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Issues and concerns in nanotech product development and its commercialization

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ABSTRACT

The revolutionary and ubiquitous nature of nanotechnology has fetched it a considerable attention in the past few decades. Even though its enablement and application to various sectors including pharmaceutical drug development is increasing with the enormous government aided funding for nanotechnology-based products, however the parallel commercialization of these systems has not picked up a similar impetus. The technology however does address the unmet needs of pharmaceutical industry, including the reformulation of drugs to improve their solubility, bioavailability or toxicity profiles as observed from the wide array of high-quality research publications appearing in various scientific journals and magazines. Based on our decade-long experience in the field of nanotech-based drug delivery systems and extensive literature survey, we perceive that the major hiccups to the marketing of these nanotechnology products can be categorized as 1) inadequate regulatory framework; 2) lack of support and acceptance by the public, practicing physician, and industry; 3) developmental considerations like scalability, reproducibility, characterization, quality control, and suitable translation; 4) toxicological issues and safety profiles; 5) lack of available multidisciplinary platforms; and, 6) poor intellectual property protection. The present review dwells on these issues elaborating the trends followed by the industry, regulatory role of the USFDA and their implication, and the challenges set forth for a successful translation of these products from the lab and different clinical phases to the market.

1. Introduction to nanotechnology

The ideas and concepts behind nanoscience and nanotechnology started with a talk by Dr. Richard Feynman, a physicist, way back in December 29, 1959, delivered at an international forum in the meeting of American Physical Society at the California Institute of Technology (CalTech). He may not have conceived at that time, that his talk, on 'There's Plenty of Room at the Bottom' wherein he discussed the scope of manipulation and control of individual atoms and molecules, will set the pace for the present era of nanotechnology [1].

Nanotechnology is an amalgamation of science, engineering, and technology conducted at the nanoscale that is about 1–100 nm. Howsoever OECD refers to nanotechnology as a 'set of technologies that enables the manipulation, study or exploitation of very small (typically less than 100 nanometres) structures and systems. It includes an all pervasive definition for it, stating that nanotechnology contributes to novel materials, devices and products that have qualitatively different properties.' Advancement in the nanotechnology has the potential to affect virtually every area of economic activity and aspect of daily life [2].

Drug delivery application in nanotechnology is proposed to be the most happening and an all-purpose technological engine for growth in the 21st century. Although lofty public R&D investments have been made and are reflected in the growing scientific database, however nanotechnology is still in an uncertain phase of commercialization [3]. Further to this, its 'responsible development' on one hand is a concern, while on the other hand, it holds a key opportunity to develop a science that is explicitly and self-consciously in step with and for the society. Current efforts in ethical analysis, public engagement, and new forms of governance and regulation of nanotech-based drug delivery systems though impressive are still in a nascent stage [4].

The potential market size of nanotechnology is catching the eye of investors, economic developers and public officials, and is being looked upon as a futuristic rather than a contemporary industry with over 500 manufacturers already identified [5]. Nanotechnology-based products in general have already been catalogued and their global market, in 2007, totaled $147 billion [6]. Lux (an independent research and advisory firm) and other industry analysts project that in the year 2015 the market size for these nanotech-based products will grow to $3 trillion [7]. An analysis of the Total Addressable Market (TAM) in 2010, for the key technologies in drug delivery, shows that among the major players, drug nanocrystals may capture a market of US$596 million, followed by nanocarriers (US$434 million), targeted delivery (US$178 million) and systems to improve solubility and bioavailability (US$139 million). Drug nanocrystallization (nanosized drugs) is proposed to be the key technology that will hold the leading TAM in 2021 of about US

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$81,921 million. Among all the evaluated nanocarriers, it is assumed that liposomes may lead TAM in 2021 by holding a US$15,313 million market [8].

The success of nanotechnology in the healthcare sector is primarily driven by the possibility to simultaneously work at a nanoscale on several biological processes, cellular mechanisms, and organic molecules; for this reason, nanomedicine is being looked upon as ideal solution for the detection and treatment of many diseases [9]. From more than 80,000 articles on nanoparticles that were available on PubMed in January 2014 over half were published after 2010, revealing the interest and progress that is being made in this area [10]. It is a technology that positively promises to influence several facets of life—including several areas under FDA oversight, be it the prescription drugs, the individual's medical devices and therapeutics, the nutraceuticals, and the cosmetics [11]. Looking at the purported claims, government agencies are pumping an extensively large amount of funds for research in this area. In the US budget of 2014, the US government provided over $1.7 billion for the National Nanotechnology Initiative (NNI), a sustained investment in support of the President's priorities and innovation strategy, cumulatively totaling almost $20 billion since the inception of the NNI in 2001 (including the 2014 request) [1,12]. Such ample support reflects the expectations from nanotechnology especially in terms of its potential to combat diseases and improve the health status of general public.

2. Commercial breakdown

Though commercialization of nanotechnology is still in its infancy, the rate of technology enablement is increasing, in no small measure, owing majorly to the substantial government-mandated funds directed toward nanotechnology. Commercialization is the process of turning new technologies into successful commercial ventures, which may involve an array of professionals from technical, commercial, and economic background to successfully transform a new technology to useful products or services [13]. The process includes a series of steps starting from the conception of idea, technology development, and its commercialization; fostering those ideas to development of technology; building up a prototype to establish the validity of the idea; development of the new process or optimization of the existing processes, finally leading to the supply of proposed deliverables to the market, its promotion, and creation of new infrastructures for facilitated supply and purchase [14]. Comprehensive studies by VDI Technologiezentrum in Germany have found that although, more than 1000 nanotechnology organizations, several of which are concentrated in some active countries [15] exist, however, there is a lack of new firm creation in nanotechnology. This is accredited to the fact that the number of nanotechnology companies that have achieved initial public offerings (IPOs) is very low; perhaps a handful in Europe in the last few years, and taking a cue from this observation, no new companies are being launched in this area. Due to a significant concern and disapproval the nanotech-based pharmaceutical companies are left with limited financial options, while the co-founders of start-up companies are committing their own money and expertise into it. Current state of the global economy is not 'nano-friendly,' and the companies are facing great difficulty in obtaining initial fundings. Considering the risk of funding companies prematurely, the investors are reluctant to pour large amounts of capital into these companies until they have dependable technologies; ready to commercialize products; defendable patents; growing target markets in sight; chance of high profitability; and strong management teams [16]. According to Lux Research, the heydays for nanotech products were the earlier part of 21st century i.e. before 2010, when overall investment reached approximately $1.4 billion in the year 2008. In 2009, the sector raised only $792 million, a 42% decline from the prior year. It is predicted that investments in this area will decrease or remain flat in the near future [17].

3. Challenges to product development and commercialization

The present era is a 'no or low controversy era' wherein aversion to or apprehension toward new technology is at an all time low. Hence the general attitude rather welcomes the new technologies like nanotechnology [18]. However, just achieving a technical knowhow or a newer technological product does not necessarily mean successful sales. The technology needs to be well taken by the industry i.e. the industry should have faith in its performance only then will it harness all its energies and efforts to get the public support. In this regard the nanotech-based products seem to face numerous challenges to their successful commercialization (Fig. 1) as discussed below. Formulating an efficient and a nontoxic product are the two primary prerequisites for a product to be successfully marketed. Most of the nanotech-based products, however, at times fail to achieve either or both the requirements and thus fail to reach the market [4,19].

3.1. Safety

The guidance document of USFDA indicates that for a test product generating plasma levels that are substantially above those of the reference product, as usually observed with nanobased systems, the regulatory concern is not therapeutic failure, but the adequacy of the safety for the test product [20]. Owing to the nano size of these products, they invariably encounter issues of bioaccumulation, superaoptimal bioactivity [21], biocompatibility, metabolism, and elimination from the body [22] during their use. Further to this, there are some reports that question their safety for human use. Recently, some Chinese researchers have observed that during animal testing, the absorption of nano-silver may interfere with the replication of DNA molecules and can re-route molecular networks that could create genetic mutations. Nanosilver, among myriad other uses, is incorporated into food packaging materials to kill pathogenic bacteria and thereby extend a food's shelf life [23]. Reports like this have created a general negative perception regarding these products.

However, the first successful application of nanoproducts in the clinic was that of contrast agents. Numerous nanoproducts have been launched over the years by various leading companies (Omniscan by Salutar; Magnevist by Bayer Schering Pharma; OptiMARK by Mallinckrodt; MultiHance by Bracco group and many more) [19,24]. These agents are biologically inert, optically transparent, water dispersible in nature and do not suffer from the concern of bioaccumulation as they are not absorbed by the body and are efficiently eliminated from body [24]. Near infrared (NIR) fluorescence-based contrast agent like ICG-doped calcium phosphate nanoparticles are cleared by a hepatobiliary mechanism from body [25]. Further to this, these agents are generally for single use, this lessens the chances of their accumulation and hence toxicity associated with repetitive use.

Another significant field which employs a large number of nanotechnology-based components is that of cosmetics. Table 1 gives an insight into the wide range of nanotechnology-based cosmetics sold worldwide by global cosmetic giants. Nanosized ingredients are either used to provide better UV protection in sunscreens or to act as carrier systems for the actives to improve their skin penetration and hence efficacy. Use of nanosized titanium dioxide and zinc oxide has led to the development of transparent sunscreens with better sun protection. However, safety concerns have risen for such products because the ultrafine particles of these metal oxides may catalyze generation of free radicals which could cause skin damage and even cancer [26]. Studies have shown that 500 nm titanium dioxide particles have lesser ability to cause DNA strand breakage while a 20 nm particle may cause complete destruction of super-coiled DNA, even at low doses and in the absence of exposure to UV [27].

From the mechanism point of view, potential nanoparticle cellular interactions that may induce cytotoxicity and other cellular responses include: (1) interaction with plasma membrane leading to instability