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Major Obstacles in Technology Transfer of Nanomedicine from Conception to Commercialisation

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ABSTRACT: The "Nano" word itself state that the successful technology transfer of nanomedicine from conception to full scale commercialisation must require nano planning to encounter countless nano challenges to be exist during the technology transfer. Therefore, the particular aspect of the nanomedicine field which has received a great deal of attention is successful technology transfer of nanomedicine from conception to full scale commercialisation. This paper highlights the numerous critical challenges related to different stages of technology transfer, starting from business strategy, regulatory requirements, cost of investment, pharmacokinetic challenges of nanomedicine, translation of pilot stage clinical study to pivotal stage clinical study and challenges in translation of small-scale development to large scale commercial product.

Keywords: Nanomedicine, development, technology transfer, clinical study, regulatory requirement

I. INTRODUCTION

Due to the painless administration, an oral route become a highly preferable, most convenient and widely used route for an administration of most medicine compared to other routes, i.e. intravenous, intramuscular, nasal, rectal, pulmonary. Despite, oral route is most preferable route, several drugs having shorter half-life, low solubility, low bioavailability, etc made difficulties in development of conventional dosage form for oral administration. Although, this challenges can be overcomes by applying novel drug delivery system such as Osmotic drug delivery system for the drug having shorter half-life to extended the therapeutic efficacy of the drug over the longer period of time [1], by increasing solubility and their by increase drug absorption (bioavailability) of drug using surfactant or micronizing particle size of API, etc. However, the novel drug delivery system also have some limitation. Prior to the orally administered drug reach to its target, it will require to pass on many compartments of a human body and thus it is highly challenging for a broad spectrum of pharmaceuticals, particularly for peptide or protein based molecules due to high risk of degradation in higly variable pH medium, challenges in absorption, etc. The only highly promising approach to overcome the aforesaid obstacles for delivery of drug to target site is nanomedicine [2].

Due to a necessity and demand followed by awareness and knowledge of the applications of nanotechnology in medicine existed the emergence of a novelhighly growing multidisciplinary area, namely a"nanomedicine". The term "nanomedicine" refers to a rapidly evolving and emerging field that comprise utilisation ofnanotechnology to treat as well as diagnose the different kinds of disease that the convention medicine or technology, respectively, being not able to successful because mostbiological mechanisms in the mammal body occur at very nano-scale, as nanoparticles are very small in size, it may potentially cross the natural barriers of biological membrane and enterinto difficult to reach sites of the body, wherein they can interact with biomolecules within the organs or in blood, cell or tissues; which is highly advantageous for gene or drug delivery. Prior to successful application, nanomedicine must require to undergo extensivecharacterization, toxicity assessment, clinical trials as well as monitoring and extensive regulatory for theassessment prior to their full potential benefits for patient isrealized.[3]

The first liposomal licensed nanomedicine of Propofol was introduce in 1989 for anaesthesia and then after additionall iposomal colloidal suspensions and pegylated forms of active ingredients introducein chemotherapy, ophthalmology andinfectious

International Journal of Pharmaceutical Research and Applications
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diseases. The current advancementin existing knowledge as well as novel approaches of nanotechnology in nanomedicine now offer potential revolutionize treatment in diverse clinical areas that have expanded the scope of nanotechnology, along with the types of nanostructures and the types of active molecules to be incorporate, in nanomedicines[4]. The very high upper trend in Numberof Patents and Publication on Nanomedicine research over the time is seen after 2004[4] andthe application of nanomedicine for clinical purposes has received significant attention from researchers including academia andindustry along with it's supporterincluding government funding agencies and regulatory bodies. The application of nanotechnology as medicine has the great potential to have a significant impact on human health by improving the diagnosis, prevention and treatment of diseases. Generally, nanomedicines encapsulate active drug and/or imaging substances in nano sized carrier materials, [5]that gives the opportunity to protect the fragile substance prone to degradation easily in biological environments and provide solubilization to compound in terms of delivering the compounds which have physicochemical properties that strongly limit their solubility in biological fluid and therefore enhance systemic bioavailability. For example, nanomedicine as targeted drug delivery and nanomedicine with triggered release approach have been shown highly beneficial inenhancing the therapeutic index of the compounds, by improving the in vivo fate of the compound in a way that more efficiently deliver the compound to the target site (to yield improved therapeutic effects) with very low accumulation in different parts of healthy body andthereby potential to reduce toxicity of the drug compound. In add on, ability of thenanomedicines havealso been studied to stimulate target cell uptake and improve intracellular trafficking and some target delivery processes that sometimes required when they have localized in target tissues[6]. Because the nanomedicine have a combination of chemical, physical, and biological properties, they are onlycapable for these unique applications[5].

As illustrated in figure 1, nanomedicines are intended to enhancethe therapeutic index of drugs (i.e., increase efficacy and/or reduce toxicity) bydelivering them in different forms via different release mechanisms which mainly include:

(a) conventional nanomedicine - these type of nanomedicines can be modified with charged lipids/polymers, thermosensitive lipids/polymers and/or components for triggered release (e.g., pH-sensitive coating)

(b) theranosticnanomedicine – these type ofnanomedicine systems usually consisting of an imaging component and a therapeutic component, and it may also include a targeting element

(c) PEGylated nanomedicine–characteristics of nanomedicine as well as it's in vivobehaviour can be modified by the addition of a hydrophilic polymer coating, namely, polyethylene glycol (PEG), to the nanomedicine surface to confer steric stabilization, (d) ligand-targeted nanomedicine–these type of nanomedicine can be used for active targeting by attaching ligands (e.g., peptides, antibodies, and carbohydrates) to the terminal end or on its surface of the attached PEG chains.

Therefore, to have successful potential clinical translation of nanomedicine from R&D scale product to commercial one, the complexity in their design and development must be carefully needed to be minimized at certain level that could create asystems that are able to be reproducibly prepared and characterized the nanomedicine[7, 8]. Even though there is rapid growth of application of nanotechnology in medical applications, the current most urgent need in nanomedicine is developing and validating practical approaches that are able to determine potential long-term and short-term risk to the health of individual, including the extrapolation of acute in vitro results for the prediction of chronic in vivo effects[9].

Yes, there is no doubt that there are vast number of nanomedicines are at different preclinical and clinical development stage along with in clinical use for targeting a wide variety of cancerous tumor. However, there are multiples factors that imposing significant obstacles in successful technology transfer of Nanomedicine from conception to full scale commercial production with irrespective of whether they are therapeutically beneficial to patients or not[5]. Key issues related to successful technology transfer of Nanomedicine from conception to full scale commercialproduction include intellectual property, government regulations, biological or pharmacokinetic challenges, biocompatibility and safety, small scale to large scale manufacturing, and the most important is overall cost-effectiveness in comparison to current therapies[6] Till date, multiple efforts has been made to overcome major obstacles in nanomedicine. For example, novel approach in nanomedicine is exosomes as a delivery system that open up a new promising

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avenue for cancer treatment [10]. Application of an alternating magnetic field following administration of cancer-targeting magnetic nanoparticles that accumulate in the tumor allows preferential heating of malignant cancer cells.[3]

Despite promising results in different preclinicalstudies, there are still numbers of challenges that creating obstacle in Technology Transfer of Nanomedicine from Conception to full scale Commercialisation.Therefore, one particular aspect which received a great deal of attention for Nanomedicine in today's world is the design, development and successful technology transfer of nanoparticulate nanomedicines from conception to commercialisation. This paperhighlights the major current challenges in technology transfer of Nanomedicine from Proof-Of-Concept to full scale Commercialisation.

II. MAJOR OBSTACLES IN TECHNOLOGY TRANSFER OF NANOMEDICINE FROM CONCEPTION TO COMMERCIALISATION

With respect to the pharmaceutical industries, "technology transfer" refers to the strategy that are intended for successful product transfer from product conception to full-scale commercialization. Therefore, technology transfer is part of the innovation process; it is neither predictable nor linear, being multi-stages and involve multiple factor for successful transfer, i.e.conception to identifying and developing new technologies; protecting them with an appropriate intellectual property strategy, via patents and/or copyrights; translation of manufacturing process to commercial scale from small scale and establishing development and commercialisation plans (e.g. licensing or company creation)[11]. The scheme 1 described the current a major Obstacles in Technology Transfer of Nanomedicine from Conception to Commercialisation

2.1 Business Strategy

Development of novel nanomedicine mainly trigger uncertainty of success vs the very high investment for development process. Considering the uncertainty vs high investment requirements, the business strategy for development of novel nanomedicine mainly divided into 2 parts: one is Development of Novel Nanomedicine (product conception) and second is commercialisation of Developed nanomedicine into the market.

The Research and Development (R&D) department is the department that mainly characterize and potentially identify a research driven nanomedicine company. At the product conception (Development of novel nanomedicine), any research driven company first evaluate two best possible alternative options. The first is to perform entire research and development of nanomedicine within the R&D department of the company,composing a highly experienced scientists' team. The second is tie up with universities or research institutes to perform entire research and development of nanomedicine by highly experience and scholar academic professionals. The main benefits in the second option is that it will certainly reduce company's costs because the academics or research institute frequently cofound the companies based on their discoveries and become part of the scientific boards. Morigi et al gathered the strong evidence for the second option for the R&D strategy of product development at R&D stage[12].

After the successful conversion of product conception to clinically usable nanomedicine, the next part of business strategy is the commercialization. The research and technology-based company typically license out the manufacturing and commercialization of the nanomedicine-based product to larger companies. If this is the case, the business model pursued will not include commercialization[12].

2.2 The Cost of Investment on Development: Recovery Vs Loss

The inventor initially possesses primary output of innovation is obtaining the know-how. Unfortunately, the confidentiality of this knowledge can be breached and its use by one company cannot preclude the use of the same by another one. Therefore, investors approaching novel projects are aware of the fact that they will not be able to easily appropriate the total returns of the investment undertaken[12]. As a consequence, there is a lack of attractiveness in financing innovative projects. In fact, according to the perspective of economic theory, it is very difficult to find funds for innovative concept in a competitive market place. Even in large firms, there is evidence of shortages in resources to spend on the innovative projects that the managers would like to undertake [13]. There are a number of reasons for this phenomenon: low expected returns due to an incapacity to capture the profits from an invention, the exaggerated optimism in undertaking

International Journal of Pharmaceutical Research and Applications
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an investment on breakthrough projects, and most notably the uncertainty and risk associated with these projects. Technology driven companies some time also consider imitating the inventions developed by competitors. However, Edwin et al. [14], using survey evidence, found that imitating is not costless and could result in expenses equal to 50% to 75% of the cost of the original invention, not eliminating the underinvestment problem. Policymakers are trying to change the funding situation, by facilitating the invention process, rationalizing the interventions through government encouragement of innovative activities, sustaining the intellectual property system, allowing Research and Development tax incentives, and supporting research collaborations. Nonetheless, the path that leads the nanoscale outcome from the laboratory to leads the nanoscale outcome from the laboratory to the marketplace is long and expensive, putting the inventor in a position of disadvantage.

2.3 Product Development: Translation of Small-Scale Development to Full Commercial Scale

Although, nanoparticles are highly structured and integral compositions, criticality in nanoparticles manufacturing process is that this process is not simple addition of components and mixing of individual components together. The most crucial property of nanoparticle is physicochemical properties of intact nanoparticles and the structural integrity that must be preserved throughout the small-scale formulation development to the large-scale production. Therefore, unique challenges in pharmaceutical development is successful scale-up and manufacturing of a nanomedicine at large scale. The methods for preparing nanoparticle can be broadly classified into 2 approaches (1) “bottom up” approach, and (2) “top down” approach. In bottom up approaches, smaller components arrange into more complex assemblies by polymerization of molecular or monomers self-assembly resulting into single molecule components that automatically arrange themselves into a useful conformation. In contrast, in top down approaches, smaller entities create from larger ones, for example by grinding of large particles into smaller one using the milling technique [15,16]

Many formulation processes of nanoparticle often involves the use of high speed homogenization, organic solvents, crosslinking, evaporation of organic solvents, sonication, milling, centrifugation, filtration, emulsification, and lyophilization. Therefore, at initial stage of development, i.e. at the small-scale development, it is ideal to consider appropriate approach that is ease and having lesser complexity in manufacturing if the product were to be scaled up. Optimum process conditions identification is critical to achieve key attributes and functions while translation of small scale process to large scale process that produce lesser effect in translation of small scale process to large scale production of nanoparticles. For examples, the type of organic solvent, targeting moieties, the ratio of polymers and drugs, and emulsifier/stabilizer/crosslinker, mixing, temperature, the oil-to-water phase ratio, pressure, and the pH[15]. The process condition some time may lead to alteration of chemical structure of the drug substance, substantial amount of impurities and the other components. Particularly for biologics, change in process condition some time may result in changes in chemical structure and conformation, crosslinking, coagulation, denaturation, and degradation[16].

The manufacturing process for nanoparticles often requires multiple processing steps that involve multi component systems. Therefore, another critical consideration at development of nanoparticle is that the formulation process must be robust such that it ensure higher reproducibility, and be streamlined to allow for the ease of scale-up production. It is easy to achieve reproducibility at small-scale processes with well characterised components, but after the early prototype, the consistency and reproducibility to constructs similar type of nanoparticles at large scale remain a major challenge for the scaling up of manufacturing process. Therefore, manufacturing process must require to define acceptable limits for key attribute of nanoparticle and identification of critical process conditions that are crucial to achieve these key attributes and functions of nanoparticles. Therefore, at the small scale production, these critical process conditions and stages must require to be identified through extensive experimental work to gain a complete understanding that how manufacturing process conditions could impact the product at both from a biological and physicochemical perspective. This indicate that the biological and physicochemical tests must be sensitive enough to identify discrepancies in the product that could affect performance. In multistep manufacturing processes at small scale and during transfer to scale up batches, in process testing for crucial parameters with a reliable and rapid analytical method is many time highly very informative to learn and gather the

important information about how well the process is controlled. To ensure success at the commercial scale, building up a information database along with crucial targeted in process tests may be vital.[16]

2.4 Pharmacokinetic Characteristics of Nanomedicines

Pharmacokinetic characteristics of various nanomedicines with different formulations are determined by particle size, shape (chemical structure) and surface chemical characteristics [17, 18]. Nanoparticles with particle size greater than 10 nm are often elongated and removed by the mononuclear-phagocyte system (MPS) and / or the liver whereas Nanoparticles with particle size lower than 10nm are removed by kidneys. Due to changes in pharmacokinetic properties of the drug substance, pharmacokinetic characteristics of the drug's nanomedicine are change, which include greater distribution to target tissues, longer stay in the body, alleviating adverse reactions and possibly increasing their efficacy [19]. Regulation of adverse reactions and / or efficacy of nanoparticles (nanomedicine) is affected by alteration of pharmacokinetics such as in vivo distribution, absorption, metabolism and excretion in the body[17]. Physiochemical properties of nanomedicines depend on their formulation composition and manufacturing process, which ultimately affect their efficacy and toxicity[17,20,21]. Adjustment of the degree of binding between biomolecules and nanomedicines and control of physiochemical properties (e.g. composition or formulation) of nanomedicines eventually regulate in vivo distribution of nanomedicines. For example, it has been reported that the type and amount of binding proteins are significantly reduced when nanomedicines are prepared using PEGylated particles. Further, binding of polysorbate coated particles to ApoE was reported to increase their migration to the brain [17,20,21].

2.5 Translation of Pilot Stage to Clinical Stage

Whilst pilot pre-clinical experimentation has been used effectively to generate proof-of principle and drive optimisation of new nanomedicine technologies, it is important to identify weaknesses and remain objective about their relevance for later development. The primary aim of early preclinical testing should be to identify both the therapeutic potential and any clinical risks, to select formulations that will be safe and efficacious and possess the required pharmacokinetic and biodistribution properties because the significant financial investment required for clinical trials. In the past, anti-cancer nanomedicine research has used the standard formulation-driven approach: novel nanomedicines are developed and then evaluated using in vitro cytotoxicity assays, in vivo pharmacokinetic/ biodistribution studies and anti-tumour experiments in xenograft models sensitive to the payload. This paradigm has not generated the data that yield insight into the key issues that enable the successful translation of nanomedicines to the clinic[22]. Therefore, in order to reduce investment risk for nanomedicine, the preclinical data sets need to comprehensively evaluate therapeutic efficacy, safety, biodistribution, and pharmacokinetics in appropriate animal models of the disease that are relevant to human disease. Evaluation of nanomedicine in multiple preclinical animal models that represent aspects of the clinical disease is preferred to achieve reproducibility of results for the specific disease and not for a specific animal model. In addition, animal models that reflect only a narrow spectrum of the clinical disease may provide useful data that can predict their suitability for treating a specific patient sub-group [22]. Based on different routes of administration, differences in physiology and / or the anatomy of the animal species compared to humans must be taken into account. Preclinical studies of nanomedicine should also be conducted under appropriate randomization and blinding to reduce bias, as well be evaluated against proper controls, including the gold standard treatment and not just free drug solution. These factors are currently lacking in many published studies, which makes it difficult to assess clinical applicability and translatability[6].

2.6 FDA Regulatory Requirements

Drug development delivery time in the 1960s was 8.1 years for preclinical, clinical, and approval. In the 1970s it was 11.6 years, in the 1980s it was 14.2 years, and in the 1990s, 14.1 years [10]. The FDA's lengthy approval process and regulations make nanomedical applications different from other industries where nanotechnologies are currently being used across a wide spectrum of industry and there are no constraints of regulatory bodies. In the most cases, the FDA evaluation approach for nanomedicine is varied to a case-by-case along with applying the combination product framework to evaluate the product type according to resulting regulatory

requirements. The FDA also faces various challenges as per the progresses of nanomedicine (figure 2)[23]. The first challenges is the adequacy in framework of the regulatory itself because nanomedicine highlights the rigidity of domains products that dictate requirements for product approval. For the new generation nanoscale products, very old definitions of mechanical and chemical action are not be suitable for characterizing products with new mechanisms of action andit's properties. As a result, to evaluate nanoscale nanomedicine, the traditional definition that accompanying legal requirements of review, approval, and postmarketstudies and assessment may not be ideal procedure. A second challenge is associated with the potentiality of novel risks associated with novel mechanism of action of nanomedicinesthat may raise questions forappropriateness assessment of traditional requirements mainly safety and efficacy. The main questions persist includes whether nanoscale properties alter established risk-benefit measures and assessments of clinical trials and research protocols; at what time and in which phase abbreviated review of nanomedicine products is most critical; and whether and when assessments of post approval study should be tailored to gather the information aboutexposure concerns and nanospecific toxicology. A third challenge is whether labelling information about nanomedicine products is suffice for customer to inform them that nanotechnology or nanomaterials are utilised in manufacturing of product. This means not explicit to say that labelling is must requirement; but the FDA must contemplate to increasedconsumer engagement and consumer and patient education is warranted.

2.7 Intellectual Property

The filing of patents, a major part of intellectual property, often takes years and, minimally, tens of thousands of dollars to properly address.The cost to bring a new product to market required millions of dollars and that the big pharmaceutical and biotechnology companies have no option without investment to bring product into the market and thus all the companies go for patent filling to get protected and to prevent other from selling the generic product.Therefore, the area of intellectual property will be a major battle zone as the companies will watch for infringement of one technology as it converges with another new technology because any infringement may prevent selling of developed nanomedicine after spending millions of dollar into the market and the CEOs of the companies ultimately answerable to stockholder[24]

III. CONCLUSION AND FUTURE REMARKS

At the end, we can say that nanomedicine has the potential to have major impact on human health for the prevention, diagnosis and treatment of diseases because thenanomedicines have been employed to improve the efficacy, safety, physicochemical properties, and pharmacokinetic/pharmacodynamic profile of pharmaceutical drug substances. In particular, functionalized nanomedicine can offer enhanced bioavailability of orally taken drugs, prolonged half-life of injected drugs (by reducing immunogenicity), and targeted delivery to specific tissues.

Although the nanoparticles possessesthese potential advantages, only a relatively very small number of nanotechnology based medicinal product have been approved for clinical use, with numerous hurdles and challenges at different development stages. To achieve a consistent product with the intended pharmacological profiles, biological behaviours and physicochemical characteristics, the multi-component threedimensionalcomplexity to construct nanoparticles must requires careful engineering in designing, reproducible scale-up, manufacturing process and detailed orthogonal analysis methods. As the safety and efficacy of nanomedicines can be altered by small variations in one or more process parameters which need to be carefully examined in preclinical and clinical studies, particularly in context of the targeting to intended sites, biodistribution and potential immune toxicities. Overall, nanotechnology application in making nanomedicines present add on development challenges and complex regulatory expectation or considerations compared with conventional medicinal product.[16]

Future opportunities for nanomedicines are looking towards delivering the next generation of drugs: molecularly targeted agents, toxin-like agents that induce cell death, DNA-/RNAbased therapeutics, peptides, drug combinations, etc [22]. The future development of nanomedicines will also likely to include a personalized medicine approach as an integral part of the clinical development strategy to identify subgroups of that particularly benefit from therapy[16].

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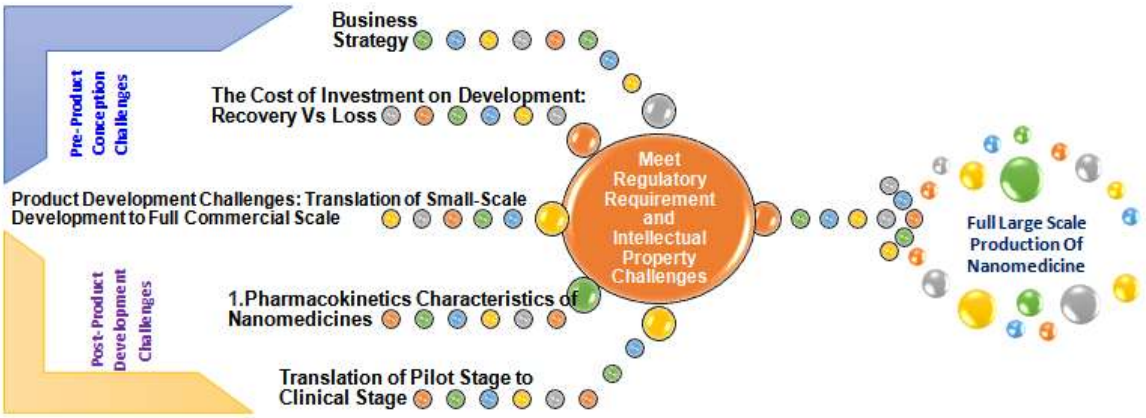
Graphical Abstract



Scheme 1: A Major Obstacles in Technology Transfer of Nanomedicine from Conception to Commercialisation

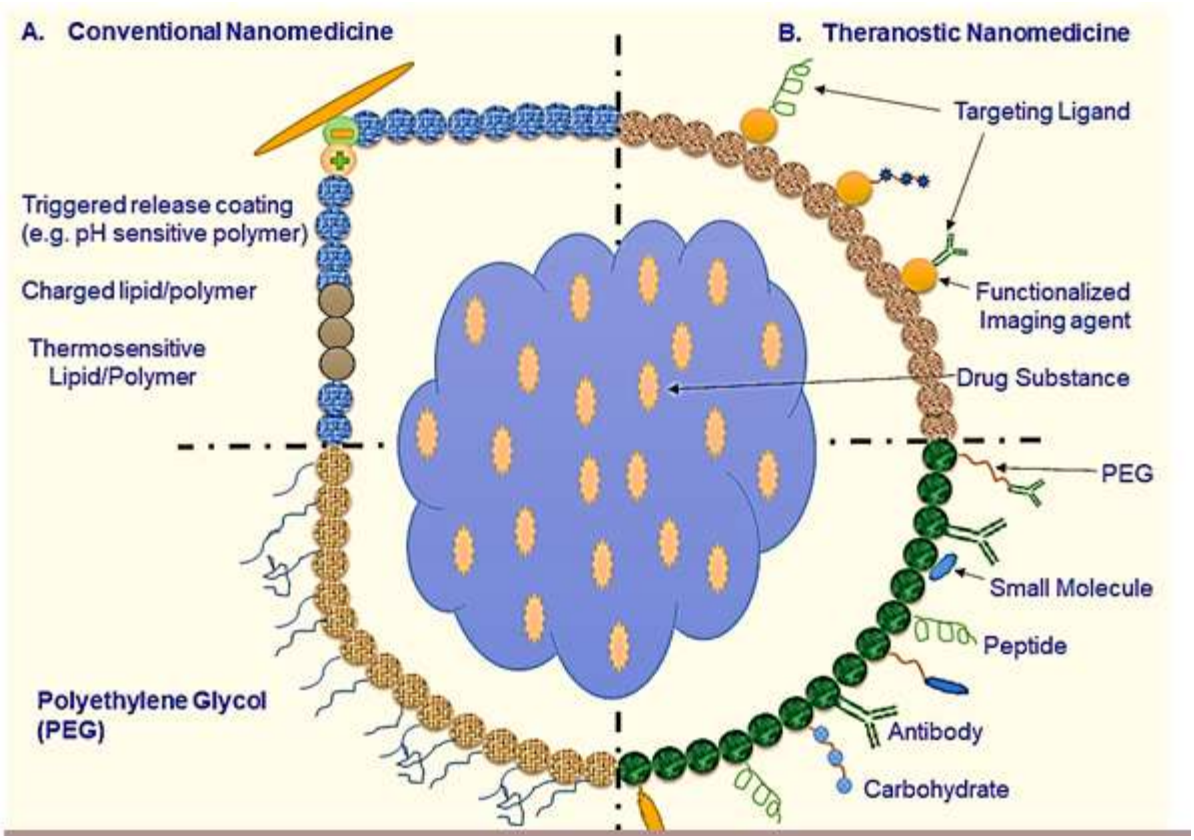


Figure 1: Schematic representation for strategic different forms of Nanomedicine: A. Conventional Nanomedicine, B. Theranostic Nanomedicine, C. PEGylated Nanomedicine and D. Ligand Targeted Nanomedicine

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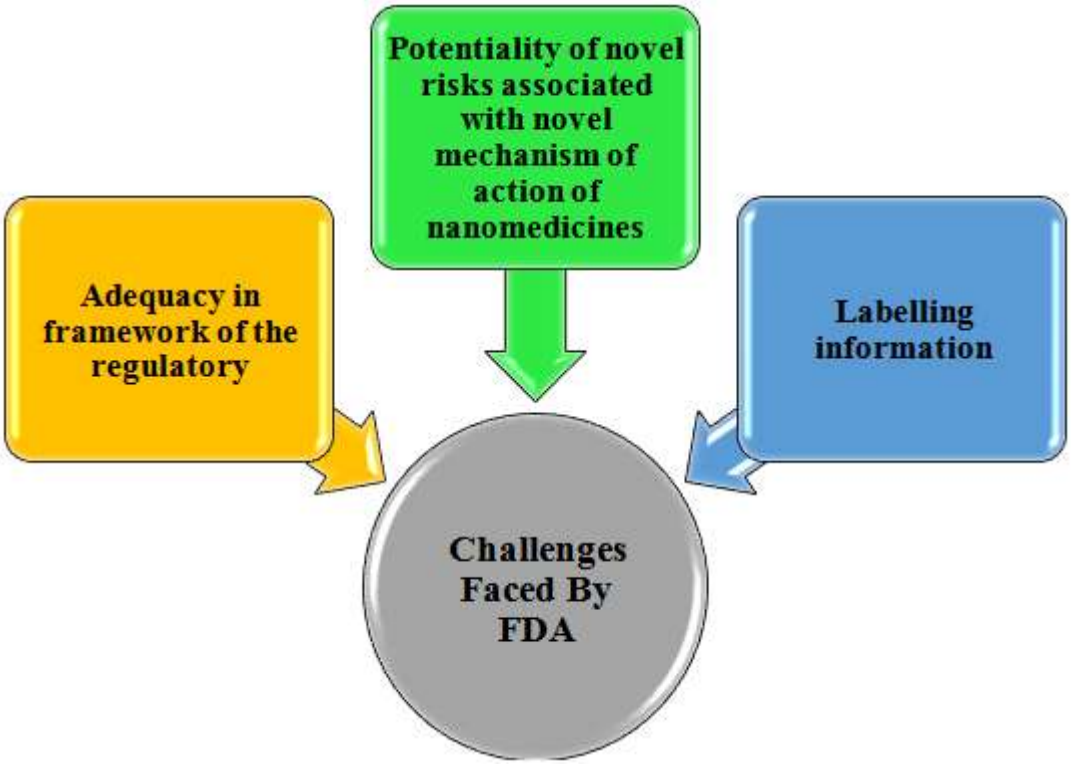

Figure 2: Challenges faced by FDA during evaluation of Approval Process of nanomedicine