Nanotechnology and Its Medical Applications: Revisiting Public Policies from a Regulatory Perspective in Australia

Regulatory issues in nanotechnology contribution

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Abstract: Nanobiotechnology is an immensely potential invention, which is expected to bring about revolutionary changes in many aspects of essential human needs including medical treatments and foods. Although the technology has passed through its embryonic stage, its medical applications in preparing and delivering drugs to target cells of human bodies to cure incurable diseases are still under scientific scrutiny. A 2007 study suggests that Australia needs to have a review of its regulatory framework for nanotechnology by 2017. This article examines the current regulation of nanotechnology and its medical applications in Australia, and observes that it would be premature to impose any stringent regulation at this stage on medical experimentations. We are of the view that an excessively precautionary policy may hinder further research, which is critical to discovering the benefit and harm with certainty. Hence, in the greater interest of the facilitation of research and affirmation of benefits of this technology, we recommend that adopting a hybrid regulatory method composed of self-regulation and accommodating government regulation would be an appropriate policy approach to the regulation of nanobiotechnology. We also accept the need for a set of internationally harmonized policy principles to guide our actions in relation to this technology.

Keywords: Australia; nanobiotechnology; public health; regulatory policy.

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1 Introduction

"Plenty of room at the bottom"– a 1958 prophetic saying of Richard Feynman is believed to be a breeding ground of today's nanotechnology [1], which represents a large and multifaceted area embracing several potential technological discoveries [2]. It is a multidisciplinary area of study that embraces materials science, biology, physics, chemistry, and engineering, which has already led to developing new materials in several areas including health care, food, and cosmetics, and has the potential to influence every sector of our national economy and aspects of our daily life [3]. The term "nano" is originally derived from the Greek word meaning "dwarf" [4], and nanotechnology is defined as "the design, characterisation, production and application of structures, devices and systems by controlled manipulation of size and shape at the nanometre scale… that produces structures, devices and systems with at least one novel or superior characteristics or property" [5]. This technology has "the ability to arrange atoms and molecules with a level of precision that produces materials and processes that either improve the performance of an existing product or process (e.g. lighter, stronger, more efficient, transparent

sunscreens or coatings) or create an entirely new product (e.g. targeted drug delivery, diagnostics…)" [5]. It is, thus, a way of manipulating and utilizing materials on a small scale, measuring at the scale of tenths of a million to one billionth of a meter.

Nanotechnology is said to be "an extremely powerful emerging technology" having the potential of significantly impacting medical technology [6]. Nanobiotechnology, a subset of nanotechnology, is a fast-growing area of medical research with many innovative developments being made worldwide [7]. Its application to medical science is considered as "a milestone on the road to pioneering technologies adopted for the diagnostics and treatment of various diseases that were once considered grave" [6]. Nanotechnology is widely believed to be a solution to, among other things, several critical health problems including cancers and will predictably bring about fundamental changes in the existing health care system. Although this technology has been used in a range of products such as cosmetics, food, pesticides, and so on, its direct application for medical purposes, other than using as a contrast agent for the MRI image and as a drug carrier in a very restricted manner, is still largely in an experimental stage on animals. However, it is a matter of concern that a safe experimentation on animals does not necessarily provide any certainty that the same device would be safe for humans [8]. Likewise, a potential risk assessment carried out using the standards of bulk materials of a given substance may not have an absolute correlation to the safety concerns of the same substance when used in a nanoscale [9].

Numerous experiments carried out in different countries indicate unique potentials for the revolutionary development in medical treatment in terms of both the preparation and delivery of medicines. However, these potential benefits are overshadowed by some still uncertain suspected health risks [10], which equally concern both the governments and the general public across the globe. This is so because the functional system of engineered nano-bio-products and procedures largely remain undiscovered when it comes to toxicity and health safety concerns, for which nanotechnology is sometimes called a double-edged sword [10]. Hence, it invites regulatory guard in order to ensure its responsible growth, and safe and effective application to humans, and this new challenge has to be dealt with "an appropriate and balanced oversight" [3].

At present, no specific regulatory measures exist to eliminate or minimize potential risks mainly because the risks are yet to be accurately ascertained. Admittedly, the regulations currently in place are not sufficient to ensure public safety from nano-products [11]. Amid the uncertainty of risks at hand, regulators, to date, are mainly reliant on the existing regulatory regimes designed for general public health and safety when the technology comes to medical treatment, and the predominant policy as widely adopted particularly in Europe and the US is precautionary [3]. The precautionary policy has its critics who argue that such a policy will inhibit the discovery of the full potential of nanobiotechnology. For example, Perez asserts that the precautionary principle aims to halt all usage of the technology until proven to be safe [12]. It means the predominant policy adopted for the regulation of this important technological development itself is under its critics' microscope, demanding further research for a more acceptable method of its regulatory oversight.

This article examines the public policies dominating the current approach to the regulation of bionanotechnology in Australia in view of regulations in major jurisdictions including the US and the European Union (EU). It considers the potential regulatory impacts on the flourishment of this emerging technology for public health and safety. We conclude with recommendations on the usage of nanobiotechnology for various medical purposes aimed at striking a balance between facilitation of its development and assurance of public safety in Australia. The following section demonstrates the medical uses of nanobiotechnology and its corresponding regulatory needs.

2 Medical application of nanobiotechnology and the need for regulation

Human societies have been constantly striving to improve health care services around the world since time immemorial. Achieving an improvement in relation to preparing medicines or conducting medical procedures is inherently connected with the corresponding development of science and technology. As dividends for investment in health care, it has been evidenced that significant improvements have taken place worldwide in the area of scientific investigations, and further developments are generally always in the horizon. Some of the major applications of nanotechnology for medical purposes are briefly stated below more applications can be found in ref [4].

a. Drug delivery through a non-therapeutic delivery vehicle

   The traditional drug delivery system is thought to be inefficient in that it is effected either through medicine to be swallowed by the patient or to be injected

typically into certain body parts of the sick person allowing the drug to freely travel all over the body, being carried by blood, instead of delivering the treatment to precisely the very affected cells. Thus, the traditional methods of delivery naturally produce both benefits and detriments for the patient in that the medicine indefensibly affects the healthy cells causing their permanent damage or temporary impairment. Conversely, the application of nanoparticles can avoid harm to the healthy cells of the patient by delivering the drug molecules exclusively to the cancer or diseased cells; hence, drug delivery is currently one of the prime concerns of nanobiotechnology. This way of drug delivery into cells is termed as "transfection", and, in fact, researchers have only begun to develop the potential applications for this transfection, which is believed to play a significant role in advancing the application of biomedicines [13]. Nanoparticles for drug delivery and vaccines were first developed in the late 1960s, even before the very word "nanoparticle" was coined [1]. The advantages of drug delivery using nanotechnology are significant. These include (i) the control of pharmacokinetics; (ii) the separation of pharmacokinetics from therapeutic activity; (iii) payload capacity; (iv) multiple affinity effects; (v) the combination of therapy effects; and (vi) Trojan horse effects [for details, see Ref [1]. A nano-carrier could enable a drug to breach certain biological obstacles to reach the target cells in the human body more efficiently than the existing method of drug delivery can do [14].

b. Formulating and developing nanomedicines
Nanomedicines aim to improve "traditional medical approaches of diagnostics and therapeutics by taking them to the cellular and molecular level with nanotechnology" as characterized by the European Commission [1]. Several nanomedicine products, such as miniaturized nanofluidic devices and systems may transfer fluids efficiently to the target area, preventing turbulence and mixing. Such a medicine could successfully reach the target cells, such as cancer cells, with a greater sensitivity and specificity as well as improved effectiveness. Also, this helps in minimizing the side effects that could have been produced by an alternative drug not containing nanomaterials [15, 16]. It is still an emerging hypothesis that nanomedicines, otherwise called nanorobots, can deliver and efficiently distribute drugs to targeted cells of human bodies, which could make a breakthrough in the treatment of many complicated diseases such as cancer [6].

c. Disease diagnosing and monitoring system
Nanorobots can be used for better diagnosis of various pathological conditions and can also help reduce intrusiveness and achieve greater fidelity of results because they can examine the target cells keeping them active in the actual host environment [6]. The US Food and Drug Administration (FDA) has approved "immunoassay" as a type of test reliant on nanotechnology, which is able to identify or quantify certain harmful toxins or other foreign substances such as antigen and antibody bindings [17]. This test can be carried out using gold nano-particles.

d. Preparing pharmaceuticals
Separate chemical constituents of a nanomedicine that might be individually incapable of therapeutic use on humans are mixed up to create a new nanoscale medicinal product with therapeutic benefit [17]. This new product offers an advantage over its traditional equivalent with respect to both its absorption and administration [17]. Some vaccines, for example, are engineered by employing this preparation process. Nanoparticles, in the preparation of these vaccines, are made to mimic viruses, and these particles are made up of a lipid envelope that undergoes a form of surface modification [17]. Following this modification, "these nanoparticles are functionalized with the surface proteins of a virus such as influenza; this confers therapeutic activity to the nanoparticles by allowing them to fuse with target cells and stimulate an immune response response" [17]. Epaxal, which is an aluminum-free vaccine for hepatitis A, is an example of this type of drug [17].

e. Anticipated wider future applications
The extent of future usage of this technology is virtually beyond comprehension at this stage. It is expected that nanotechnology will immensely contribute to the advancement of both medicines and medical procedures, for example, pharmaceuticals, drug delivery, disease diagnosis, gene tissue repair, therapy, and cell therapy, just to name a few [18]. This technology is also expected to assist in regenerating human organs and tissues to supplant those that have been somehow damaged [15].

The immense potentials stated above may be hindered by several impediments, such as complexity of clinical trials and safety concerns, as feared by stakeholders including the government, which persuasively invite regulation of this area. However, formulating and implementing this regulation in a meaningful way, ensuing public safety and fostering innovations, are not an easy task. The challenges

are extremely complicated as the potential risks are still poorly understood by researchers and will remain so for years to come [19]. The risks are undeniably uncertain at its best, and unknown at its worst – that makes the challenge to deal with the potential harm complex and confronting [10, 19, 20]. Consistently, Miller describes, in agreement with Dr. Landrigan, that "the problem of nanotechnology is a complete lack of knowledge, not only on the part of the government and researchers, but also on the part of the public in general" [21]. Miller further adds that this unawareness extends to almost every aspect of this technology such as "the potential effects, benefits, uses, and regulations necessary for new nano-containing products" [21]. Dana echoes a similar view that risks are still theoretical in the absence of any credible studies suggesting substantial health harm of nanoparticles [19].

Amid such uncertainties, no country has yet developed any comprehensive set of rules to regulate nanomaterials for preventing their potential harm [5], possibly due to lack of knowledge of the risks involved [20]. This further demonstrates the complexity of regulation of this emerging technology primarily because it involves dealing with a "two-edged sword" that embraces both risks and rewards [14], and it requires managing or controlling little known or completely unknown risks [20]. Pointing to different problems, Quinn infers as the bottom line that "it is very difficult to regulate these unknowns to adequately ensure safety, without unnecessarily hampering the development of the technology" [9]. Despite these uncertainties, the issue of regulation has been a concern of all stakeholders calling for regulation worldwide.

3 Need for regulation of nanotechnology-based biomedical innovations

While we are looking for the benefits of nanobiotechnology, we need to give due consideration to its potential detriments, otherwise the benefits will not be enduring. The motivation for such a call for regulation pertains to the potential harm that the nanobiomedical innovations may cause [22]. Nanomaterials, by virtue of its very nature, are able to travel into human bodies defeating or evading any ordinary defences [14]. Regulation, in general, requires an assessment and ascertainment of the inherent harmfulness or toxicity of a particular material or procedure. Some Australian scientists noted that "the unique physiochemical properties of nanomaterials include their unique bioavailabilities and other characteristics that make them potentially toxic to humans" [23]. This makes nanomedical interventions frightening for recipients of unforeseeable or indeterminate harm [14]. As scientists anticipate, nanomaterials may miss the target cells/tissues and affect unintended parts of a human body including vital organs such as the brain, liver, and kidneys [24]. So they could undesirably damage normal functions of active cells by triggering DNA damage or producing harm including inflammation, immunoreaction, or cancer [14]. A major concern is their long-term detrimental effects because, unlike the molecules used in conventional medicines, some nanomaterials cannot be efficiently removed by the recipient human body [14].

Risks may vary depending on the nanomaterials used in a given medicine or medical procedure. Engineered nanoparticles designed for drug delivery can be made of different materials that include gold, silver, carbon, diamond, iron, and silica. Among these different conduits, gold nanoparticles are found to be more effective than others particularly for drug delivery in that "gold nanoparticles are exposed to infrared light, they melt and release drug payloads attached to their surfaces" [25]. On the other hand, nano-silver is said to be the safest one [21]; nonetheless, it may not be completely harmless [13]. Apart from the harm that may be caused by nanomedicine and medical procedures while employing nanobiotechnology, nanomaterials may harmfully pollute the environment, contaminate food, taint cosmetics, and so on. However, this article is confined to the usage of nanotechnology for biomedical purposes only, although the discussion and recommendations may also be applicable to other harmful impacts of this technology.

The risks related to nanobiomedical interventions are not only associated with the direct use of the material itself but also to its size. The most significant feature of nanoparticles is their extremely small size compared to bulk materials. Nanoscience dealing with nanomaterials is described as "the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales" [10]. Nanoparticles are engineered at atomic, molecular, or macromolecular levels of approximately 1–100 nanometers. A major safety concern is that the large proportion of atoms in a very small size making the exterior of the nanoparticles would be free to participate in many chemical reactions with human tissues [6]. There are various ways in which nanoparticles can come into the human body, such as via the lungs, the intestinal tract, kidneys, and the skin for details, see ref [6]. This intrusion poses potential threat, which entails biocompatibility of materials to be used while employing nanotechnology [6].

Nanoparticles can migrate from the target tissue and penetrate into the healthy organs and can, in turn, lead to its malfunction [19]. The uncertain risks need to be identified and effectively addressed because such risks may deadly harm the patients causing a panic among all stakeholders that may hinder development of this technology, and contrariwise, its benefits may be optimized by avoiding or minimizing those risks [19]. Also, regulatory attention to the risks will help generate public acceptance of the technology; however, emphasis should be given to the credible identification of potential risks and the means of managing them effectively [5]. In quest of the credibility of risks and their efficient management, a new discipline of study called "nanotoxicology" has emerged.

The nanotoxicology, as an emerging discipline, is concerned about the effects of engineered nanoproducts on living beings [19]. Nanobiotechnology operates relying upon metallic nanomaterials that raises some critical issues: biodistribution, circulation, immune response, toxicity, sedimentation, and clearance [for details, see ref [1]. These solid particles can create further health hazards if they accumulate in tissues or can prematurely decompose and discharge their contents on the way to targeted issues [1]. As these particles are extremely small compared to their parent bulk materials, exposure to such nano-scale materials could cause unique consequences [1]. Potentially harmful effects may vary depending on the type of materials used in nanobiotechnology as analyzed by Rollins [13]. For example, the effect of carbon nanotubes compared with of its original asbestos form causes mesothelioma [26]. Another example, "silver nanoparticles may interfere with DNA replication fidelity and bind with DNA and can cause impairment of mitochondrial function, due mainly to alterations of mitochondrial membrane permeability that reflect an uncoupling effect on the oxidative phosphorylation system, being toxicity dependent on particle size" [13]. Similarly, gold nanoparticles may contribute to cytotoxicity, whereas other nanoparticles such as diamond, iron, and silica nanoparticles can pose different types of threats to human health [for details, see [13]. Taking into account all these risks, the US National Cancer Institute (NCI) has, nonetheless, been a fervent supporter of nanotechnology, as evidenced by the following positive note:

> In fact, most engineered nanoparticles are far less toxic than household cleaning products, insecticides used on family pets, and over-the-counter dandruff remedies. Certainly, the nanoparticles used as drug carriers for chemotherapeutics are much less toxic than the drugs they carry and are designed to carry drugs safely to tumors without harming organs and healthy tissue [27].

However, despite such an optimistic assertion, NCI prudently concludes that:

> Whether actual or perceived, the potential health risks associated with the manufacture and use of nanomaterials must be carefully studied in order to advance our understanding of this field of science and to realize the significant benefits that nanotechnology has to offer society, such as for cancer research, diagnostics, and therapy [27].

So the NCI's notes welcome regulation to secure full medical benefits of this technology. Commenting on the NCI's aforesaid optimistic comment, Dresser pessimistically terms it as "premature", relying on concerns expressed by experts in the area of health and environment [14]. Nevertheless, NCI is not alone; there are many studies suggesting that "engineered nanotechnologies to be safe and, in many cases, highly beneficial to individual and public health" [28].

However, all these diverse views and claims are essentially still expectations or trepidation in the absence of credible trials on humans. As Dresser further states "Nanomedical interventions present a higher level of uncertainty than do more conventional biomedical interventions… Nanotechnology's recent emergence means that many innovations have not yet undergone the animal and other laboratory testing necessary to establish a proper evidentiary basis for human trials" [14]. Other commentators suspect whether the traditional laboratory approaches to safety assessment will be sufficient to accurately identify the risks that may be posed by nanotechnology on human beings [16]. There is also suspicion that the publicity in connection with nanomedicine could generate "unrealistic expectations" among patients who will be invited to participate in the clinical trials with nanomedicine [14]. Regardless of the truth in the apprehension of risks raised by many, the general public may not be willing to support the nanotechnology industry or experimentations without regulation being put in place in advance [21]. Brazell, upholding the need for regulation, describes it (regulation) as "fundamental to modern government" [29].

Although a huge amount of research has been carried out and efforts are constantly ongoing throughout the world particularly in developed economies, researchers are yet to discover any harmonized standards or established methods for accurately identifying potential dangers associated with the use of nanobiotechnology [30]. It means that though a lot has been done, still much more remains to be done in order to accurately find out a "big-picture" of the potential risks embedded in nanomedical interventions [14]. There is, thus, a public demand that all

nanomaterials they are exposed to one way or another are rigorously tested [4]. Logically, there is little disagreement among national and international authorities as well as researchers on the need for an efficient regulation of this technology, but their views fundamentally differ in terms of the timing and methods of formulations of regulatory parameters. So the considerations – when and how this regulation should be formulated and implemented – are now critical concerns of all stakeholders.

4 Regulation of nanobiotechnology

The most challenging aspect of the regulation of nanobiotechnology is that the government, public, researchers, and the relevant industry all lack adequate knowledge of the potential risks, which has compounded the regulatory complexity at hand [31]. Law and economic literature does not provide a single definition of "regulation" [32]. The Organisation for Economic Co-operation and Development (OECD) offers a definition (of regulation) in a relevant context for the purposes of a survey on the regulation of nanotechnology with respect to food and medical products. As articulated by OECD, "regulatory frameworks consist of the standards and rules which regulate a particular class of persons, acts, or items promulgated by government agencies pursuant to authority granted by statute" [3]. Hertog defines regulation somewhat differently when describing it as "the employment of legal instruments for the implementation of social-economic policy objectives" [32]. In the present context, as described by Matsuura, regulation refers to the legal requirements to be met in carrying out research on nanobiotechnology and on commercializing products and services containing nanoparticles [33]. Also, it is to be noted that only the engineered or manufactured nanomaterials are to be regulated, in exclusion of those produced naturally as mere by-products, as viewed by Brazell [29].

Thus, a uniform definition of regulation is not readily available. Brazell adds to this definitional ambiguity stating that if nanomaterials are needed to be regulated separately from bulk materials, the lawmakers should work out which materials are to be brought to the regulatory lens and how to determine these materials for legal clarity and certainty [29]. Ambiguities exist with respect to not only the materials to be regulated but also the risks to be averted. As an emerging and very dynamic area of research, perhaps the most difficult issue in regulation is that risks are unknown and uncertain, and the state of knowledge is constantly changing – in such a situation, regulation can only set out principles of behaviour and allocate responsibility in a non-mandatory form [29]. This is not a single or uniform view contained in the existing research literature.

Researchers are divided as to the appropriate method of regulating nanotechnology. For example, legal analysts Breggin and Carothers suggest concerning nanotechnology that the most effective way of regulation would be taking a multi-pronged approach that requires "the adaptation and integration of various existing laws, strategies, and governance tools" [10]. Conversely, others favor an entirely new legislative regime exclusively for overseeing nanotechnology by arguing that this would be "neater and perhaps more effective" instead of updating the existing regulations in order to apply them to the governance and encouragement of this new technology see ref [10, 21]. While arguing that the present regulations of the EU are applicable to nanotechnology, Quinn advocates precise tailoring of the existing statutory regime to better "meet the specific needs of nanotechnology", and asserts that it "could go a long way to striking the correct balance" [9]. To justify this view, Quinn points out that it may be problematic to make an assumption based on the size of bulk materials to nano-scale amount of the same substance [9]. While this view merits consideration, purely size-based regulatory formula may not be optimal in the present context. As Dana comments, although size is central to nanomaterials, a size-based definition of such materials may not be useful for regulatory purposes [22]. Dana explains, this is because they "require a dynamic, fluid definition that accounts for their rapid development and the fact that they can be distinguished from one another on a range of dimensions and not just the traditionally employed dimension of chemical identity or the size dimension that typically has dominated regulatory definitions of nanomaterials, to date" [22]. A third view favors interpreting existing laws and regulations in a way that incorporates nanoproducts [11]. Besides, yet another opinion submitted by Ramsay in the context of consumer protection, in general, suggests that a fair treatment may necessitate "informal methods of regulation … a form of self-regulation…In the language of economics, self-regulation offered the possibility of reducing information, rule-making and enforcement costs" [34]. Thus, a multifaceted debate continues as to whether nanoproducts or procedures warrant government special regulatory treatment because of their size [10]. or whether self-regulation or mandatory government regulation would be the best approach to such regulation.

All these views are enriched with their own merits. However, we support a regulatory regime that strikes a

balance between public safety and adequate stimulus for flourishing the nanobiotechnology in the greater interest of further improving medical science.

5 Public policy considerations: concerns and dilemma

a. Regulation vs. no regulation
Some commentators argue that the basis for the regulation of nanotechnology by reference to risks associated with the usage of nanobiomedicines or procedures is insufficient, and they give emphasis to the need for exploiting its enormous benefits – they virtually oppose the precautionary principle for this technology [35]. Conversely, the Public Health Association of Australia (PHAA) strongly supports the formulation and introduction of mandatory regulation of nanobiotechnology with immediate effect [36]. PHAA emphasizes that mandatory regulation is imperative for a responsible development of nanobiotechnology. It goes further in asserting that as nanoproducts contain novel properties as well as potential risks, these must be categorized as a new substance for risk assessment and regulatory purposes [36]. Perhaps more strongly, advocating a strong form of precaution, some others demand moratorium on the release of nanotech-products until their manufacturers can demonstrably show safety of their products [35]. Both of these two contrasting views sound extreme [35]. The dearth of knowledge creates suspicion contributing to forming these extreme views, we believe.

Information asymmetry undeniably exists, as research, to date, could not discover the actual risks with certainty. All groups – such as academic commentators, scientific societies, legislators, and industries –agree that only little research has been carried out, and still much remains to be done in order to unearth the full potential of this technology and the risks associated with it [35]. Further comprehensive research on its different aspects needs to be undertaken focusing particularly on "(i) information regarding risk assessment and monitoring metrics; (ii) information regarding the behaviour and associated risks of different categories of nanotechnology and the significance of different pathways for the different categories of nanotechnology; and (iii) information regarding risks associated with particular products that include nanotechnology" [35]. A major policy consideration should emphasize facilitating rigorous research activities to fill in the prevailing information gaps by accurately identifying both – risks and rewards. Only further research devoted to discovering these risks and rewards with convincing precision and credibility can eliminate or at least minimize the skepticism by delimiting the safe and unsafe usage of this technology.

b. Government regulation vs. self-regulation
A complete perfection in a regulatory strategy is not generally attainable regardless of its subjects because no area of regulation is entirely free of imperfections. Also, neither of these two methods of regulation (government and self-regulation) may be effective for nanobiotechnology at this stage, in that no regulators are currently reasonably aware of, let alone being well acquainted with, the risks we need to elude and the rewards we can earn. Both risks and rewards will progressively emerge following the accomplishments in research pursuits. The imposition of an *a priori* restriction on certain research could jeopardize the potential of great inventions, and at the same time, merely *a posteriori* remedy for injuries could be too late to respond. Most important consideration warrants that researchers should responsibly undertake research programs with a sense of accountability to themselves under a set of well-drafted self-regulatory principles, in addition to or outside the scope of government regulation. Hence, at the invention stage, self-regulation through ethical principles and industry code of conduct should be put in place [37] alongside the government regulation. However, strict mandatory regulation should only be imposed once problems are scientifically proven. Self-regulation alone may not sufficiently motivate patients to be a human subject of experiment as the public generally prefer a formal government regulation to self-regulation. This regulatory preference is true although the primary objective of these complementary methods of regulation is to avert or manage risks, with a secondary benefit of ensuring that technology is being properly regulated and reasonably flourished [38].

In a US context, some commentators suggest to effect self-regulation of nanobiotechnology through a Nanobiotechnology Information Board (Board) [13]. The Board is proposed to be acting "as the chaperone of a public nanobiotechnology information database as well as a secret nanobiotechnology information database" with limited direct government oversight [13]. It also recommends the enactment of new legislation imposing increased liability for future harms, which is intended to minimize unintentional and

unknown hazards [13]. This hybrid method of regulation effected through both a self-regulatory authority and stringent remedies against violations of proscriptions.

c. Precautionary model vs. reactive model of regulation
Two models of regulation being "precautionary or proactive model" and "reactive model" are dominant in both the US and EU [19]. The precautionary or preventive model is based on a risk-averse principle, which requires *a priori* regulatory approval showing that the relevant product or procedure is safe. The reactive method of regulation, on the other hand, relies on remedies if any proscription is contravened, so it kicks in only after the breaches and resultant injuries have occurred [39]. So, one emphasizes prevention of breach, while the other seeks remedies against the breach.

No consensus exists that precautionary principle would be most appropriate to this regulation [35]. The precautionary model is not suitable because it will fail to keep pace with the rapid growth of the technology given the information gap on the potential risks and risk assessment, while the reactive model alone may be too late to come into play because specific risks and harm are yet to be finally identified and understood [35]. Moreover, the reactive model will not allow any measure to prevent the harm from occurring until the substantiality of the risks and harm is crystallized [35].

Neither of the two, but a third model of regulation would be more effective for nanotechnology as viewed by Kysar and Dana [35]. The third model should be more "flexible, adaptive and fluid", which is warranted by uncertain risks [35]. This view sounds logical given the nature and the currently emerging stage of the technology at hand. It can also comfortably match with the hybrid regulation of government and self-regulation as we have advocated above.

d. Soft law vs. hard law
These are virtually alternate expressions of self-regulation and government regulation. Self-regulatory codes of conduct or principles of good practice are generally known as soft law as these are not typically made or enforced by state machineries, nor are these provisions regarded as law of the land. On the contrary, the body of hard law refers to the laws made by the legislatures or courts of law of the relevant jurisdiction (case law or judge-made law), and legal remedies or penal sanctions are attached to these laws which are enforced through the competent judicial institutions of the state. It is debatable as to which one of these sets of rules would be more useful than the other for the regulation of nanobiotechnology, as seen above with respect to government and self-regulation.

Marchant and Abbott have found soft law less effective in our present context as they describe that "[t]o date, the benefits of these soft law programs have been modest at best, and many programs suffer from serious structural weaknesses and resource limitations" [40]. Nevertheless, they recognize merits in soft laws in that although most of the soft laws are "relatively weak and underutilised" they still provide "potential sources of valuable regulatory learning" [40]. They suggest that soft laws can play a more effective role if these norms receive greater support from national and international organizations as well as from other public institutions [40]. They further add that soft law approaches dominate governing international relations as these laws apply across national boundaries unlike the limits of municipal laws (as hard laws), which restrictively apply within their territorial boundaries only [40].

Hard laws are undeniably more forceful than their soft equivalents; however, a soft law can more firmly touch the heart of its subjects simply because it is made by them reflecting their own desires, sense of responsibility, and urge of accountability – one way or another. This self-enforcing regime may not be binding with legal sanction, but it does have the force to compel a wrongdoer where the media and public activists can inflict serious or intolerable reputational damage on the defiant company or individuals [37]. Finding the way of developing a new technology and showing its utility is a task of relevant researchers and professionals, rather than any political authorities. Therefore, a particular community tasked with such responsibility should be in a better position to articulate the regulation of their own conduct as well as of their creations. However, the state authority is accountable to its people who seek more confidence in the oversight by state authorities than in self-regulatory bodies. Hence, generally, a hybrid method of regulation embracing both hard and soft laws would be a more acceptable approach to the public whose confidence is critical to achieving a durable success of this technology.

e. Fostering public acceptance vs. imposing technology on the public
Whichever regulatory model is adopted, awareness is a key to public acceptance of this emerging technology. Although nanomaterials are prevalent in nature as an old phenomenon, and man-made

nanomaterials came into being in the middle of the 1950s, people are either not or little informed of this discovery and its beneficial usage [2]. A national survey reveals that even the people of the US, which is regarded as the pioneer of this new discovery and the investment of which in this area is greater than the combined amount of similar investments by the rest of the world [2], are ill informed [2]. Not only lack of information but also information overload in complex and ambiguous terms is regarded as an impediment to creating public awareness [2]. A "systemic elaboration" on the potential benefits and harms is critical to creating lasting understanding, knowledge, and awareness [2]. Consumers of manufactured products, such as foods and cosmetics, are already exposed to nanomaterials largely unknowingly, and this lack of knowledge may make them frightened. The usage of nanotechnology for medical purposes is a relatively new concept, and it is believed to have the potential to revolutionize the health care system [2]. No technology can adequately flourish without public acceptance, which entails awareness of potential benefits and detriments, and this is particularly relevant to health care [2].

The development of technological innovation has never been smooth, as public concerns triggering resistance sometimes inhibited such creations; for example, the cases of genetically modified food (GM food) and stem cell [37]. Nanotechnology is going through a similar set of challenge of public confidence emanated from a lack of confidence and dearth of scientifically proven information on the benefits of this technology [37]. Nanotechnology has transformed from a promising invention to a controversial creation within a relatively short span of time [37]. Losing public trust may contribute to tougher regulation further preventing its flourishment and limiting customer acceptance [37]. Research suggests that public resistance is largely uninformed and prompted by ignorance and not based on scientific arguments [37]. So transparency in decision making on nanotechnology should be a vital consideration that can be implemented through accurately labeling consumer products (nanomedicines), specific protective measures to be taken in order to avoid risks, and easy access to health and safety information by the general public [36]. Emphasis should be given to "public education and meaningful participation in the decision-making process must be facilitated. Social impact, ethical assessments, equity, justice and individual community preferences should guide the allocation of public policy development" [36].

Publicity via electronic and press media, and educating people at the secondary level about the development of nanotechnology, its potential benefits and yet uncertain or unforeseeable risks, can play a pivotal role in convincing the general public to accept experimentation and application of nanobiotechnology. In addition to the disclosure requirements, proper labeling of nano-products is also essential for upholding consumers' right to make an informed decision.

6 Public policy in Australia on the regulation of nanobiotechnology

A 2007 Monash University Report found that the existing Australian regulatory framework was well suited for addressing the concerns surrounding nanotechnology that could arise in the next 10 years [41]. The report also stipulated that "…whilst there is no immediate need for major changes to the regulatory regimes, there are many areas of our regulatory regimes which, potentially, will need amending…." [41]. This 10-year period is about to elapse, and a need for undertaking a careful assessment of the present regulatory regime seems to have crystallized by now, as at present, there is no specific regulation being introduced particularly for nanomaterials in Australia, and the current regulatory framework provides inadequate oversight of nanomaterials [36]. Instead of a separate regime, different statutes currently in operation for the regulation of areas that may be affected by nanotechnology are generally extended to nanomaterials as well [42]. An example is the *Australia New Zealand Food Standards Code* (Code), which requires mandatory labeling of food ingredients including disclosure of nanoparticles, if there are any [see ref [29]. About medical usage of nanotechnology, the *Therapeutic Goods Act 1989* (Cth) applies to nanomedicine as good as all other types of drugs. Section 25 read with ss 23 and 7D of the *Therapeutic Goods Act 1989* (Cth) would require drugs to be safe, showing nontoxicity for containing nanoparticles or delivery systems, though no nano-specific standards or regulation have been put in place [29].

Although Australia has a legislative and regulatory framework for food products that applies to foods containing nanomaterials arguably including food grown or cultivated using nanotechnology or materials (grains, fruits, etc.), it does not have a corresponding framework for nano-medical products as those that appeared in a recent OECD survey [3]. However, the thought of the Australian government on the regulation of nanomaterials is

expressed in several documents that include the *Australia National Industrial Chemicals Notification and Assessment Scheme 2010* (NICNAS), which is tasked with the responsibility for assessing all chemicals new to Australia, before placing them on the market. NICNAS is also responsible for dealing with any concerns raised by the public about its health effects and environmental safety. However, NICNAS has formulated a separate regulatory process specifically to address concerns connected with "industrial nanomaterials" effective January 1, 2011 [29]. Australia is the first developed country that has made such process [29]. Presently, there is no internationally agreed definition of "industrial nanomaterials" that should be regulated. NICNAS, however, provides a working definition in consistent with other available international descriptions of the term, which reads:

> …industrial materials intentionally produced, manufactured or engineered to have unique properties or specific composition at the nanoscale, that is a size range typically between 1 nm and 100 nm, and is either a nano-object (i.e. that is confined in one, two, or three dimensions at the nanoscale) or is nanostructured (i.e. having an internal or surface structure at the nanoscale) [43].

NICNAS adds an explanatory note to the definition as follows:

i. intentionally produced, manufactured or engineered materials are distinct from accidentally produced materials
ii. "unique properties" refers to chemical and/or physical properties that are different because of a material's nanoscale features when compared with the same material without nanoscale features, and result in unique phenomena (e.g. increased strength, chemical reactivity or conductivity) that enable novel applications
iii. aggregates and agglomerates are considered to be nanostructured substances
iv. where a material includes 10% or more number of particles that meet the above definition (size, unique properties, intentionally produced) NICNAS will consider this to be a nanomaterial [43].

The above explanatory notes exclude the nanoparticles, produced accidentally as part of the production of bulk materials, from the regulatory ambit of NICNAS. However, if a particle size distribution contains 10% or more number of particles at nanoscale, this substance will qualify to be assessed for risk assessment purposes as apparent in the above explanatory note.

Any chemical substance that is new under this definition as it is in nanoform requires to obtain NICNAS's permit or certificate generally with no exception; if any exemption is claimed, the applicant must prove that the substance is not a nanomaterial [29]. However, the transhipment as well as research and development exemptions remain unchanged [29]. All materials containing nanoparticles are required to be accurately identified when produced in volumes over 100 g, and their full chemical or generic name should also be disclosed [29]. Further information such as the size and shape of the nanoparticles may be required to be supplied where NICNAS deems necessary [29]. Then, a risk assessment of a nanoproduct will be carried out where it contains at least 10% of nanoparticles [29].

In another development, the federal government of Australia has enacted the *Product Stewardship Act 2011* (Cth) aimed at managing waste primarily for the protection of the environment, and it operates at the discretion of the environment minister who makes a list of products to be regulated [44]. The current list does not include nanomedicines or drug carriers; hence, it can be inferred that this legislation does not affect our concerns directly or indirectly.

Nanobiotechnology is an area that should concern everyone, and its medical applications are foreseen to create unique or heightened policy challenges for safety regulation by governments [45]. PHAA, referred to earlier, points out that the chemical regulatory process currently in place in Australia is cumbersome and lacks uniformity across its states and territories that may produce diverse outcomes [36]. Taking advantage of the absence of an overarching regulatory framework, different agencies are contributing in the same area in a heterogeneous manner depending on their capacity [36]. This warrants formulation of a uniform regulatory framework across the country in order to ensure public health and safety at the same level. In view of its findings that nanotechnology poses significant health and safety hazards, PHAA notes that the research, to date, has focused too much on commercialization with scant attention to health and safety issues [36]. To address this disparity in focus, PHAA affirms seven principles to be embraced in formulating regulatory oversight of nanotechnology for public health and safety. These principles include (i) taking a *precautionary* approach as a fundamental requirement of oversight; (ii) imposing a *mandatory* regulation as an integral aspect of the development of nanotechnology and classification of nanomaterials as new substances for assessment and regulatory purposes; (iii) Arranging *effective oversight* of *occupational health and safety* (OHS) to prevent known and potential exposures to nanomaterials that are yet to be proven safe, and increasing government research funding to address the OHS issues; (iv) emphasizing *health and safety* issues before commercialization of nano-products, and increasing *research funding*,

delineating a *risk strategy* plan; (v) ensuring *transparency* in decision making and making adequate *disclosure* of health and safety information concerning products containing nanomaterials; (vi) developing *public policy* based on public *education* and their meaningful *participation* in the decision making, having due *regard for* social impact, ethical assessments, equity, justice, and individual community preferences; and (vii) imposing *liability* on manufacturers and sellers of harmful nano-products for injuries caused [36]. PHAA recommends both the federal and state/territory governments to develop a nanotechnology strategy and regulatory framework relying upon the principles ensuring a uniform approach across all relevant nanotech areas including medicines and medicinal products [36].

These principles give strong emphasis, among other things, to regulation, further research, and public awareness with an overarching objective of ensuring public safety. PHAA also unequivocally asserts in these principles that further research on nanotech should be funded by the government. We do passionately agree with these principles; however, we are skeptical that strict mandatory regulations excessively limiting research pursuits may hinder the development of this technology to its full potential. We, therefore, recommend a hybrid of mandatory oversight and self-regulation to be articulated in a way that strikes a balance between the facilitation of research and protection of public. Both sets of regulations should be drafted by bodies to be composed of recognized experts in all areas of knowledge relevant to this technology and its potential usage. The formulation of these regulations should be guided by two predominant objectives being public safety and medical innovations in our present context.

Taking into account all views presented in the foregoing discussion, we can logically infer that (i) Australia currently lacks specific regulations on the medical application of nanotechnology; (ii) the regulation is necessary as a public demand and the state responsibility to save people from avoidable health and safety harm; (iii) neither mandatory government regulation nor self-regulation alone seems sufficient to generate and enhance public confidence in the benefits of nanotechnology without potential health and safety risks; (iv) public education is necessary to increase confidence and stimulate informed consent to be a subject of experimentation on humans; (v) this education can be imparted via public media (electronic and print) and through formal teaching at the secondary level; (vi) huge investments in nanotechnology research are essential; (vii) transparency and public participation in policy making is warranted; (viii) adequate disclosure of nanomaterials in nanoproducts is imperative; (ix) nanoproducts need to be registered with a competent authority; and (x) the regulation should impose liability of manufacturers and sellers of harmful nano-products without proper authorization and useful content disclosure.

The key public policy issues that can be drawn from the above findings could be summarized as follows:

(i) Regulation of nanobiotechnology is necessary, and a *separate* regulatory framework exclusively devoted to nanotechnology should be put in place.
(ii) A *hybrid method* of regulation could be effected through both – mandatory government regulation and industry self-regulation.
(iii) Extensive *rigorous research* must be facilitated by the governments and academia with specific aims to ascertain the immense potential of nanobiotechnology in terms of credible rewards and associated risks.
(iv) Public *education* on nanotechnology should be fostered, and their participation in the decision-making shall be ensured.
(v) Mandatory content *disclosure* of nano-products and procedures shall be required

The regulation of nanotechnology is a global issue and is often referred to as the catalyst of the looming fourth industrial revolution; hence, it needs to be addressed globally [40]. Many commentators argue that effective regulation fostering the culmination of nanotechnology with adequate safety for the people should be applied to nanoproducts or nanoprocedures based on international standards or harmonized principles [46–49]. We support the harmonization of principles and regard that the above-stated policies could be taken into account in formulating harmonized principles by any international authority including the specialized agencies of the United Nations Organization. However, it should be acknowledged that a contrary view against harmonization also exits [40], and this debate can be a topic of further research.

7 Conclusions

Both medicine and technology have played a critical role in the past and will continue to play such a role in the future to change the way of people's lives contributing to enhancing safety, well-being, and life span of human beings ranging from new born to elders (for details, see ref [1]). Some may be more optimistic than others, as Dresser

predicts that "nanotechnology as one of the innovations that will lead to a significantly extended human life span" [14], while extreme enthusiasts prophetically enunciate that nanotechnology "will ultimately enable us to redesign and rebuild, molecule by molecule, our bodies and brains…." [50]. Also, "nanotechnology is changing the world and the way we live, creating scientific advances and new products that are smaller, faster, stronger, safer, and more reliable" [51]. The innovative medical use of nanotechnology poses complex challenges to policymakers and regulators worldwide [10]. Central to these challenges is achieving an acceptable balance between public safety and innovations. The complexities of these challenges are compounded by uncertainties as to, and a lack of, adequate understanding of the nature and manageability of health risks associated with the application of nanomaterials [10]. At the same time, an uncertainty also exists as to whether the existing laws and regulation are capable of effectively regulating this fast growing and highly innovative technology [10].

To date, public understanding of this technology is rudimentary resulting in concerns about health and safety – sometimes driven by misconceptions. So the utilization of its full benefits warrants public confidence. There is no alternative to continue research in order to reveal the full potential of nanotechnology, and in so doing, flexible science-based approach to regulation should be adopted to protect public health and stimulate economic growth, innovations, and competitiveness [52]. As Matsuura describes, nanotechnology has the prospect to reach very far and "its long-term impact for society will be profound" [33]. This effect can go either way – to benefit or harm us. It is mainly the potential harm that triggers regulation.

As advocated above, a hybrid method of separate mandatory government regulation and voluntary industry self-regulation would be the best way of dealing with nanotechnology, particularly while it is in its growing stage. Both modes of regulation should be founded on well-drafted public policies as articulated above, aimed at nurturing the technological growth in a responsible manner and safeguarding public interests by protecting us from potential harm. Nanotechnology industry should develop its own regulatory policies commensurate with those to be laid down by public authorities of respective jurisdictions in a homogeneous fashion. It is to be borne in mind that a lack of responsibility at any level of governance may place our hopes in jeopardy making the immense benefits of nanotechnology short lived. Also, both levels of oversights should give emphasis on facilitating comprehensive research, creating public awareness, and ensuring content disclosure of nano-products. In addition, we recognize that it is a global issue and, thus, accept the need for a set of internationally harmonized policy principles to guide our actions. Finally, we reiterate the overarching US policy as pronounced by President Obama that "Our regulatory system must protect public health, welfare, safety, and our environment while promoting economic growth, innovation, competitiveness, and job creation. It must be based on the best available science" [53].

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