LETTER TO THE EDITOR

Design, Translational, and Regulatory Barriers in Advancing Nanocrystal-Based Therapeutics

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Dear Editor,

Poor aqueous solubility is a critical issue that hinders the clinical integration of nearly 90% of the drug candidates in the discovery pipeline. Addressing that biopharmaceutical problem, nanocrystal-based drug formulations have emerged as a promising solution, particularly for BCS Class II and IV drugs, where oral absorption is compromised mainly due to inadequate solubility or permeability. Nanocrystals consist of crystalline particles of the pure drug, stabilized by minimal concentration of excipients and do not contain any carrier system[1,2]. By engineering these crystalline active ingredients into the nanometer range, dissolution velocity is significantly increased, resulting in better aqueous solubility, improved bioavailability and potential dose reduction[1-3]. However, several translational, design, and regulatory barriers continue to limit the seamless transition of nanocrystal therapeutics into clinical use[4].

The design of nanocrystal formulations poses multifaceted challenges because of their nanoscale physiochemical traits and sensitivity to both formulation and manufacturing parameters[3]. Firstly, the control of particle size in nanocrystal drugs is of considerable importance as minor variations can directly influence therapeutic efficacy of the product by altering dissolution rate, solubility, bioavailability, and cellular internalization. Another major challenge is aggregation which comes due to the greater surface area of nanocrystals, although it improves dissolution but simultaneously causes crystal growth, as high surface energy thermodynamically favors this phenomenon, compromising the desired advantages of nanocrystals[5]. Additionally, electrostatic stabilization and maintaining particle shape of nanocrystals is pivotal as the morphology and zeta potential affects biological activity. Stabilizers are used to control these parameters but currently their selection criteria is mainly empirical, rather than mechanistic insights which can lead to unpredictable toxicity or immunogenicity. Moreover, there is a definite lack of systematic QbD frameworks for nanocrystal-based product development. Opting Qbd and QRM driven design frameworks is necessary for a reproducible, high quality nanocrystal formulation[1,6].

The clinical success of nanocrystals is also restricted by many translational barriers, notably the incapability of current in vitro in vivo correlation (IVIVC) models to accurately predict the behavior of nanocrystals in complex physiological environment. Besides, the in vivo performance of nanocrystals differs greatly from the in vitro outcomes. Moreover, the phenomenon of Ostwald ripening during in vivo circulation of nanocrystals can highly increase the risk of embolism in fine capillaries, questioning their safety profile. In addition, the formation of a 'protein corona' as a result of interaction of nanocrystal drug particles with plasma proteins, may alter a nanoparticle's surface properties, mask the targeting ligands, and increase recognition and clearance by the immune system[2]. Furthermore, the field suffers from an over-reliance on animal models that lack clinical relevance, combined with a deficiency in long-term human safety data[6].

Lastly, regulatory barriers and insufficient pharmacovigilance studies complicate the global development of nanocrystals as drug delivery systems[1,7]. The lack of nanocrystal-specific guidelines brings about variability in classification and approval amongst defined regulatory bodies e.g. FDA and EMA[1]. Insufficiency of post marketing surveillance and reporting of nano specific adverse effects may result in compromised patient safety. Likewise, absence of

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validated analytical standards for characterisation compromises batch-to-batch consistency and large-scale production[6]. Focus on strengthening global harmonization, development of clear regulatory pathways, and establishing rigorous pharmacovigilance systems will ensure industry confidence[1,7].

All things considered, nanocrystals hold undeniable clinical potential to further enhance the prior mentioned gaps that must be addressed. Aligning the respective intent of academia, industry, and regulatory bodies, is an effective way to develop a future which is rational, safe, and effective in nano medicine[6,7].

FDA — Food and Drug Administration; EMA — European Medicines Agency; QbD — Quality by Design; QRM — Quality Risk Management; BCS — Biopharmaceutics Classification System

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