV and Beyond.**

- After the product enters the market, conduct post-marketing surveillance, communicate with the regulators as appropriate, assess adverse reaction reports and respond accordingly.
- If needed, conduct additional studies focusing on new patient populations, previously unknown side effects or related risk factors.

This process is presented schematically in Figure 1.



**Figure 2. Schematic of a drug development process.**

The commercialization of medical devices is likewise preceded by various types of studies to meet regulatory requirements that are tailored to the level of risk represented by the device. The exact process and terminology vary between the US, European Union and other world regions, but the approaches are similar and the goal is the same: to ensure safe and effective performance of the device in accordance with its intended use.

The current regulatory approaches for medicinal products and devices reflect many years of the regulatory, scientific and public health experience and are adequate for the hundreds of new drugs, biologics and devices approved yearly around the world and used by millions of people.

**AS SCIENCE EVOLVES, ADDITIONAL SCIENTIFIC AND REGULATORY APPROACHES MAY BE DEVELOPED.**

Regulatory approaches are always evolving in response to scientific evidence. With respect to nanoscale materials, FDA, EMEA and other regulatory bodies have launched significant efforts to understand and develop appropriate approaches and to engage the public in an open dialogue.

The Alliance of Research Industries for Scientific Evaluation of Nanomedicines supports these efforts and is committed to contributing its expertise as appropriate.

**CONCLUSION**

Existing regulatory approaches are sufficient to ensure safety of medicines and devices using nanomaterials. As further scientific evidence is generated, the need for additional regulation may be considered.

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