U.S. Food and Drug Administration

Science & Research

Frequently Asked Questions

1. What is nanotechnology?

While many definitions for nanotechnology exist, the National Nanotechnology Initiative (NNI) (a federal R&D program established to coordinate the multi-agency efforts in nanoscale science, engineering, and technology, in which FDA and 22 other federal agencies participate) calls it "nanotechnology" only if it involves all of the following:

1. Research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1 - 100 nanometer range.
2. Creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size.
3. Ability to control or manipulate on the atomic scale.

For more information, see http://www.nano.gov/html/facts/whatIsNano.html[1].

2. What is the FDA's definition of nanotechnology?

The FDA has not established its own formal definition, though the agency participated in the development of the NNI definition of "nanotechnology." Using that definition, nanotechnology relevant to the FDA might include research and technology development that both satisfies the NNI definition and relates to a product regulated by FDA.

3. What products does FDA regulate and how does it regulate them?

Specific references to the types of products FDA regulates, the FDA "Centers" responsible for their regulation, and guidance on the regulatory processes are found on the FDA Internet Web Site (http://www.fda.gov/[2]). The following list is provided only for illustrative purposes:

- Biological products (vaccines, blood products, tissues)
- Cosmetics
- Devices
- Foods (for humans and animal feed, though generally not meat and poultry)
- Dietary supplements
- Drugs (human and animal)
- Radiation Emitting Electronic Products
- Color additives used in food, drugs, cosmetics, devices
- Combination products (i.e., drug-device, drug-biologic, and device-biologic products)

4. Does the FDA conduct nanotech research?

FDA has a Grants Program in support of Orphan Products Research and Development. FDA does not otherwise conduct research in support of particular product applications. FDA does not have a grants program to support other research in non-FDA laboratories. FDA conducts research in several of its Centers to understand the characteristics of nano-materials and nanotechnology processes. Research interests include any areas related to the use of nanoproducts that FDA needs to consider in the regulation of these products. As an example of current research, FDA is collaborating with the National Institutes of Health, National Institute of Environmental Health Sciences (NIH/NIEHS) on studies, as part of the National Toxicology Program, examining the skin absorption and phototoxicity of nano-sized titanium dioxide and zinc oxide

preparations used in sunscreens.

5. What are some of the issues anticipated by FDA relating to regulation of nanotechnology?

Issues that FDA anticipates include:

- The likelihood that many of the nanotechnology products that the Agency regulates will be Combination Products (i.e., drug-device, drug-biologic, or device-biologic products).
- Because FDA regulates products based on their statutory classification rather than the technology they employ, FDA's regulatory consideration of an application involving a nanotechnology product may not occur until well after the initial development of that nanotechnology.
- Because FDA has limited regulatory authority over certain categories of products, the Agency may have limited authority over the use of nanotechnology related to those products. For example, there is no premarket approval of cosmetic products or their ingredients, with the exception of color additives.

6. What will be required for nanotech products to receive FDA approval? Should consumer products be regulated any differently because they are made with nanomaterials? Are there any risks associated with these products because of their nanomaterial components?

As noted above, FDA only regulates certain categories of products. Existing requirements may be adequate for most nanotechnology products that we will regulate. These products are in the same size-range as the cells and molecules with which FDA reviewers and scientists associate every day. In particular, every degradable medical device or injectable pharmaceutical generates particulates that pass through this size range during the processes of their absorption and elimination by the body. To date, FDA has no knowledge of reports of adverse reactions related to the "nano" size of resorbable drug or medical device products. If new risks are identified, arising from new materials or manufacturing techniques for example, new tests or other requirements may be needed.

7. Are there any FDA-regulated products currently on the market that employ nanotechnology?

FDA is aware of several FDA regulated products that employ nanotechnology. However, to date, few manufacturers of regulated products have claimed the use of nanotechnology in the manufacture of their products or made any nanotechnology claims for the finished product. FDA is aware that a few cosmetic products claim to contain nanoparticles to increase the stability or modify release of ingredients. Similarly FDA is aware of nanotechnology-related claims made for certain sunscreens. We are currently not aware of any safety concerns but FDA is planning additional studies to examine the effects of select nanoparticles on skin penetration.

8. Does/Will the FDA coordinate policy on nanomaterials with other government agencies?

Coordination of activities and policy of the US Government regulatory agencies is facilitated by FDA's participation in the National Science and Technology Council, Subcommittee on Nanoscale Science, Engineering and Technology (NSET) and its Nanotechnology Environmental and Health Implications (NEHI) working group.

9. What is the FDA approval process for multiple component nanoproducts?

Current policy regarding combination products helps prevent duplication of effort and a protracted approval process. If the product meets the definition of a combination product (i.e., drug-device, drug-biologic, or device-biologic products), it will be assigned to an Agency center that will have primary jurisdiction for its regulation. The assignment of a "lead center" is based upon a determination of the "primary mode of action" (PMOA) of the combination product. For example, if the PMOA of a combination product is that of a biological product, then the combination product would be assigned to the Agency component responsible for premarket review of that biological product.

FDA published a proposed rule defining the primary mode of action of a combination product in the May 7, 2004, Federal Register[3]. The proposed rule

defines primary mode of action as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product." In some cases, neither FDA nor the sponsor can determine the most important therapeutic action at the time a request is submitted. A combination product may also have two independent modes of action, neither of which is subordinate to the other. To resolve these types of questions, the proposed rule describes an algorithm FDA would follow to determine the center assignment. The algorithm would direct a center assignment based on consistency with other combination products raising similar types of safety and effectiveness questions, or to the center with the most expertise to evaluate the most significant safety and effectiveness questions raised by the combination product.

Depending upon the type of combination product, approval, clearance or licensure may be obtained through submission of a single marketing application, or through separate marketing applications for the individual constituent parts of the combination product. For most combination products, a single marketing application is sufficient for the product's approval, clearance or licensure.

The Office of Combination Products is responsible for developing policies and processes to help clarify the regulation of combination products, and is available as a resource to combination product manufacturers throughout the development of a combination product. Its website at www.fda.gov/oc /combination [4]includes regulations, guidance documents, jurisdictional information, answers to frequently asked questions, and a variety of other information related to combination product development and regulation.

10. Who performs the safety studies that have been done on the new skin care products on the shelves that are made with nanomaterials - nanocrystalline sunscreens, deep-penetrating skin creams, personalized skin care products and dental adhesives products? Where can I find more information about this on the internet or elsewhere?
Some of these products are regulated as drugs, some as cosmetics, and some as devices, depending on medical claims made for the product and the product's mode of action. Cosmetics must be safe and truthfully labeled. The manufacturer of a cosmetic product is responsible for the safety of the product and its ingredients. Applications for new drugs must demonstrate the product's safety and efficacy or the product's bioequivalence to a previously approved drug product. Device applications must show a reasonable assurance of safety and effectiveness or substantial equivalence to a legally marketed device. Although proprietary product data may not be available, published research may include both analysis and summaries of these data

11. What new guidance or regulation will FDA publish related to nanotechnology products?
Watch for federal register announcements, and posting on FDA's website, of new guidance.

12. Is there any international regulation of nanotechnology products? Are there any penalties for not following this regulation?
There is no international regulation of nanoproducts or the underlying nanotechnology. FDA participates in multinational organizations, such as the Organization for Economic Cooperation and Development, ASTM International, and the International Organization for Standardization, where cooperative work on nanotechnology has been suggested. FDA will also work with its foreign regulatory colleagues to share perspectives and information on regulation of nanotechnology."

13. What has FDA done within the Agency to insure that nanoproducts are regulated in a coordinated fashion across all product types?
The Office of the Commissioner FDA has established a NanoTechnology Interest Group (NTIG) on which all FDA's Centers and all FDA Offices that report directly to the Office of the Commissioner participate. Within the Centers of FDA, staffs have established multidisciplinary working groups. The goal of these FDA working groups is to share information about nanotechnology and to provide a level of coordination of review for the various product types. The working groups are charged with identifying and defining the regulatory challenges in the various review disciplines and to propose a path forward. The mission of the groups is then to propose solutions to overcome these challenges.

14. What types of nanotechnology products need to be manufactured

in a sterile environment?
The current regulations and Good Manufacturing Practice guidance documents of all FDA Centers describe the requirements with regards to product sterility.

15. What is "nanosizing" of drugs?
"Nanosizing" is a term developed in the pharmaceutical industry to describe how some previously approved products with particle sizes greater than 100 nm are being produced with smaller particle sizes, in order to change certain physical and performance characteristics, such as pharmacokinetic profile (i.e. the rate and extent of absorption and clearance from the body).

16. What additional controls for the workplace need to be established by manufacturers of nanoproducts?
The National Institute for Occupational Safety and Health (NIOSH) (http://www.cdc.gov/niosh/homepage.html) and the Occupational Health and Safety Administration (OSHA) (http://www.osha.gov) provide guidance for the protection of workers.

17. What method should be used to dispose of unused/expired nanotechnology products to have the least impact on the environment?
The Environmental Protection Agency (EPA) (http://www.epa.gov[5]) provides guidance on the disposal of unused or expired nanoproducts.

18. What are the environmental impact considerations of waste products from the manufacture or use in the approval of nanoproducts by FDA?
The National Environmental Policy Act (NEPA) requires federal agencies to consider the environmental effects of any "major federal action" they propose to take, by preparing an environmental assessment (EA) or environmental impact statement (EIS) as appropriate. Agencies can establish categorical exclusions for categories of actions that do not individually or cumulatively have a significant effect on the human environment. However, agency procedures must provide for extraordinary circumstances in which a normally excluded action may have a significant environmental effect. Extraordinary circumstances identified in FDA's regulations under which its categorical exclusions would not apply include potential for serious harm to the environment and actions that adversely affect an endangered, threatened or otherwise specially protected species.

Many regulatory actions by FDA constitute major federal actions, including: actions on and withdrawal of applications to market new drugs and biological products; actions to prohibit or otherwise restrict the use of a substance in food, food packaging or cosmetics; and actions on pre-market notifications and pre-market applications for devices. Such regulatory activities may not require preparation of an EA or EIS, however, because FDA has established categorical exclusions for these and other categories of regulatory action.

For example, environmental considerations relating to drug approvals can include toxicity to organisms because of the introduction into the environment or increased levels in the environment of the active moiety due to use and disposal of the drug product. These considerations can warrant analysis of factors including the expected environmental fate of the product (involving identification and characterization of the substances of interest, environmental depletion mechanisms and environmental concentration). Under FDA's regulations, drug approvals generally can qualify for a categorical exclusion however if either: the approval does not increase the use of the active moiety; the estimated concentration at the point of entry to the aquatic environment will be below 1 part per billion; or the application is for a substance that occurs naturally in the environment and the approval will not alter significantly the concentration or distribution of the substance, its metabolites or degradation products in the environment.

19. Does the FDA guidance for the approval of drugs include Oncology Drugs?
The development of drugs, including oncology drugs, is addressed in published FDA guidance. In addition, a publication written in 1998 by DeGeorge et al. offers some additional thoughts about preclinical studies for evaluation of safety of oncology drugs. [ref: DeGeorge et al. (1998) Regulatory considerations for preclinical development of anticancer drugs. Cancer Chemother Pharmacol 41: 173-185]

20. In the development of nanotechnology medical products will it be

possible to develop characterization protocols for classes of materials such that, once one, or a few, members of the class have been characterized, no additional testing will be required to justify the use of similar members of the class in medical products?
FDA has not taken a position on this issue. FDA has experience with many "classes" of materials, nominally for the same indication or use, in which members of the class behaved very differently from one another, e.g. statins for lipid therapy. FDA has experience with implant materials such as polyurethane that are safe in one part of the body and not in others. FDA also has experience with materials for which the relationship between the physical or chemical characteristics and the biological response has been established. It may be possible to establish this relationship for nanomaterials.

21. In the development of nanotechnology medical products, particularly Combination Products, will it be possible to obtain direction from FDA on the product assignment and regulatory pathway at the point that the in-vitro characterization is completed but before any animal toxicity testing has begun? There is substantial cost associated with animal toxicity testing and the resources expended if the initial toxicity testing needs to be followed by additional toxicity testing at a later date. What beyond the physical and chemical characterization would FDA/OCP need to determine the product's 'primary mode of action'?
Most sponsors would like to know their regulatory pathway as early in the product development process as possible, and FDA strives to do just that. In fact, most combination products are assigned very early in their development. FDA/OCP generally does not need preliminary animal toxicity data to make an assignment, because toxicity data per se usually would not be reflective of a product's mode of action. OCP needs to have enough information to determine with reasonable certainty a product's modes of action and its primary mode of action. Animal data aimed at studying the mechanism of action or proof of concept usually would be very helpful though not always necessary. In determining the jurisdiction of any product, nanotechnology related or not, FDA/OCP follows the basic reasoning below:

- **Is the product a "single-entity" product (i.e., a drug, device orbiological product)? If so, which definition does the product meet?**
  Thedefinition of a drug is the most general, including articles intended foruse in diagnosis, cure, mitigation, treatment, or prevention of disease,or an article (other than food) intended to affect the structure or functionof the body. The definition of device is essentially the same, except thata device may not achieve its primary intended purposes through chemical actionwithin or on the body nor can it be dependent upon being metabolized forthe achievement of its primary intended purposes. A biological product meansa virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood componentor derivative, allergenic product, or analogous product, or arsphenamineor derivative of arsphenamine (or any other trivalent organic arsenic compound),applicable to the prevention, treatment or cure of a disease or conditionof human beings. See http://www.fda.gov /oc/combination/faqs.htm#_Toc88444667[6]for links to additional information.
- **Is the product a combination product (i.e., a product comprised ofboth a drug and a device, a device and a biological product, or a drug anda biological product)?**
  As discussed above at question 9, a combinationproduct is assigned based on its PMOA to an Agency Center or alternativeorganizational component that will have primary jurisdiction for its premarketreview and regulation. For example, if the PMOA of a device-biological combinationproduct is attributable to the biological product, the Agency component responsiblefor premarket review of that biological product would have primary jurisdictionfor the combination product.

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