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Opinion

On the evaluation of the safety aspects of nanomaterials in medical devices – a regulatory perspective

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Abstract

Nanotechnology is widely used in many aspects of the design and manufacture of medical devices. To date, many of these new medical devices, referred to as nano medical devices, have been submitted to health authorities for premarket regulatory review. There are ongoing discussions between medical device manufacturers and regulatory authorities regarding the standards and methods required for the evaluation process. Taking into consideration aspects including nano-toxicology and biocompatibility, the clinical effects of nanotechnology and risk management, there are issues yet to be resolved. In this article, we will discuss nano medical device safety from the regulatory control point of view.

Keywords

nanotechnology; nanomaterial; regulatory; medical device; risk management; usability.

1. Introduction

There is no single official definition of nanotechnology in the application of medical use, but the US FDA refers to nanotechnology as engineered materials or end products or the exhibition of properties or phenomena that are attributable to at least one of the dimensions in the range of 1 to 100 nanometers in general [1]. Due to these dimensions, the physical and chemical, and thereby the biological properties of these materials may not necessarily be the same as the same material in the bulk configuration.

The use of nanomaterial has been successfully explored in many areas such as chemical materials, electronics, IT and the biomedical industry. In Taiwan, nano-products are becoming more and more common in the domestic market, including nano-rags, nano-clothing, nano-silver deodorant liquids, ceramic nano-energy cups, nano-toilets, etc. The advertising of these products infers that they are better than their traditional counterparts with additional benefits from nanotechnology. It seems that all products designated as "nano" will offer some sort of magical and, more importantly, beneficial effects. Consequently, the Ministry of Economic Affairs of Taiwan has commissioned the Center for Measurement Standards of the Industrial Technology Research Institute (ITRI) to assess and verify the specifications of nano products. A “Nanomark” will be granted to those nano products that meet these criteria. The purpose of this assessment is to ensure that products issued with the “Nanomark” do in fact possess

certain pre-defined nanotechnology characteristics and scientific evidence to support claims regarding pollution control, antibacterial activity, deodorant properties, wear-resistance and other characteristics as described in the product specification, in order to protect the interests of consumers.

With regard to nano medical devices (medical devices that involve the use of nanomaterials or nanotechnology in general), safety and efficacy are of paramount importance. It is necessary to point out that any medical device, in particular those that employ novel technology like nanotechnology in which the toxicity of nanomaterials is not yet fully understand or there is little history of a comprehensive evaluation of the technology, their performance and safety should be properly evaluated. It is for this reason that nano medical devices have raised the regulatory concerns of the health authorities regarding safety and efficacy. For example, nano-fiber socks that are advertised as possessing antibacterial, deodorant and other functions can attract the attention of customers and increase the selling price of the product. However, the use of such products for medical purposes has garnered the attention from the health authorities, resulting in additional safety assessments on the nanomaterial used before granting marketing authorization. In this context, it is crucial to ensure that the nanomaterial creates no new hazards to human health or the environment compared with the traditional product, and the product offers the features depicted in the specifications. For that, functions such as antibacterial and deodorant activity may not seem critical compared with a safety evaluation. The situation is further complicated by developments in nanotechnology, whereby nanotechnology applications in different disciplines are integrated into a single purpose, like combination products that combine any two or even three of nanotechnology utilizing medical devices, drugs and biologics, making product classification difficult. Consequently, the product review can be problematic. A systematic and multi-disciplinary approach is therefore necessary, and particular attention should be paid during the regulatory review of these products.

2. Medical applications of nanotechnology

Nanomedicine generally refers to the clinical application of nanotechnology to provide a novel therapy or diagnosis, including diagnostic equipment, drug delivery devices, gene therapy and tissue engineering. In 2003, Miller recommends the definition of nanomedicine as "the monitoring, repair, construction and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures" [2]. As nanotechnology manipulates nanostructures at the molecular level, it could potentially generate substantial changes in properties such as the melting point, electrical, magnetic, optical or surface properties and chemical activity and thereby have an impact on the biological properties within a limited space. These modifications could make products that are not just smaller but also lighter, more flexible, mechanically stronger, more sensitive, more selective or more efficient.

The regulatory control of nano medical devices should consider the product's safety, efficacy and quality. The safety of nano products is of particular importance, especially when in contact with the surface of the human body. Additionally, it is unclear whether or how the absorption and distribution of nanomaterials in the human body would introduce new risks. With regard to product efficacy, the manufacturer should determine the material's size, shape, structure and distribution to ensure that the nanomaterial reaches the nanoscale, resulting in the predetermined and desired new properties, features or enhancements. In terms of quality, manufacturers should pay attention to validation, verification, uses and manufacturing processes in relation to the nanomaterial. To sum up, the important issues related to the regulatory control of nano medical devices include the definition of the nano medical device, classification, premarket approval procedures, good manufacturing practices, labeling and postmarket

surveillance. In view of the complexity of the technology involved, it will be a challenge to establish a regulatory requirement and procedure to control nano medical devices, whether it is a nano medical device used on its own or in combination with other equipment or drugs. Ultimately, the aim of regulatory authorities is to ensure that the product offers improved treatment to the benefit of patients without incurring unacceptable risk.

There are already a variety of nano medical devices that have been allowed onto the market by the US FDA [3]. Generally, these products serve the same clinical purpose as the related traditional medical device. However, the incorporation of a nanomaterial improves its effectiveness, performance or functionality, such as in antimicrobial dressings, dental materials, orthopedic materials like bone cement, and *in vitro* diagnostic reagents [3]. It is the FDA's current thinking that regulations can only be based on the current best information, and the product has to be fundamentally safe and effective, independent of whether the product employs a nanomaterial [4-5]. The product should, therefore, comply with the basic, relevant premarket review procedure and registration regulations and, if necessary, comply with relevant nanotechnology evaluations like toxicology assessments.

The assessment of the safety and effectiveness of nano medical device is very much an ongoing development process for health authorities as well as academia in many countries. In fact, many nano medical devices that are currently on the market were approved through the conventional medical device approval procedure without taken full consideration of the presence of the nanomaterial. Having said that, some health authorities are becoming more aware that the traditional assessment approach may not be fully appropriate for nano medical devices, particularly in terms of assessing the risk associated with the nanomaterial. Recent animal studies have also demonstrated that nanomaterials exhibit many unique toxicological properties. Therefore, in contrast with traditional products, nano medical devices require more careful consideration in the safety assessment and the development of a standardized evaluation protocol.

In Taiwan, the Ministry of Health has expressed a high degree of concern regarding the regulatory control of nano medical devices, and is looking into the relevant regulatory procedures for control nano medical devices. Future regulations for nano medical devices may include a pre-market review, quality management systems and post-market surveillance. Of those topics, there are issues of particular interest, including risk management, safety and efficacy assessments, nano process validation, labeling and warning, adverse event reporting and recall, and monitoring. The risk assessment of the effects of nanomaterials on public health should be a long-term, evolving process. It is important to maintain communication with experts in the area to ensure the speedy exchange of information, and to plan and adjust the risk assessment/management procedure accordingly. At the moment, although the international community does not regard the development of new legislation for nano medical devices as being necessary, it is important to pay close attention to the development of any international standards in order to formulate or adjust the relevant review mechanisms.

3. Risk assessment for nanomaterials

For the regulatory control of nano medical devices, in addition to regulations and product pre-market review mechanisms, risk management forms the basis of nano medical device assessment and the establishment of nano medical device regulations. For many nano medical devices, there is a fine balance between risk and effectiveness, especially in the medical field where nanomaterials are emerging as a promising approach for diagnostic technology and new treatment modalities [6]. In contrast to bulk

materials, nanomaterials can exhibit very different physical, chemical and biological properties that differ from expectation, which could result in new risks that need proper evaluation and even control before marketing is permitted.

There is currently no specific standard for risk management regarding nano medical devices; however, the international standard ISO 14971 (Medical devices – Application of risk management to medical devices) could be used for this purpose. Like traditional medical devices, the existing standard operating procedures can be used, with special attention paid to potential hazards related to the properties and phenomena that can result from the nanomaterial or nanostructure. These potential hazards should be first identified, estimated and evaluated according to the predefined risk acceptance criteria. If necessary, risk control measures should be implemented, thereby ultimately ensuring that the product's benefits outweigh the risk [7]. The Identification of nano-hazards requires in-depth and in some cases multi-disciplinary knowledge of the product's technology, application environment, regulatory requirements and even usability. Nano medical devices may on first appearance look exactly the same as their traditional counterparts, but for this exact reason, their usability becomes very important and the use hazards should be properly evaluated if necessary, as usage error may result from failure to tell the nano device from the traditional product. The use of standards like ISO/IEC 62366 [8] and ANSI/AAMI HE75 [9] are just some of the best currently available tools to address the usability issue. The identification of hazards can be performed systematically according to the different characteristics of the nanomaterial. For a nanomaterial with a novel structure, the hazards are usually more difficult to predict (as compared with a micronized material such as metal oxide, titanium dioxide or zinc oxide). In cases where these nanomaterials are enclosed within a surface coating or matrix material, the biological reactivity and mobility will be contained. However, the durability of the enclosure would then need to be considered in order to avoid the unexpected leaching of these nanomaterials into the environment.

Toxicology is obviously a major risk of nanotechnology that needs to be addressed. Nanotoxicology risks are still very much debatable issues, and most result from various pathways of adsorption into the body. Therefore, a nanomaterial unexpectedly or uncontrollably entering the human body through the skin or by inhalation is a concern. Research studies have shown that as a material's particle size becomes smaller, the total surface area of the potentially inhaled or adsorbed particles becomes greater, leading to increased toxicity [10]. Airborne nanomaterials are often the main culprit in terms of toxicity. In order to assess the effects of exposure, adsorption, transport and distribution within the human body, various factors need to be taken into consideration, including the particle concentration in air, particle size, shape, surface area and surface chemistry.

4. Nano-toxicology

Some types of nanomaterials may be harmful to humans. They can be classified into the following two kinds of nanomaterial structure:

1. Free form nanoparticles: this refers to the direct use of nanoparticles in the manufacturing process. This usually consists of a single element, compound or complex mixture type that can be released into water and air or accumulate in soil.
2. Fixed form nanoparticles or nanocomposites: this refers to a nanomaterial that becomes part of a product, which may be nanocomposites or nano surface structures.

Compared to fixed nanoparticles, it is imperative to explore the possibility that free nanoparticles could be harmful. Since nanomaterials are quite different from the original material, the related toxicity is expected to be unlike that of the original material. Generally, it is difficult to obtain a uniform particle size distribution (monodisperse) in a nanoparticle formulation. In the absence of a stabilizing agent, nanoparticle aggregation is likely to occur, which could deteriorate the properties of the product and introduce complications in particle size characterization. Some nanomaterials, such as carbon nanotubes and metal oxides, tend to form clusters [10-11]. A larger particle size could potentially reduce membrane permeability and discourage dispersion throughout the human body, such as in the respiratory tract [11-12].

There are four ways that nanoparticles can enter the human body: through the skin, by inhalation, oral ingestion or during a medical procedure (e.g. release from implants). Exposure assessments are used to evaluate the risk of human in contact with the nanoparticle product. This should include the whole life cycle of the product starting from synthesis to disposal. Although the main concerns are the hazard to the customer during product usage, assessments should also be done after disposal to evaluate nanoparticle release into the environment. Furthermore, the manufacturing staff remains the most likely population to be exposed to nanoparticles, and should be properly evaluated during risk management. The nanoparticle exposure assessment could vary between different products, and should depend on the product design to assess any potential risks.

The dimensions of the nanomaterial affect its toxicity. For nanoparticles, smaller particles are usually more active and potentially more toxic. Moreover, one should take into account the shape factor. The human immune system is poorly defensive against nanoparticles, and does not recognize nanoparticles. For instance, the defense mechanism in the lung cannot deal with nanoparticles less than 70 nm in size [6,13]. Nanoparticles less than 50 nm in size can easily enter and move into the nucleus of human cells, and 30 nm particles may damage the central nervous system [6,13].

It is evident that nanomaterial research and risk assessments are urgently needed to clarify the potential effects of these materials on humans, particularly in terms of cardiovascular, carcinogenic, reproductive, developmental, immunological and neurological aspects. Although there are still many uncertainties and limitations in the current understanding of nanomaterials, it is essential to conduct risk assessments on nanomaterials and nano medical devices before the product is allowed to be marketed.

5. Conclusions

In view of rapid advancements in the field of nanotechnology, it is very challenging to come up with a set of nano medical device regulations that can cover all the relevant issues. For currently listed nano medical products, such as those containing nano silver antimicrobial dressings, the FDA review process has been completed. This will serve as a classic example for the regulatory regulations on a nano medical device. However, it is questionable whether such an example can be directly extended to other kinds of nano medical devices because the risk and benefit factors are likely to be very different. For instance, nanoparticle drug delivery systems that work by targeting tumors and nano silver antimicrobial dressing products are based on completely different scientific principles. Nevertheless, it is mandatory for the manufacture of nano medical devices to meet quality, testing and safety and other regulations in order to protect the manufacturing staff, customers and end users. Equally important, device manufacturers are also required to submit product development, testing and registration applications with other related information to the relevant regulatory body for proper evaluation. Because of the diversity of

nanomaterials that can be applied to medical devices, regulatory regulations are important, and frequent updates are needed to keep pace with rapidly emerging applications.

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