Challenges associated and approaches for successful translation of nanomedicines into commercial products

“The successful clinical translation of nanomedicine has challenges of reproducible manufacturing and scale-up, lack of acceptable screening platforms and reliable techniques to evaluate the efficacy, toxicity and stability *in vivo*.”

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Nanomedicines are complex engineered nanoscale structures and are widely used in the treatment and targeting of diseases because of their numerous therapeutic benefits. These benefits are: protection of biomolecules from degradation, enhanced solubility and bioavailability, improved pharmacokinetics, reduced toxicity, enhanced therapeutic efficacy, decreased drug's immunogenicity, delivery at the target site and diagnostics/treatment options in one system [1–4]. Several nanomedicine products have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for various therapeutic indications [2,5–6]. High therapeutic efficacy and safety are the two primary qualifications for a product to become commercially successful. But, most of the nanomedicine products fail to accomplish these requirements and thus their successful commercialization [7]. Limited clinical success of nanomedicines is mainly due to challenges in formulation optimization, batch-to-batch consistency, robust and reproducible manufacturing and scale-up, characterization and screening methods, regulatory barriers and instability under biological environments [2,7–8]. Specific properties of nanomedicines those are responsible for their numerous benefits also generate safety and translational challenges.

Thus, understanding the fundamental, clinical and regulatory aspects of nanomedicine is of paramount significance. In this editorial, challenges associated with the successful translation of nanomedicines from pre-clinical to commercial stage and suggested approaches to achieve this translation are discussed. Nanopharmaceutical drug delivery and therapeutic systems are collectively referred as nanomedicines in this article.

Challenges in manufacturing scale-up & reproducibility

A successful manufacturing and scale-up of nanomedicines under regulated conditions present unique challenges [5,7–9]. The nano-formulation process often involves multiple steps such as homogenization, sonication, centrifugation, solvent evaporation, extrusion, size reduction, lyophilization, sterilization, etc. At small-scale, the formulation/process optimization and reproducibility can be achieved relatively easily; however, at large scale it poses a challenge to achieve a robust manufacturing process and minimize batch-to-batch variability. This severely limits the clinical and/or commercial translation of nanomedicine [8]. The subtle variations in the formulation and/or manufacturing process can significantly affect the critical physico-chemical properties such as size, crystallinity,

Vivek Agrahari

Author for correspondence:
Technical Development, Bayer U.S. LLC,
Shawnee, KS 66210, USA
Tel.: +1 816 805 8048
vivek.agrahari@bayer.com

Praveen Hiremath

Formulation Technology, Bayer Animal
Health GmbH, Leverkusen 51368,
Germany

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drug-loading/-release profile, surface charge, chemistry, ultimately influencing the therapeutic outcomes. Conventional pharmaceutical industrial facilities are usually not well equipped for the manufacturing of nanomedicine products due to constraints in using organic solvents, capability to handle and process nanosized drugs/excipients due to environmental/operator/product safety concerns and requirement of sterile-manufacturing capability [7,8]. The physicochemical properties and integrity of nanomedicines also need to be maintained throughout the manufacturing process and during the shelf-life. In general, most industries have a well-established infrastructure to manufacture conventional solid, liquid, semisolid dosage forms, etc. However, nanomedicines manufacturing generally requires complicated and expensive approaches such as high-energy milling, high-pressure homogenization, lyophilization, etc. This demands in-depth process understanding, precise controls/checks, validated equipment/process train along with experienced staff to meet the critical quality attributes of the product such as size distribution, surface characteristics, charge, porosity and physicochemical stability [5,8].

Analytical characterization & quality control challenges

Lack of adequate characterization (in-process and quality control [QC]) methods and complexities involved in validating such methods poses a significant challenge to both the developers and regulators. The characterization of nanomedicines includes size, size distribution, morphology, surface charge, surface functionality, particle interactions/behavior, porosity, drug loading, solubility, pH, viscosity, toxicity and stability analyses [5]. Therefore, the characterization of nanomedicines involves advanced approaches such as dynamic light scattering, electron microscopy, and fluorescence spectroscopy, etc., whereas most of the industries are usually equipped with standard analytical equipment. Techniques to analyze nanomedicines are not only expensive, but, also require a team of experts to perform the analysis and data interpretation. This substantially adds to the cost of the nanomedicines manufacturing and testing. Another major challenge is to find an appropriate sterilization method without compromising physicochemical properties of the nanomedicines critical for their performance. The lack of reliable techniques to analyze nanomedicines stability *in vivo* and under GMP environment is another major hurdle in their successful clinical translation [10].

Pharmacological & safety challenges

Clinical translation of nanomedicine is suffering from the lack of acceptable and/or reliable screening plat-

forms that can evaluate the efficacy and toxicity with a good *in vivo* correlation [5,7]. This is particularly more relevant in case of preclinical screening techniques and models of a meaningful relevance to human clinical data. The subtle changes in nanomedicines physicochemical properties arising from small deviations in the manufacturing process may result into altered pharmacokinetics, *in vivo* clearance, drug release kinetics and toxicity/safety profiling. The extremely small size of nanomedicines can profoundly influence the drug Adsorption, Distribution, Metabolism and Excretion (ADME). *In vitro* and *in vivo* evaluations characterize the product interactions with the biological system, however, the data obtained from current toxicity tests in preclinical models are not always extrapolatable to human. *In vitro* characterizations including drug release, cellular uptake, toxicity and immunology are mostly carried out using cells culture in monolayers (2D). However, nanoformulations uptake into cells and tissues is influenced by interactions among its own physicochemical characteristics. Therefore, 3D cell systems may provide better outcomes [11,12].

At present, preclinical testing for small-molecule drugs is considered adequate to assess the *in vivo* efficacy, toxicity, and ADME of nanomedicines, if performed in at least two animal models with multiple doses over an extended period of treatment [5]. However, preclinical data, especially immunotoxicity, cannot accurately predict the safety of nanomedicines in human [5,8]. Another issue with nanomedicines is environmental safety during the manufacturing process. The handling of a nanosized powder demands special caution since such particles are capable of skin penetration (dermal exposure) and may also lead to pulmonary toxicities [8,13].

Regulatory challenges

The lack of specific regulatory guidelines for preclinical development and characterization of nanomedicine products at biophysiological level has hampered their potential in clinical practice [5,7]. Hurdles in regulatory pathways for nanomedicines translation are primarily due to the complexity of the product and the evaluation processes of the small-molecule drugs are frequently adapted [6]. Hence, there is a critical need to develop a comprehensive list of tests that cover the characterization, pharmacology, and toxicology of nanomedicines. Also, a fundamental question for nanomedicine translation is if the product meets the criteria of a scientifically acceptable definition of what can be considered a nanomedicine. Currently, when considering whether an FDA-regulated product involves the application of nanotechnology, the FDA parameters are: Whether a material or end product is

engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (~1–100 nm); and Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to 1000 nm [14]. Since the nanomedicine field is rapidly evolving and challenging, the FDA and EMA, along with other medical regulatory agencies suggest that the evaluation and approval of nanomedicine products are performed on a case-by-case basis. Therefore, the optimal approach used will be flexible, iterative, scientific, collaborative and product-focused to facilitate innovation [15].

Conclusion & opinion on nanomedicines' successful translation

The application of nanomedicines in healthcare is changing the current diagnosis and therapy concepts. Indeed, despite the significant impact of nanomedicines in healthcare, only a few products have reached the market. Thus, a better understanding of critical physicochemical characteristics as well as *in vivo* behavior of nanoformulations is needed. Implementation of a robust QC system and incorporating quality-by-design approaches can identify critical quality parameters to ensure batch-to-batch reproducibility, high-throughput optimization and the process/formulation variables for a better product profile [16]. Integration of development steps into one system may also bring exciting advances in the nanomedicines clinical translation and an opportunity for future research to significantly reduce the time and cost. Furthermore, advanced technologies should be developed to formulate new generation nanomedicines with desired physicochemical characteristics. This can be made through combinatorial approaches of microfluidics and other automation techniques as a screening tool to identify an optimal nanomedicine formulation [11,17,18].

Successful translation of nanomedicines implies upgrading of industrial infrastructures. This includes setting up equipped characterization lab, good manufacturing and pilot manufacturing/scale-up facilities according to regulatory standards. It is essential that nanomedicine manufacturing includes QC checks at every step to maintain the quality and efficacy of the batches [8]. Thus, sensitive and robust analytical techniques that are able to detect minute variations and adequately characterize the product should be established. Also, using multiple methods complementing each other to evaluate the same parameter is time saving. This necessitates the collaboration between R&D, QC and manufacturing subdivisions. It is also impor-

tant that the traditional lab-scale manufacturing process of a nanomedicine product is industrially viable. The environmental safety issue with nanomanufacturing can be solved by adopting the processing within an environment that has considerably lower safety concern such as an aqueous environment.

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The lack of adequate criteria and validated techniques to characterize nanomedicines toxicity is also a major concern [5,7–8]. Most toxicology assays are short-term, and it is therefore essential to evaluate whether these tests are predictive in providing long-term toxicity. Hence, an *in vitro* and *in vivo* characterization cascade of safety and efficacy testing is needed to accelerate the translation of nanomedicine [19,20]. Nanomedicines characterization is often performed under conditions that do not exactly reflect the real physiological and biological environments. Therefore, incorporating novel methods such as microfluidics are promising options for creating environments that mimic *in vivo* conditions [21]. Furthermore, selection of appropriate animal models is important [22] and the differences in sensitivity/specificity to the given nanoformulation should be considered.

The application of nanotechnology in medicine has led to significant progress in providing better health outcomes. According to Grand View Research, Inc., the global nanomedicine market is likely to reach \$344.0 billion by 2024. New innovations in healthcare are likely to bring more nanomedicine products to the market. Therefore, it is important to examine whether the methods and regulatory guidelines are able to adequately assess the delivery, fate, safety and efficacy of nanomedicines. Attracting investment for nanomedicine research is particularly challenging. It is therefore essential to demonstrate the social-/economic-added values such as cost-effectiveness of nanomedicine products compared with established treatments before commercialization. A significant commercial challenge also involves the physicians and patients acceptance of nanomedicine products. Approaches that could significantly enhance the nanomedicines translation may include:

- Use of science-based quality by design approaches in the formulation development, robust manufacturing, and scale up to ensure batch-to-batch

reproducibility and product quality at commercial scale;

- Profound knowledge of the key physicochemical attributes with the adequate characterization and control;
- Meaningful *in vitro* and *ex vivo* models relevant to the specific routes of administration and with *in vivo* relevance/significance;
- Understanding of the ADME and its relationship to product characteristics to predict the *in vivo* effects;
- Enhanced understanding of nanomedicines interactions with the biological system;
- Development of standardized and validated assays for analyzing stability, safety and efficacy;
- Continued research, strong collaboration and in-depth interactions with academia, industry and

regulatory organizations to further understand and develop nanomedicines regulatory and safety guidelines.

Overall, to bridge the gap of nanomedicines lab research to industrial manufacturing, collaboration and integration among academicians, scientists, industries, and regulatory agencies are required in a harmonized manner to develop comprehensive approaches to ensure safe, effective and translatable nanomedicine products.

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