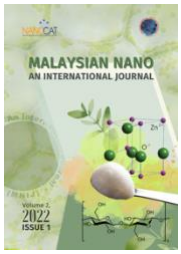
Malaysian NANO-An International Journal



Review Article

A Critical Review of Nanomaterials and Their Industrial Applications

Aiswarya Rajan, J. Ranjitha and S. Vijayalakshmi*

[1]CO2 Research and Green Technologies Center, Vellore Institute of Technology, Vellore – 632014, India

Received June 20, 2022
Revised July 25, 2022
Accepted July 28, 2022

DOI:
https://doi.org/10.22452/mnij.vol2no1.5

Corresponding authors:
vijimicro21@gmail.com

Abstract

The innovative and universal nature of nanotechnology has extensively driven the interest of scientists for the past few decades. Besides its utilization in several sectors such as pharmaceuticals & drug development, with highly funded government projects to develop a wide range of nanotech-based products, its commercialism is still comparatively poor. Although these technologies enable to resolve the issues with drugs in the pharmaceutical industry, especially reformulating the drugs to improvise their physicochemical properties & the level of toxicity (including the rate of dissolution, bioaccumulation & its toxicological nature compared to the standards recorded in scientific reports. Depending on the experience gained from decades of nanotechnology-derived drug delivery systems and an extensive literature review, it was determined that the main reason for commercialization failure was listed as follows a) insufficient regulative framework system; b) poorly accepted & supported by the consumers (the public), doctors in practice & industries; c) manufacturing criteria including the capability for large-scale production, characterization, quality control, and suitable translation; 4) issues with toxicity, ecological hazardous & safety profiles; 5) inadequate interdisciplinary platforms; and, 6) Lack of IPR (Intellectual property rights) protection. This present review elaborates on the key issues & the trends followed in the industries, the Regulatory role of the USFDA with implications, and the challenges set forth for the successful translation of nanotech-based products from the laboratory to the market.

Keywords*:* Nanotechnology, Transdisciplinary, Products, Commercialization

1. Introduction

The ideology & insights for nanoscience and nanotechnology originated from a speech by Dr. Richard Feynman, on 29.12.1959, at the international forum during the meeting of the American Physical Society at the California Institute of Technology (CalTech). He stated that 'There's Plenty of Room at the Bottom' indicating the scope of manipulating & controlling the individual atoms and molecules, which gave rise to the field of nanotechnology. Nanotechnology is the unification of science, engineering, and technology organized at the level of nanoscale around 1–100 nm. According to the OECD - nanotechnology is a 'set of technologies with the capability of manipulating, studying/exploitation structures &s systems below the range of 100 nm. Nanotechnology provides innovative materials, devices, and products with varying quality & characteristics. Improvement & development in the field of nanotechnology can potentially influence all the areas of economic activity and aspects of daily life. The drug delivery system is one of the areas which highly utilizes the concept of nanotechnology currently with increased growth. Even though provided with R&D investments still there is an uncertainty observed in the stage of commercializing these products (Palmberg, 2008). The 'responsible development' is also an issue although it has major opportunities for developing science that is clearly and self-consciously associated with & for society (Mazzola, 2003). After investing much more effort into the nanotech-derived drug delivery system yet it is found to be currently budding. The ability of nanotech-derived products at commercial levels catches the attention of business perspectives at different stages such as investment, economic development of public officials, and retailers. It has been projected as pioneering & not ongoing, only 600 industries were found to be currently existing manufacturers. Nanotech-derived materials in the global market overall totaled $147 billion in 2007 was recorded. Lux (independent research and advisory firm) & few industry analysis reports suggest commercial scope for such nanotech-based products would increase up to $3 trillion in 2015. The analytical report was given by the Total Addressable Market (TAM) in 2010 states that the market value of technologies for successful drug delivery could reach a market value ranging from the US $596 million for drug nanocrystals, nanocarriers around US$434 million, targeted delivery of about US$178 million and systems for improvising the rate of dissolution & bioaccumulation with US$139 million. Nanocrystalline drugs were anticipated to be the crucial technology that would grasp the leading TAM in 2021 with the US $81,921 million. When compared with all other nanocarrier materials, there is an assumption that liposomes might be the prime material of TAM in 2021 worth US$15,313 million in markets. The achievement of nanotech-derived products in the field of

preventive medicine & health care sector is chiefly based on the ability of simultaneous action nanoscale on several biological pathways (Metabolism at cytological & molecular level), especially for this particular rationale nanomedicine is considered to be an ultimate solution to detect & treat various disorder & diseases (Flynn and Wei, 2005). Based on the literature survey with over 80,000 articles about nanoparticles obtained from PubMed in January 2014, it was revealed that >50% were published after 2010, indicating the advancement in this field (Stein, 2014). There is a positive impact recorded in the areas under FDA-prescribed drugs that are nano-derived, the individual's medical devices and therapeutics, the nutraceuticals, and the cosmetics (Taylor, 2006). Depending on the current status of nanotech-based drugs, large amounts were allotted by the government for further research in this field. In 2014 the US government allotted more than $1.7 billion for the National Nanotechnology Initiative (NNI), 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). Nanotechnology has gained a lot of supportive services & there has been a reflection that potential nano-derived drugs were highly expected to prevent & resist diseases and for improvising the public health. Therefore, this review elaborates on the key issues & the trends followed in the industries, for the successful translation of nanotech-based products from the laboratory to the market.

2. Commercialization of nano-based products

Even though the commercialization of nano-based products was still at the initial stages, there is increased availability of the rate of technology at a large scale, due to increased extensive government-mandated funds allotted for nanotechnology. Commercializing is the process of converting novel technologies into effective commercial endeavors, involving the various & sequential stages of professionals ranging from the technical, commercial, and economic background to effectively transforming novel technology into beneficial products or services (Reamer, 2003) The procedure embraces a sequence of steps beginning initially from the ideology, concept, framework technological advancement, developing product & quality and its commercialization; nurturing such ideas for developing the technology; constructing the prototype for establishing the validity of the idea; developing innovative process or optimizing the process or procedure that already exists, ultimately resulting to supplies of the proposed end products delivered to the marketplace & promoting it, & creating a new architecture for facilitating the supplies and purchase (Spinverse, 2007). The VDI Technologiezentrum in Germany has reported that over 1000 nanotechnology organizations, most of them focused in a few active countries, currently present with inadequate firm innovation in

nanotechnology. This is due to a poor number of initial public offerings (IPOs) obtained by the nanotechnology companies probably a few in Europe recorded for the past decade, and based on the observations, it has been found that the launch of new companies was halted in that region. Based on the significant concern and rejection from the public the nanotech-derived drug companies were left out with limited financial options, whereas the co-founders of start-up companies are investing their own money and expertise into it. At present, the global economy for nano-based products is not suitable and initially receiving funds from these companies was highly difficult. Lack of funding agencies & hesitation to invest a large amount of money by the investor into these companies will change only when there is a guaranteed adequate dependable technology, immediately commercializing of the products, proper defensible patents, increase in the target marketplace, possibilities for increase in profits, strongest managing team with proper administration (Allen, 2014). Based on the report given by Lux Research, the peaks for nanotech-derived materials were expected to be at the initial stage of the 21st century i.e., before 2010, during which the investment touched around $1.4 billion in 2008 & in 2009 about $792million, totally > 42% fall was observed when compared to 2008. It leads to a prediction that investments would either fall or remained as flat in the future (Bradley, 2014).

3. Challenges in Commercialization of products

Currently, the repugnance for innovative technologies is lower hence there is a chance for welcoming innovation & creativity such as nanotechnology (Satterfield et al., 2009). Therefore, achievement in just technical /new technology will not receive any expected outcome from the perspective of purchase among the public. The technology requires demand at the industry scale i.e., with adequate effort ranging from investment to product delivery by the industries there gaining public support. Based on these facts the nano-derived products undergo various problems in order to be successfully commercialized. In order to be successful in the marketplace, the nano-derived products must fulfill the requirement that includes an effective formulation and toxic-free product. Due to the lack of these two characteristics, the nano-derived products become a failure and never reach the marketplace (Morigi et al., 2012).

3.1 Compatibility of nano products

According to the USFDA guidelines, it has been noticed that the key issues with nano-based drugs were, elevated levels exhibited by the test products comparatively than the reference level mentioned in the guidance which is a safety issue. Due to their size, these drugs constantly face numerous problems in bioavailability & optimum biological activity (Vega-Villa et al., 2008), biocompatible property, metabolic function, and their removal via the excretory mechanism of the

host (Bosetti and Vereeck, 2011) when used. Another questionable criterion is recorded with whether is it safe for human consumption/utilization. A recent report published from animal testing in China states that bioaccumulation of nano-silver interfered in the mechanism of DNA replication & resulted in genetic mutation via rewiring the pathways at the level of molecules. To obtain an extended shelf - life of food products nano-silver was integrated into the materials used for packing the food products to kill bacterial pathogens (Suppan, 2011). Based on such facts there are no significant positive impacts on nano-derived materials. Several nano-derivative drugs were introduced by numerous leading companies (Omniscan by Salutar; Magnevist by Bayer Schering Pharma; OptiMARK by Mallinckrodt; MultiHance by Bracco group (Hahn et al., 2011). These products exhibited the following characteristics such as biologically inactive/non-reactive, completely transparent, soluble in water, and free from issues regarding bioavailability & its efficient removal from the host. Near-infrared (NIR) fluorescence-based contrast agents like ICG-doped calcium phosphate nanoparticles are cleared by a hepatobiliary mechanism from the body (Altınoğlu et al., 2008). They were commonly designed for single use; which reduces the opportunity for bioaccumulation and makes them toxic-free. Cosmetics production is found to be one of the areas that largely utilize nanotech-derived compounds. The usage of nanoscale components was intended for reducing UV penetration in sunscreens or to serve as carrier molecules for improvising their skin penetration to achieve its full efficiency. Utilization of nanoscale titanium dioxide and zinc oxide resulted in developing transparent sunscreens with improved UV protection. In contrast issues regarding skin safety such as the formation of free radicals resulting in tumor/cancer were raised. Experimental reports suggest that 500 nm titanium dioxide particles have a low potential for creating the DNA strand breakage when compare to 20 nm particles with the potency to fully destroy the super-coiled DNA when administer at very low doses & even if not exposed to UV rays (Donaldson et al., 1996).

From the perspective of metabolic pathways the potency of nanoparticles to interact with the cell leading to the induction of cytotoxicity and its associated reactions includes the following: (1) interacting with plasmalemma resulting in abnormal ion transport ultimately makes it unstable, signal transduction, and cell death; (2) interacts with mitochondria thereby altering metabolic pathways or interfering with anti-oxidant defenses mechanism; (3) Binds with the DNA and ultimately results in damage, seizure in cell cycle division and protein synthesis; (4) interacting with cytoskeleton leading to arrest the vesicular trafficking and leads mechanical instability and cell death; and (5) interacts with proteins, lipids, and other biomolecules. Nanoparticles can also cause cytotoxicity by adhering to the cell membrane, degradation of adhered nanoparticles and subsequent release of cytotoxic degradation

products, e.g. as observed with cyanoacrylate nanoparticles (Lherm et al., 1992).

The long-term toxic effects of absorption of such nanoparticles have yet to be conclusively studied. The lack of safety and toxicity data regarding nanocosmetics has attracted the attention of social work groups worldwide. They are now raising their voice toward the adoption of a stringent regulatory guideline for nanotechnology-based cosmetics, as well (Raj et al., 2012). For the time being the guidelines for cosmetics were comparatively less rigorous including the absence of any requirement for the post-market surveillance. Challenges in Nanotechnology-based product commercialization as shown in Fig.1

Figure 1: Challenges in Nanotechnology-based product commercialization

3.2 Parameters of product development

3.2.1 Health benefits

One of the main essentials for any product is to be commercialized successfully by producing its experience over existing options in terms of efficacy. Doxil® and Abraxane® are two examples of successful nanotech-based products in clinics. Doxil®, a liposomal formulation of toxic chemotherapeutic doxorubicin was initially commercialized by Sequus, then it was approved by FDA in 1995 for Kaposi's sarcoma. Conventional chemotherapy involved injections of the free drug intravenously. Recent products are extremely cytotoxic that would discriminately kill both healthy and normal tumor cells (Ferrari, 2008). The phenomenon of improved permeation and retention in the tumor cells (Barenholz, 2012). Similarly, Abraxane®, approved in 2005 for the treatment of breast cancer and commercialized by Abraxis Biosciences, was another success story of a nano-drug

delivery system where systemic toxicity is significantly lowered while the therapeutic efficacy is improved by simply developing a nanocarrier system (Sakamoto et al., 2010).

3.2.2 Large-scale production

The expansion of advanced pharmaceutical products is achieved only when the production of these medicinal drugs is remarkably high (Muller and Latimer, 2009). The methodology of producing pharmaceuticals at the industrial level differs when the same is processed at the laboratory, thereby making the development of the product and its expansion an admissible step. Extensive production is accomplished using certain technologies which retain the product's distinctive features and simultaneously maximize the yield. Drugs produced from nano-particles should be customizable both in size and scale similar to other products and courier systems while maintaining their nano-size and unique properties. Production at an industrial scale should relatively reproduce the products obtained using nano-technology. Liposomes are perfect examples that elucidate the aforementioned stipulations as the process of liposome production utilizes the thin film hydration technique in the laboratory which is different when the same product is processed at an industrially large scale (Laouini et al., 2012). This is due to the reason that liposomes produced from nano-technology are not that valuable to be manufactured at the industrial level using the same production methods. Environmental concerns and the high cost of the organic solvent including safety measures are the most relevant grounds which limit the industrial application of nanotech-constructed products. Moreover, it requires an area that is germ-free and sterilized so the uncontaminated area becomes a necessity for industrial processing (Desai, 2012). The current patent (IPA/700/Del/2014) that uses unconventional industrial processing of nano-vesicular systems enclosing diverse drug molecules is defined by our group (Kaur et al., 2014). Shegokar et al. (2011) have been successful in reporting the increased laboratory production of stavudine SLNs (40g) to moderate scale (10kg) and high scale (20-60kg) by employing Avestin C-30 (Avestin Inc., Ottawa, Canada) while retaining 61.30 nm particle size and 0.169 PDI. Nevirapine SLNs (Shegokar et al., 2011) and Sesamol SLNs (Kakkar and Kaur, 2012) also experience the same scale-up reports. During the development process, it becomes relevant to observe and scrutinize all the obstructions faced while processing the product in the industry. Increased production of curcumin stacked nanoparticles using safe solvents (Ranjan et al., 2012) has been studied. Researchers now find industrially applicable techniques like SLNs more suitable as compared to the conventional lab techniques that result in a 1L batch of scaled-up products. Pharmaceutical industries operating at both large and small scales make use of a high-pressure homogenizing approach to generate products that are suspension-based (Muller et al.,

2000). Hence, the scalability and operational feasibility of nanotech-based items produced in laboratories remain distinctive features for the systematic commercialization of the products.

3.2.3 Manufacturing

The trademark of the pharmacological product reaches the commercial market by producing every set will be the same not only in the physical state but also in important features of treatment. Those products which are produced using nanotechnology also need to improve in this field, because the customer for the product is important so that the product does not look the same but also performs the same characteristics of every batch. This reproducibility should be developed in nano drug delivery systems by the quality of the authorized manufacturing procedure (Mojahedian et al., 2013). Some changes in functional conditions can have several effects on nanoparticles, sometimes it also leads to size increment so that they fail to produce the proposed range of nano (Gaumet et al., 2008). Change in size is one of the most easily noticeable variations that occur during production, most nano products consist of biologically active agents such as proteins and nucleic acids, and these products need some special consideration while manufacturing because they have a high susceptibility to degradation. The difficulty in manufacturing nano-based products in industries is controlled by 'batch-to-batch' variations. Some of the strong preparation techniques have high functioning qualifications, and these preparations will not have continuous formulation change. It is also important that the need strict in-process testing to confirm the quality, bioactivity, and uniformity of formulations from one batch to the other (Langer et al., 2008).

3.2.4. Product quality

As a result of the previous issue, it is important that the characterization techniques utilized for nanotech-based products and the industry's overview of them. The procedure for manufacturing pharmaceutical products should contain strict quality control tests at every step. These analytical checkpoints help to maintain the quality and reproducibility of the batches which is the most important feature for producing any commercial pharmaceutical product. Industries which produce nanotechnology-based products are usually ready with standard analytical equipment such as hardness testers, dissolution equipment, spectrophotometers, and pH meters. However, the characterization of nanoparticles involves utilizing highly advanced and sophisticated techniques like microscopy atomic force microscopy (AFM), transmission electron microscopy (TEM), and scanning electron microscopy (SEM), to measure the size of the particle and distribution of size using light scattering (static and dynamic); analytical ultracentrifugation, capillary electrophoresis; analysis of surface charge or zeta potential; examination of surface chemistry by X-ray photoelectron

spectroscopy or Fourier transform infrared spectroscopy; differential scanning calorimetry and X-ray diffraction, among others (Mehnert and Mader, 2001). This analytical equipment is not much expensive but the performance check should require a trained person to carry out the analysis and interpret the results. Thus, for an industry to be advantageous in producing nanotech-based product manufacturing, it should have a team of experts to handle these specialized analytical techniques and equipment. The establishment of a high industrial framework by the government will help the nano-based drug industry's development.

3.2.5. Drug formulation

The oral course of drug administration is found to be the most convenient and is highly accepted by patients today. Products from nanotech are usually manufactured in aqueous dispersion form whose conversion into solid orals is tedious work. The procedure employs extensive cryodesiccation at a very low temperature to obtain a stable semi-solid state which further can be compressed in a capsule or molded into tablets for oral dosage. However, the lyophilization process at a mass scale is not only expensive but also results in the aggregation of nanoparticles eventually increasing the size and making the procedure irreversible (Saez et al., 2000). Cryoproducts that are added during the process of lyophilization may hamper the characteristics of respective drugs (Fonte et al., 2013). The products may need to undergo the process of centrifugation or diafiltration as direct lyophilization of nano-particulate matter is not feasible. These processes account for the increased complexity of the procedure making industrial production less operational. Further, the stability, production, and nature of nanotech products are again organized to hold the integrity of the outcome. Therefore, the aqueous dispersion nature of nanoparticles converted into solid oral dosage forms is extensively costly. This justifies the reason for the presence of numerous cosmetic preparations which are nanotech-based since gels and creams are found to be easy-going topical applications while retaining their nanostructure. Thus, various techniques need to be formulated to be utilized as solid dosages or even liquid orals to gain the full potential of nanotech-based products. These products can be employed as chemotherapeutic agents in the form of parenteral that have widespread application and acceptance while maintaining sterile conditions during processing.

3.2.6. Less involvement of other teams

The products of nanotechnology-based origin are of multidisciplinary origin, in which life science relates directly to nanotechnology, nano-engineering, and nanoscience. Hence, the multidisciplinary method is needed to start new indications and for the improvement, evaluation, and large-scale production for positive commercialization of the product (Heimeriks, 2013). One specific

expert will not be able to produce nanotech-based products and the products do not come into the market. People who work in the research area don't have the knowledge on indulgence and they lack commercial knowledge and mostly they will not convert the technology into a product. Investors want to produce a big thing and they lack the endurance and they get help from technical people to produce nanotech-based products.

When people use treatment and the products give complex and it's very difficult to use single person and they are not able to answer the questions asked from the expertise. During product development, the best answer is taken into account if a team of interdisciplinary researchers and scientists including engineers responsible for the formulation, statistical experts, economists, statisticians, chemists, and scientists are joined to produce the products (Mowery, 2011). It is the reason the National Institute of Health (NIH) guide to nanomedicine future are the finance providing agencies provide funds to various life sciences joint to produce different nanotech-based products without the issues (Kantor, 2008).

3.3. Less Involvement

3.3.1. From Industries

Enterprises that are small and medium-sized played a major role in the production of products nanotechnology-based. Proof shows that these enterprises were popular in producing novel products deprived of the help of multinational companies (Wagner et al., 2006). For producing successful nanotech-based product research they should collaborate with large pharmaceutical companies (Bawa et al., 2008). For large pharmaceutical companies, the profitability for the drug is so high, that, they avoid the risk of financing therapeutics with nano for its efficacy and protection which makes the businesses high anxious. These are the several traditional areas and the investments may take 3-5 years to return in the products related to nanotechnology, major doubt is about its fewer returns, high risk, delaying of product manufacturing in the starting phase is high, which leads to increased capital reserves (Figs. 2 & 3).

Figure 2: A framework for Nanotechnology Regulatory Research plan

Figure 3: Difference between traditional and nanotechnology-based products concerning investor's perspectives

It has to be renowned that investors dislike most of the products related to nanotech-based on the myth rather than the truth (Kahan et al., 2009). Most of the marketers were waiting for the acceptance of the product in the market. On the other hand, good profits could achieve by a higher assessment

of risk by stockholders. A detailed and complete analysis of pharmacoeconomics will lead to a well-defined portion of economic resources which results in gaining more returns with less capital investment. The economic analysis will encourage the shareholders or intermediary financiers to check its competency. The focus of the profit with nanotech-based products should not only be limited to monetary benefits but also health perspectives and also should attract investments from the government for the benefit of the general public. Economic analysis is analyzing the making charge of the product is to be worthy or not. It plays a vital role in identifying the error or risk related to products based on novel nanotech which will lead to avoidance of resource expenditure. Quality-adjusted life years (QALY) is the most commonly used to estimate cost-effectiveness. Most of the researchers smartly work along with the health organizations they invest resources such as money, technical assistance, and time, to improve their expertise which will enhance the value and life of people. Currently, administrations like the National Institute of Health have started in search of QALY as the important criteria for calculating the economical point of novel medicines. Amphotericin B and AmBisome (liposomal system) are the two formulations approved by the FDA sold by Fujisawa Healthcare and Gilead Sciences, and a lipid complex by Abelcet sold by the corporation of Elan can be used to treat the diseases caused by a fungus which were undergone an extensive analysis of pharmacoeconomics. When compared to Abelcet, the AmBisome was found to be economical and can easily attract a marketplace.

3.3.2. From Community

The products of nanotech-based are commercialized successfully with the help of the general public. Unfortunately, even though it has enormous benefits for health, most of the community ignored these products. But still, due to long-term effects, issues with environmental compatibility, and toxicity debate the insights, opinions, and beliefs related to nano-based products may vary. Insufficient announcement and lack of information lead to fear and even doubts in the public.

3.3.3. From Doctors

Physicians always focus on new therapeutic options and this is the chief driven force for them to develop products that are innovative and to analyze their performance. Safety and efficacy are the two significant regards of nanotech-based products. MagForce Nanotechnologies developed a nano product and the product is the failure model, Germany plays a key role in the nanotechnology field, they produce the malignant curing product with fewer allergic reactions and this was an example of nanotech-based products developed by physicians who lack the confidence or adequacy level. MagForce developed new nanotech-based products and their markets are very high and reached the

people through television and journals and they failed to express in the medical community towards the technology. They have undergone a lot of problems with the execution of clinical trials and getting approvals from the chemical representatives and which limits the previous experience of physicians to develop products with good performance and much confidence.

3.4. IPR

Nanotech-based products require a long period to produce and the riskiest factor is the patent risk because it expires within a short period. The number of years available to produce a product and also their retrieval of the costs involved in the development and in order to gain the revenue takes too long and more research is needed in the specific part is very scarcely available. Insecurity, low returns, and risk associated is the major discouraging scenario mainly associated with nanotech-based products. As per the information obtained from the Trademark Office (PTO) and US Patent office more than 8000 US patents have been given by different trademark offices as of December 2012 (Paradise, 2012). Noteworthy disputes have been found due to overlapping patents leading to the proliferation of patents and more patents issued by the PTO in the nanotechnology field. Carbon nanotubes-related patents have got more US patents, around 200, is considered to be a typical example of overlapping and identical claims of patents. It is highly recommended that academia and industries and academia should jointly work to produce new nanotech-based products and reduces patent risks for the individual scientist. A flow chart of product to market as shown Fig.4

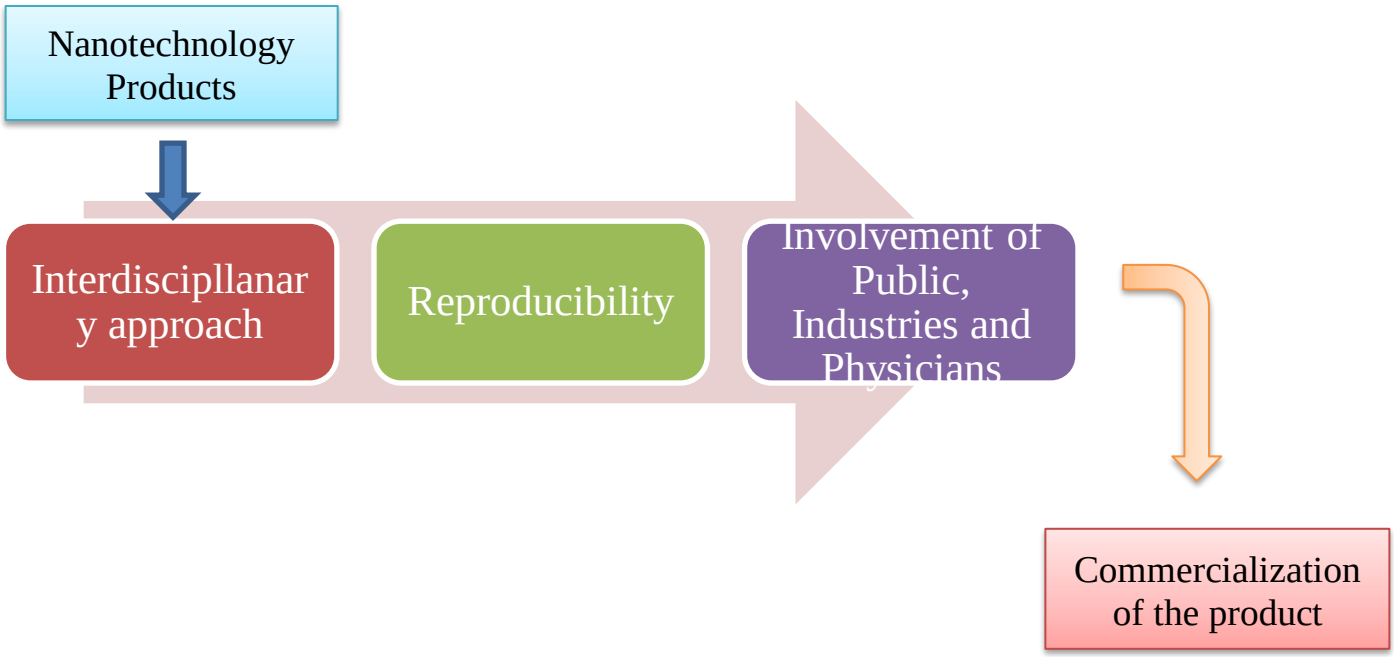


Figure 4: Product to market, a flow chart

4. Conclusions

Despite all the drawbacks including poor intellectual property protection, patent rights, safety, efficacy, scalability, reproducibility, the uncertainty of expected returns, investments in the market, meticulous and FDA regulatory processes for the products related to nanotech to increase. Some changes in the proactive compounds lead to product development, regulations and technology transfer are the different ways to increase the nanotech-based products.

Conflicts of Interest:

The authors declare no conflict of interest.

References

[1] C. Palmberg, The transfer and commercialisation of nanotechnology: a comparative analysis of university and company researches. *J. Technol. Transf.* 2008; 33: 631–652.

[2] L. Mazzola, Commercializing nanotechnology. *Nat. Biotechnol*. 2003; 21: 1137–1143.

[3] T. Flynn, C.Wei, The pathway to commercialization for nanomedicine. *Nanomedicine: NB.* 2005; 1: 47–51.

[4] R.A. Stein. Nanotechnology: is the magic bullet becoming reality? *Insight and Intelligence.* 2014.

[5] M. Taylor, Regulating the Products of Nanotechnology: Does FDA Have the Tools It Needs? *Wilson Center and The Pew Charitable Trusts, Washingto*. 2006.

[6] Reamer, L. Icerman, J. Youtie, Technology Transfer and Commercialization: Their Role in Economic Development. *U.S. Department of Commerce*.2003.

[7] T. Spinverse. Commercialisation of Nanotechnology—Key Challenges Workshop Organised by Nanoforum in Helsinki. Finland. 2007: 1–27.

[8] R. Allen. Venture capital investment in nanotechnology. 2014

[9] J. Bradley, Nanotech venture capital: healthcare and life sciences provide life support. 2021.

[10] T. Satterfield, M. Kandlikar, C. Beaudrie, J. Conti, B. Harthorn, Anticipating the perceived risk of nanotechnologies. *Nat. Nanotechnol*. 2009; 4 : 752–758.

[11] V. Morigi, A. Tocchio, C. Pellegrini, J. Sakamoto,M. Arnone, E. Tasciotti, Nanotechnology in medicine: from inception to market domination. *J. Drug Deliv.* 2012: 1–7.

[12] K. Vega-Villa, J. Takemoto, J. Yanez, C. Remsberg, M. Forrest, N. Davies, Clinical toxicities of nanocarrier systems. *Adv. Drug Deliv. Rev*. 2008; 60: 929–938.

[13] R. Bosetti, L. Vereeck, Future of nanomedicine obstacles and remedies. *Nanomedicine*. 2011; 6: 747–755.

[14] S. Suppan, Racing Ahead U.S. Agri-Nanotechnology in the Absence of Regulation. *Institute for Agriculture and Trade Policy*. 2011; 3–20.

[15] A.M. Hahn, A.K. Singh, P. Sharma, C.B. Scott, M.M. Brij, Nanoparticles as contrast agents for in-vivo bioimaging: current status and future perspectives. *Anal. Bioanal. Chem*. 2011; 399 : 3–27.

[16] E. Altınoğlu, T.J. Russin, J.M. Kaiser, B.M. Barth, P.C. Eklund, M. Kester, J.H. Adair, Near-infrared emitting fluorophore-doped calcium phosphate nanoparticles for invivo imaging of human breast cancer. *ACS Nano.* 2008; 2: 2075–2084.

[17] K. Donaldson, P.H. Beswick, P.S. Gilmour, Free radical activity associated with the surface of particles: a unifying factor in determining biological activity? *Toxicol. Lett.* 1996; 88 (1–3) : 293–298.

[18] C. Lherm, R.H. Müller, F. Puisieux, P. Couvreur, Alkylcyanoacrylate drug carriers. II. Cytotoxicity of In vitro uptake of polystyrene latex cyanoacrylate nanoparticles with different alkyl chain length. *Int. J. Pharm*. 1992; 84 : 13–22.

[19] S. Raj, S. Jose, U.S. Sumod, M. Sabitha, Nanotechnology in cosmetics: opportunities and challenges. *J. Pharm. Bioallied Sci*. 2012; 4 (3) : 186–193.

[20] US FDA, Nanotechnology: a report of the U.S. Food and Drug Administration Nanotechnology Task Force. 2007.

[21] Kumari, S.K. Yadav, S.C. Yadav, Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids Surf.* 2010; B 75: 1–18.

[22] J. Mehta, J. Blake, C. Craddock, Comparative efficacy of amphotericin B lipid complex and liposomal amphotericin B for the treatment of invasive fungal infections in HSCT recipients and other immunocompromised patient populations with hematologic malignancies: a critical review. *Open Transplant. J.* 2011; 5 : 23–29.

[23] A.C. Silva, M.L. Garcia, M.A. Egea, J. Fonseca, R. Silva, Preparation, characterization and biocompatibility studies on risperidone-loaded solid lipid nanoparticles (SLN): high pressure homogenization versus ultrasound. *Colloids Surf. B: Biointerfaces*. 2011: 158–165.

[24] R.H. Muller, S. Runge, K. Schulze-Forster, W. Mehnert, Cytotoxicity of solid lipid nanoparticles as a function of the lipid matrix and the surfactant. *Pharm. Res. 4*. 1997; 458–462.

[25] M. Nassimi, H.D. Lauenstein, R. Hussein, H.G. Hoymann, W. Koch, A toxicological evaluation of inhaled solid lipid nanoparticles used as a potential drug delivery system for the lung. *Eur. J. Pharm. Biopharm*. 2010; 75: 107–116.

[26] Consumer products inventory. The Project on Emerging Nanotechnologies, 2014.

[27] J. Pardeike, A. Hommoss, R.H.Muller, Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. *Int. J. Pharm*. 2009; 366 : 170–184.

[28] M. Ferrari, Nanogeometry: beyond drug delivery. *Nat. Nanotechnol*. 2008; 3 : 131–132.

[29] Y. Barenholz, Doxil® - The first FDA approved nanodrug: lessons learned. *J. Control. Release*. 2012; 160 : 117–134.

[30] J.H. Sakamoto, A.L. van de Ven, B. Godin, E. Blanco, R.E. Serda, A. Grattoni, A. Ziemys, A. Bouamrani, T. Hu, S.I. Ranganathan, E. De Rosa, J.O. Martinez, C.A. Smid, R.M. Buchanan, S.Y. Lee, S. Srinivasan, M. Landry, A. Meyn, E. Tasciotti, X. Liu, P. Decuzzi, M. Ferrari, Enabling individualized therapy through nanotechnology. *Pharmacol. Res*. 2010; 62 : 57–89.

F.L. Muller, J.M. Latimer, Anticipation of scale up issues in pharmaceutical development, Comput. Chem. Eng. 33 (2009) 1051–1055.

[31] Laouini, C. Jaafar-Maalej, I. Limayem-Blouza, S. Sfar, C. Charcosset, H. Fessi, Preparation, characterization and applications of liposomes: state of the art, J. Colloid Sci. Biotechnol. 1 (2012) 147–168.

[32] N. Desai, Challenges in development of nanoparticle-based therapeutics, *AAPS J*. 2012; 14 : 282–295.

[33] Kaur, S. Kakkar, M. Yadav, K. Jindal, I. Sharma, Autoclavable nanovesicular composition, IPA/700/Del/2014. 2014.

[34] R. Shegokar, K.K. Singh, R.H. Müller, Production & stability of stavudine solid lipid nanoparticles—From lab to industrial scale. *Int. J. Pharm*. 2011; 416 : 461–470.

[35] R. Shegokar, K.K. Singh, R.H. Mueller, Nevirapine nanosuspension: comparative investigation of production methods. *Nanotechnol. Dev*. 2011; 1 : e4.

[36] V. Kakkar, I.P. Kaur, Preparation, characterization and scale-up of sesamol loaded solid lipid nanoparticles. *Nanotechnol. Dev.* 2012; 2 : 40–45.

[37] A.P. Ranjan, A.Mukerjee, L. Helson, J.K. Vishwanatha, Scale up, optimization and stability analysis of Curcumin C3 complex-loaded nanoparticles for cancer therapy. *J. Nanobiotechnol*. 2012; 10 : 38.

[38] R.H. Muller, K. Mader, S. Gohla, Solid lipid nanoparticles (SLN) for controlled drug delivery - A review of the state of the art. *Eur. J. Pharm. Biopharm.* 2000; 50 : 161–177.

[39] M.M. Mojahedian, S. Daneshamouz, S.M. Samani, A. Zargaran, A novel method to produce solid lipid nanoparticles using n-butanol as an additional co-surfactant according to the o/w micro-emulsion quenching technique. *Chem. Phys. Lipids*. 2013; 174 932: 32–38.

[40] M. Gaumet, A. Vargas, R. Gurny, F. Delie, Nanoparticles for drug delivery: the need for precision in reporting particle size parameters. *Eur. J. Pharm. Biopharm*. 2008; 69 : 1–9.

[41] K. Langer, M.G. Anhorn, I. Steinhauser, S. Dreis, D. Celebi, N. Schrickel, S. Faust, V. Vogel, Human serum albumin (HSA) nanoparticles: reproducibility of preparation process and kinetics of enzymatic degradation. *Int. J. Pharm*. 2008; 347 (1–2) : 109–117.

[42] W. Mehnert, K. Mader, Solid lipid nanoparticles: production, characterization and applications, *Adv. Drug Deliv. Rev*. 2001; 47: 165–196.

[43] Saez, M. Guzman, J. Molpeceres, M.R. Aberturas, Freeze-drying of polycaprolactone and poly(D, L-lactic-glycolic) nanoparticles induce minor particle size changes affecting the oral pharmacokinetics of loaded drugs. *Eur. J. Pharm. Biopharm*. 2000; 50 : 379–387.

[44] P. Fonte, S. Soares, A. Costa, J.C. Andrade, V. Seabra, S. Reis, B. Sarmento, Effect of cryoprotectants on the porosity and stability of insulin-loaded PLGA nanoparticles after freeze-drying. *Biomatter*. 2013; 2: 329–339.

[45] G. Heimeriks, Interdisciplinarity in biotechnology, genomics and nanotechnology. *Sci. Public Policy*. 2013; 40 : 97–112.

[46] D.Mowery, Nanotechnology and the US national innovation system: continuity and change. J. *Technol. Transf*. 2011; 36 : 697–711.

[47] L. Kantor, NIH roadmap for medical research. *Alcohol Res. Health*. 2008; 31: 12–13.

[48] V. Wagner, A. Dullaart, A. Bock, A. Zweck, The emerging nanomedicine landscape. *Nat. Biotechnol.* 2006; 24: 1211–1217.

[49] R. Bawa, S. Melethil,W. Simmons, D. Harris, Nanopharmaceuticals—patenting issues and FDA regulatory challenges. *Am. Bar Assoc. Sci. Technol. Lawyer*. 2008; 5: 10–15.

[50] D. Kahan, D. Braman, P. Slovic, J. Gastil, G. Cohen, Cultural cognition of the risks and benefits of nanotechnology. *Nat. Nanotechnol*. 2009; 4: 87–91.

[51] J. Paradise, Claiming nanotechnology: improving USPTO efforts at classification of emerging nano-enabled pharmaceutical technologies. *Northwest. J. Technol. Intel- lect. Prop*. 2012; 10: 171–189.