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REGULATION OF NANOMEDICINE: ARE THE AGENCIES GEARED UP?

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ABSTRACT

This article is intended to focus on importance of nanomedicine whether the existing regulations or laws are appropriate to maintain safety or if a new *ad hoc* regulatory framework is needed. The regulatory agencies face significant barriers to reform regulatory guidance for nanotoxicological evaluation and the future of nanomedicine will depend on how these challenges are addressed. There is absence of clear regulatory guidelines for regulation of this developing trend of medicine. I think nanomedicines is difficult to address using existing regulations so a new law may be required to manage potential risk of nanotechnology based medicine. Current guidelines for the assessment of medicines, medical devices are based on the application of voluntary standards, none of which contain standard validated specifically for nanoparticles. New methods and standards need to be considered (e.g. particle size and material characterization) simultaneously with new analytical tool to assess drug inside nanosystem. For setting up new guidelines the integration of experience by EMEA's, US FDA, ACADEMICS, SCIENTIFIC COMMUNITY etc. must be considered.

Keywords: Nanomedicine, Nanotoxicological evaluation, Nanoparticles

INTRODUCTION

In the United States a critical basis for environmental regulations is the Toxic Substance Control Act (TSCA) enacted in 1976, the TSCA Authorized the environmental protection agency (EPA) to assess safety and risk on human health and environment due to conventional medicines and nanomedicines. The regulatory challenge is therefore to ensure that society can benefit from novel applications of nanotechnology, whilst a high level of protection of health, safety and environment is maintained and benefit over weigh's the risk. Authorities regulate products in a product by product basis they do not regulate technology unless claimed. The US FDA has a task force, but feels that existing regulations can govern

nanomaterials. According to FDA there was no evidence that nanoproducts are more risky than comparable non-nano products but the properties, characteristics, risk, benefit may be altered due to very small size. In European Union also there is no specific nano-medicinal legislation. However in the long term none of these regulations or directives was written with nanomedicinal applications in mind and will need to be revised accordingly to take into account specific risk and challenged posed by nano medicine. [1] According to EU perspective if existing regulations are modified to make them more nano-conversant, existing risk methodologies will also have to be adopted to introduce agglomeration, particle size, shape and surface reactivity into the assessment criteria. Our focus is on five jurisdiction (US,UK,EU,AUSTRALIA and CANADA) and selected a set of six recommendations according to US EPA regarding regulations of nanomedicines .The article contains FDA task force report, EU guidelines, ICH guidelines and Scientific Community reports regarding nanomedicines and reports of various papers on nanoethics. Nanotechnology in biomedicine presents a number of highly complex problems for which the solutions should came from the frontiers of scientific knowledge in a global integrated manner, improving regulation and promoting better access to this new technology.

Nanomedical Development:

Nanopharmaceuticals are part of the therapeutics area of nanomedicine which is divided into "nanopharmaceuticals" and "nano-enabled devices". Other areas include surgery, diagnostic (including imaging), implant technology, bionics, bioactive surfaces, tissue engineering, textiles and actuators.Nanopharmaceuticals refer to innovation in drug delivery and medicines based on the use of nanoparticles of the active ingredient. Nanoparticles can also be used as a carrier material or porous material from which the active ingredient is released in a controlled manner.

The general EU pharmaceuticals regime under which nanomedicines may fall is a well-established, dynamic and complex system of multi-level regulation .It is composed of European and national legislation which is accompanied by a large body of soft law. To date, in the EU no specific rules have been established with regard to nanomedicines. Thus the current regime as it stands is applicable to the market authorization of nanodrugs as well. The approval follows either the centralized or the mutual recognition procedures laid down in the medicinal product regulation. [2]

Nanopharmaceuticals that are qualified as advanced therapy medicinal products can be approved only by the centralized procedure. To nanomedicinal products that combine medical devices and medicinal products ('borderline products') provisions of the EU medical devices Directives may apply. The application of the regulatory regime depends whether the product falls within the definitions of medicinal products, ATMPs or medical devices. The primary mode of action is the criteria for determining the applicable regulatory regime. This means, for example, that nanomedicines with a primary mechanical action and secondary pharmacological action are brought under the medical devices regulation regime.

Overview:

Medicinal products (mps)

I GENERAL CONDITIONS (GC)

Marketing Authorization Conditions:

1. 2001/83/EC (Mutual Recognition Directive - optional)
2. 2.EC/726/2004 (Centralized Procedure Regulation –mandatory and optional)

Principles and Guidelines

1. Good Clinical Practice – clinical trials of MPs (Directive 2001/20/EC)
2. Good Manufacturing Practice for MPs (Directive 2003/94/EC)

3. Good Clinical Practice – investigational MPs (Directive 2005/28/EC)

II ADDITIONAL CONDITIONS (GC+)

Specific Product Regulations (Implies Additional Conditions)

1. Advanced Therapy MPs (Regulation EC/1394/2007)
2. MPs for Pediatric Use (Regulation EC/1901/2006)
3. Orphan MPs (Regulation EC/141/2000)

Specific Substances Directives (Implies Additional Conditions)

1. GMOs (Specific provisions under Dir. 2001/83EC)
2. Human Blood and Plasma (Directive 2002/98/EC)
3. Human Tissue and Cells (Directive 2004/23/EC)

COMBINATION PRODUCTS (Conflict Rules under Directive 90/385/EEC as amended by Directive 2007/47/EC)

- AIMD administering MPs (Each part separate evaluation- under Directive 2001/83/EC and Directive 90/385/EEC)
- MPs incorporated as integral part of device/AIMD (Directive 90/385/EEC)

MEDICAL DEVICES (MDs)

- Active Implantable MDs (Directive 90/385/EEC)
- MDs (Directive 93/42/EEC)
- In Vitro MDs (Directive 98/79/EC)

Regulation of nanomedicine in USA:

Under federal law, medical devices are subject to jurisdiction of the FDA, according to the Food, Drug and Cosmetic Act, for the purposes of ensuring that they are safe and effective. It is foreseeable that the FDA will be fully charged with regulating nanomedical devices and drugs. The FDA will need to be able to determine that the nanodevices are safe, that, when used as intended, the probable benefits to health will outweigh any possible risks of harm or injury, and that they are effective, meaning the products do what they are supposed to do in a reliable fashion. The FDA must also attempt to balance the promotion of timely patient access and the fostering of innovation against the need to protect the public's health by guarding against potentially unsafe technologies. [4]

The FDA has chosen to attempt regulation of nanomedicine by applying current regulations to the emerging technology. The FDA made a similar decision when it first encountered the issue of regulating biotechnology. Biotechnology is the "use of living organisms or their products to modify human health and the human environment. When first confronted with biotechnology, the FDA did not create any new regulations or establish a new center to handle its regulation; it just incorporated the biotechnology products into the current regulatory scheme by looking at products on a case-by-case basis. Before attempting to predict issues that might arise by applying the current regulatory scheme to nanomedicine products, it is important to look at how the FDA functions. Despite recent economic shortfalls, the FDA has made an effort to educate itself on the topic.[5]

In August of 2006, the FDA launched the Nanotechnology Task Force to "identify and recommend ways to address knowledge or policy gaps and to facilitate the safe and effective use of nanoengineered materials in FDA-regulated products. This Task Force investigated topics such as the FDA's ability to identify products containing nanoscale materials, its scope of authority to evaluate the safety and effectiveness of such products, and whether the FDA should require or permit products to be labeled as nanoscale materials.FDA expects many nanotechnology products that we regulate to span the regulatory boundaries between pharmaceuticals, medical devices and biologicals. These will be regulated as" Combination Products" for which the regulatory

pathway has been established by statute. In such cases, FDA will determine the "primary" mode of action of the product. This decision will determine the regulatory framework for the product, i.e. a drug, medical device or biological product. The product application will be managed by the appropriate FDA Center with consultations from the other Centers. It is valuable to repeat here that FDA has traditionally regulated many products with particulate materials in this size range. FDA believes that the existing battery of pharmacotoxicity tests is probably adequate for most nanotechnology products that we will regulate. Particle size is not the issue. [6]

As new toxicological risks that derive from the new materials and/or new conformations of existing materials are identified, new tests will be required.

FDA regulates products, not technology. FDA, for example, regulates very few materials but many types of products. This will affect the stage at which the FDA becomes engaged in the regulation of nanotechnology and when, in the process, regulation takes effect. In addition, FDA regulates only to the "claims" made by the product sponsor. If the manufacturer makes no nanotechnology claims regarding the manufacture or performance of the product, FDA may be unaware at the time that the product is in the review and approval process that nanotechnology is being employed. Within this issue is embedded the definition of nanotechnology. It is quite likely that new therapeutic benefits are being derived from products that are smaller than their traditional form but fall above the 100 nm size-range limit of nanotechnology.

ICH Regulation of Nanomedicine:

An international treaty or convention on nanotechnology generally or nanomedicine specifically would be the most formal approach to international harmonization. There are currently no international treaties in existence that directly apply to nanomedicine, and the likelihood of such an agreement in the near future seems low, given the lack of any sense of crisis (cf. global warming), the absence of any preparatory activities to date, and recent activities in the European Union in particular starting down their own regulatory path that is likely to differ from that of the United States. Moreover, attempts to negotiate such a treaty would likely face formidable obstacles, such as the ongoing disagreement between the United States and European Union on the appropriate role of the precautionary principle in international agreement. For example, a key sticking point in the negotiation of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity, which governs international trade in genetically modified organisms, was the role to be given to the precautionary principle. [7] In the absence of a formal international treaty or convention, which appears to be unlikely for the near future at least, a number of other international harmonization approaches are possible and in some cases are being pursued. The Organization for Economic Co-operation and Development ("OECD"), an organization of 30 industrialized countries, has taken a lead role in encouraging harmonization of nanotechnology polices and regulations. The OECD has established two working groups to promote this objective – the Working Party on Manufactured Nanomaterials ("WPMN") and the Working Party on Nanotechnology ("WPN") [8] (It is perhaps a troubling sign of the challenges of achieving a unified approach that the OECD itself has established two separate working groups with similar names and missions rather than a single, unified committee).

UK:

In terms of activity on nanotechnology research and policy development by Government

departments in the UK, a few of the key players to date have been:

- The Department for Environment, Food and Rural Affairs (Defra);
- The Food Standards Agency (FSA);
- The Department for Business Enterprise & Regulatory Reform (BERR);
- The Department of Health (DH);
- The Health and Safety Executive (HSE); and
- The Department for Innovation, Universities & Skills (DIUS).

Defra has played a leading role on the development of nanotechnology policy and regulation in the UK. Defra plays an oversight role for the regulation of the food industries, and is the government department responsible for environmental protection in the United Kingdom (among other responsibilities, including fisheries and rural communities). Notably, Defra leads for the UK at the EU level on the environment file (with the exception of climate change) and has thus also been actively involved in the nanotechnology debate at the EU and international levels. As its name implies, the Food Standards Agency also has a role in the regulation of food products – it is an independent regulatory agency with the mandate to protect the public's health and consumer interests in relation to food in the UK. The Department of Health has responsibility for the regulation and medicinal products, through the Medicines and Healthcare products Regulatory Agency, an executive agency of the DH. The Health and Safety Executive, an agency of the Department for Work and Pensions, has a mandate over the regulation of nanotechnology as it relates to worker safety. The Department for Innovation, Universities & Skills is also heavily involved in the nanotechnology policy debate, but it is not a regulatory department; DIUS is mainly involved with the innovation and research aspects of nanotechnology. [9] The Ministerial Group on Nanotechnologies is currently chaired by the Minister of State for Science and Innovation from DIUS. Finally, the Department for Business Enterprise & Regulatory Reform (BERR) has responsibility for broad oversight over regulation in general. BERR houses the Better Regulation Executive, and leads the regulatory reform agenda across government.

AUSTRALIA:

In Australia, the federal regulatory agencies with jurisdiction over areas of particular relevance to the nanotechnology debate are as follows:[10]

- The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) – responsible for the regulation of industrial chemicals;
- Food Standards Australia New Zealand (FSANZ) – governmental body responsible for developing food standards for both Australia and New Zealand; and
- The Therapeutic Goods Administration (TGA) – the regulatory body for therapeutic goods (including prescription, over-the-counter, and complementary medicines; medical devices; blood and tissues; and other therapeutic goods) in Australia.

Occupational health and safety (OHS) in Australia is regulated at the State level rather than federal level. However, a federal body – the Australian Safety and Compensation Council (ASCC) – is charged with leading and coordinating national efforts to promote best practice in OHS and with developing national policy on OHS issues and matters of worker compensation. [11]

The 2007 Monash Report on nanotechnology regulation recommended that all federal regulatory agencies should undertake to conduct their own in-house regulatory assessments to identify potential gaps in the regulation of products falling under their oversight. [12] To date, both NICNAS and TGA

have undertaken this activity, although the results of these evaluations are not yet publicly available. In the case of NICNAS, representatives from industry, the community and academia make up the Nanotechnology Advisory Group, which has been established to advise on strategies for addressing the regulatory and safety impacts of nanomaterials. [13] The work of this Advisory Group is ongoing. On the TGA website, a question and answer section on *Nanotechnology and therapeutic products* indicates that while the existing regulatory framework of the TGA has been adequate to date to identify, assess and manage the risks associated with therapeutic products incorporating nanotechnologies, the continued development of nanotechnologies will likely pose regulatory challenges in the future. The TGA response to nanotechnology has been to undertake an in-house, science-based review of the capacity of their regulatory framework to deal with future generations of nanotechnologies. The results of this in-house review are not yet publicly available.

Conclusion:

Nanomedicine offers enormous promise for improving health care and health outcomes, but also involves uncertain risks that will need to be adequately managed for this new technology to achieve its promise. As regulatory agencies around the world are simultaneously struggling with regulatory issues of nanomedical products, there may be important benefits from attempting to harmonize national regulations. [14] Given that a formal convention or other international agreement seems unlikely in the near-term, a variety of informal governmental and non-governmental initiatives exist to promote international harmonization or at least coordination. Only time will determine how successful these initiatives will be.

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