COMMENTARY

The Growing Field of Nanomedicine and Its Relevance to Pharmacy Curricula

Volkmar Weissig, PhD,[a] Tamer Elbayoumi, PhD,[a] Beat Flühmann, PhD,[b] Amy Barton, PharmD[b]

[a] Midwestern University, College of Pharmacy Glendale, Glendale, Arizona
[b] Vifor Pharma Group, Vifor Pharma Management Ltd, Glattbrugg, Switzerland

Submitted August 5, 2020; accepted February 10, 2021; published September 2021.

The field of nanomedicine is a rapidly growing scientific domain. Nanomedicine encompasses a diverse number of active pharmaceutical ingredients. Submissions of Investigational New Drugs and New Drug Applications have risen dramatically over the last decade. There are over 50 nanomedicines approved for use by the US Food and Drug Administration (FDA). Because of the fundamental role pharmacists will play in therapeutic and administrative decisions regarding nanomedicines, it is imperative for future pharmacists to gain exposure early in their training to this rapidly evolving class of drugs. This commentary describes nanomedicines, discusses current regulatory challenges, and provides recommendations for judicious incorporation of nanomedicine topics into the Doctor of Pharmacy curriculum based on emerging pharmaceutical and clinical science applications.

Keywords: nanomedicine, pharmaceutics, student pharmacist

INTRODUCTION

Significant advances in nanoscale material science during the last quarter of the 20th century have spurred the development of nanotechnology as an independent scientific discipline. Its merger with medicine and pharmacy around the turn of the century brought about the advent of nanomedicines. There are over 50 nanomedicines (referred to by the Food and Drug Administration [FDA] as drugs containing nanomaterials) on the US market.[1] In comparison to their small molecule parent drugs, nanomedicines display different and complex pharmacokinetic (PK) and pharmacodynamic profiles and thus have different safety and efficacy. In keeping with their broad recommendations for pharmacy curricula, the Center for the Advancement of Pharmaceutical Education (CAPE) Educational Outcomes suggest including the "evaluation of future advances in medicine" in the Doctor of Pharmacy (PharmD) curriculum. Thus, judicious incorporation of nanomedicine topics into the PharmD curricula appears warranted.

DISCUSSION

History and Definition of Nanomedicines (Nanopharmaceuticals)

The term *nanotechnology* was used for the very first time in 1974 by Norio Taniguchi.[2] Based on many more major discoveries and developments in nanoscale material science, the National Institutes of Health (NIH) launched the National Nanotechnology Initiative in 2000.[3,4] This federal program facilitated nanoscale-related interdisciplinary research, which quickly led to the well-funded merger between nanotechnology and medicine, giving rise to nanomedicine as a new scientific discipline. The NIH defines Nanotechnology as "The understanding and control of matter at dimensions between approximately 1 and 100 nanometers (nm), where unique phenomena enable novel applications."[3] Drug products containing nanomaterials may be developed as active ingredients or carriers loaded with active or inactive ingredients.[4,5] Emphasizing the unique nanoscale properties and expanding the size scale beyond 100 nm, the FDA also suggests that a drug product can be considered a nanomaterial if the material or end product is engineered to exhibit specific properties or phenomena and if these features are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range of up to one micrometer (1,000 nm).[5] In addition to the nanomedicines currently in clinical use, there are many nanomedicines that are in different phases of preclinical and clinical development.[6,7] These include products exhibiting a potential therapeutic effect based on their unique nanoscale physicochemical properties, such as *superparamagnetism* exhibited by iron oxide nanoparticles or improved bioavailability and disease specificity with lipid drug delivery carriers such as those that have been used for COVID-19 vaccines approved by the FDA.[8]

Corresponding Author: Volkmar Weissig, Midwestern University, College of Pharmacy Glendale, 19555 N. 59th Avenue, Glendale, AZ 85308. Email: vweiss@midwestern.edu

The growth of the field of nanomedicines is also exemplified by the rapid growth of indexed publications (Figure 1). Correspondingly, according to an analysis by the Center for Drug Evaluation and Research (CDER, USA), since 1970 there have been more than 600 investigational new drug (IND), new drug (NDA), and abbreviated new drug (ANDA) applications for human drug products containing nanomaterials, with half of these applications being submitted during the last decade.[4] The widespread clinical use of nanomedicines is also demonstrated by sales of liposomal doxorubicin, which is projected to be 1.4 billion by 2024.[9] A recent analysis of Medicare Part B expenditures from 2006-2017 showed the total spending for the nanomedicine Abraxane (protein-bound paclitaxel) was more than 100 times that of the standard small molecule formulation of paclitaxel.[10]

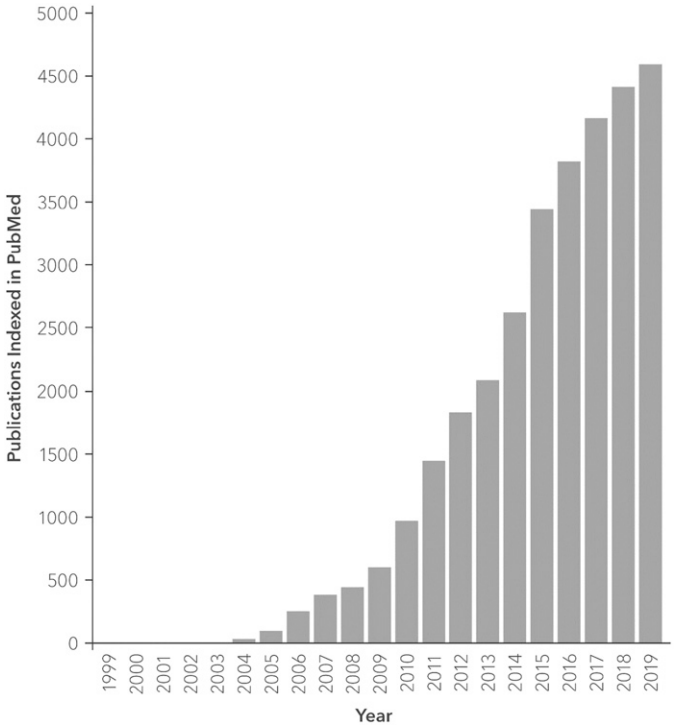

Figure 1. Growth of Indexed Publications on PubMed with the Search Terms "Nanomedicines or Nanopharmaceutics"

Types of Nanomedicines

The majority of nanomedicines in clinical use are based on liposomes. Liposomal encapsulated doxorubicin (Doxil) is considered to be the very first FDA-approved nanomedicine and was approved in 1995.[11] Liposomal doxorubicin has been shown to be a good alternative to paclitaxel when used in combination with carboplatin as a first line treatment for epithelial ovarian cancer and is associated with reduced risk of alopecia and neurotoxicity.[12] Other liposomal nanomedicines include AmBisome, Depocyt, Myocet and DepoDur. Liposomal Amphotericin B is recommended as a first-line therapy for invasive, restricted compartment infections such as mucormycosis because of its enhanced ability to penetrate target tissues while delaying relevant toxicities (eg, acute kidney injury).[13] Proteins, polypeptides, and aptamers, which have been covalently linked to a varying number of polyethylene glycol (PEG) chains, display very different PK and possess a totally altered bioavailability in comparison to their non-PEGylated parent molecules. Examples are Adagen, Eulasta, Oncaspar and Somavert. Nanocrystals constitute a unique group of nanomedicines as they are entirely composed of a water-insoluble drug substance and contain no other nanomaterials. Emend, Rapamune, and Tricor are examples. Polymer-based nanoformulations involve Copaxone, Eligard, Genexol, and Opaxio. Protein-drug conjugates use common proteins like albumin as nanodrug carriers as in Abraxane, which is paclitaxel linked to albumin nanoparticles. Another group of nanomedicines is based on metal nanoparticles. The first iron carbohydrate nanomedicine, Venofer, was approved in Switzerland in 1949, and later, Ferrlecit, Injectafer, and Feraheme were approved. All of these colloidal solutions are comprised of iron carbohydrate nanoparticles, and are approved for intravenous treatment of iron deficiency and iron deficiency anemia. A schematic overview of the major types of nanomedicines is shown in Figure 2. For a comprehensive discussion of their composition, please refer to previously published reviews.[7,8]

Nanomedicines belong to a class defined by the FDA as complex drugs products, which acknowledges that evaluation of nanomedicines poses unique challenges compared to evaluations of small molecule medicines.[5] Characterizing nanomedicines is inherently challenging because of their structural complexity and heterogeneity, which limits the utility of traditional analytic chemistry techniques in fully describing the physicochemical characteristics of nanomedicines.[14,15] For example, some experimental conditions (eg, dilution) can alter or degrade the intact nanoparticle structure.[14] Additionally, there are no standards for many new physicochemical characterization techniques; however, these efforts are ongoing.[14,15] Because nanomedicines are designed to target specific tissues and cell types, simple plasma PK profiles may not accurately predict the biodistribution profiles.[16] Additionally, there are few assays that can distinguish the free from encapsulated active drug.[17] All of these factors naturally extend from the approval of a new nanomedicine to the evaluation and approval process for generic and follow-on copies of a nanomedicine.[14,17] For instance, despite the originator and generic formulations having similar plasma

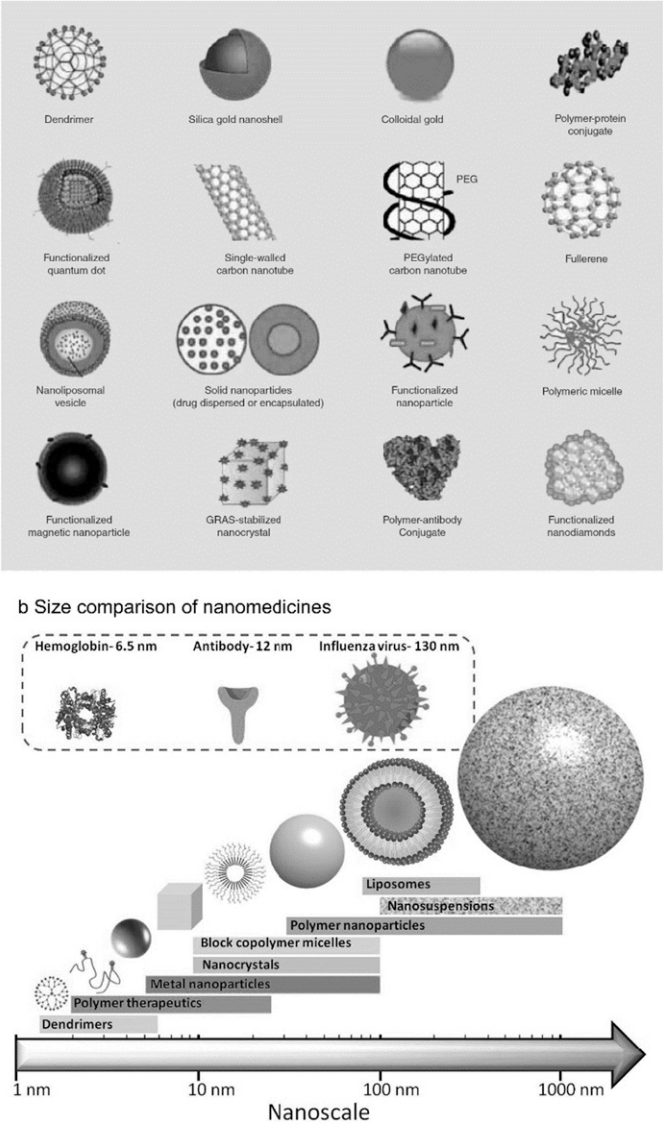

Figure 2. Schematic of Types of Nanomedicines and Size Comparisons of the Various Types of Nanomedicines[17]
Figure reproduced under the terms of the Creative Commons CC-BY license

PK profiles that met criteria for bioequivalence, a reduction in tumor activity was observed in a preclinical model with the generic liposomal doxorubicin compared to Doxil.[18] In a case control study in recurrent ovarian cancer only 4.3% of patients responded to the generic drug Lipidox vs 18% of patients receiving Doxil.[19] Because the proprietary process of manufacturing nanomedicines dictates product composition, it is nearly impossible to manufacture an exact copy of the reference listed drug.[14,17] However, despite these challenges, many product-specific guidance documents from the FDA do not propose bioequivalence evaluation methods that cover all of the challenges outlined in the nanomedicine guidance.[5] Therefore, it is critical for student pharmacists to learn about the gaps in regulatory science for current nanomedicines in their curriculum and bring these skills into their practice. Pharmacists also need to be aware of new scientific discoveries that affect the regulatory evaluation of nanomedicines. They will be the primary member of the interdisciplinary team that has adequate training in pharmaceutical science to synthesize data on known research gaps and new discoveries and apply these concepts to clinical therapeutic decision making and formulary management.

Nanomedicine in Pharmacy Education

Within the past few years, nanomedicine has become one of the driving forces of therapeutic and diagnostic developments within the medical field. Furthermore, the regulatory approval of nanomedicine drug products is projected to grow exponentially over the next two decades.[6] There is also an upward trajectory to clinically utilize nanodiagnostics and nanotherapeutics to profoundly enhance the bench-to-bedside approach to patient care.[7,20] Therefore, it has become imperative for both current and future pharmacists to be adequately familiarized and equipped with essential knowledge of nanotechnology, particularly nanotechnology that has medical applications, to face the developing demands and challenges in their professional practice. Fundamentally, part of the current educational reform within professional pharmacy programs is to integrate foundational science and clinical science education. Thus, these efforts need to effectively incorporate education and training in emerging technological and scientific medical advances, namely nanomedicines and nanodiagnostics, because of their increasing impact on health care. This will not only better prepare pharmacy professionals for clinical practice, but also expand their career opportunities.[20] The 2016 Standards from ACPE, as well as their underlying 2013 CAPE Supplemental Educational Outcomes, underpin foundational science knowledge as an essential framework for understanding clinical knowledge. Hence, in view of CAPE Domain 1 learning objectives, the constructive integration of nanomedicine topics and concepts into foundational pharmaceutical sciences is needed. This is in order for the pharmacy "learner" to evaluate future advances in medicine, explain how specific drugs or drug classes work, and evaluate their potential value in treating diseases in individuals and populations. Additional pharmacy education data also indicated that pharmacy learners seem to still perceive the safety of nanomedicine with caution, despite having positive attitudes and perceptions regarding the use of nanotechnologies.[20-23] For this reason, the authors suggest including course material on nanomedicine in the PharmD curriculum.[10]

The integration of nanotechnology content into the PharmD curriculum can be explored at both the curricular and cocurricular levels to provide multiple opportunities for students to gradually construct integrated basic and clinical science knowledge. Key concepts of nano-size surface effects and quantum mechanical effects should be introduced early within pharmaceutics topics, emphasizing the behavior of material at the nanoscale and how it correlates with the physicochemical properties of final nano-pharmaceutical formulation.[7] The application of these nanotechnology concepts in pharmaceutical dosage courses is also facilitated through many dedicated textbook chapters, in their recently published editions.[24,25] Within the biopharmaceutics and pharmacokinetics curriculum, nano-scale drug properties can be compared with conventional ones in terms of routes of drug administration, localized and systemic tissue absorption/permeability, biodistribution, and pharmacokinetics profiles. With nanomedicines constituting almost 10% of oncology drugs today, the enhanced tumor delivery of nanomedicines can be presented in relevant pharmacology and pharmacotherapy content via commercial nanomedicines, such as Doxil for passive targeting of Kaposi sarcoma and Abraxane as a safer alternative to conventional paclitaxel in ovarian and breast carcinoma protocols. Clinical knowledge framework activities should also conceptualize foundational nanomedicine content and illustrate clinical relevance via learning objectives and clinical case examples. Elective courses and joint (eg, industrial-clinical) advanced pharmacy practice experiences for interested students, focused on the design and clinical applications of nanotechnology-based medical products, can integrate, and apply knowledge from both pharmaceutical and clinical foundational sciences to evaluate the scientific literature, explain drug action, solve therapeutic problems, and advance population health and patient-centered care.[20-23] A variety of co-curricular activities can also be employed to further integrate basic science nanomedicine concepts with clinical decision-making. These may include early non-patient care related to interprofessional education/collaboration/innovation (eg, research activities, independent study), medical technology focused seminar series, or meetings. Additionally, professional service organizations related to nano-pharmaceutical career training and postgraduate education, such as Industry Pharmacists Organization (IPhO) student chapters and Pharmaceutical Industry Fellowship programs, offer venues where interested student pharmacists work in teams on clinical cases that integrate the complex pharmacokinetic and pharmacodynamic principles associated with nanopharmaceuticals.[21,23] In view of the imminent impact of nanomedicines on the medical field, basic and applied nanomedicine education needs to be proactively integrated within PharmD programs, which can potentially occur at multiple levels within ACPE-structured curricular and cocurricular activities.[21,23]

SUMMARY

The nanomedicine domain is expanding rapidly. Because of the complexity of this class of drugs, pharmacists represent the discipline with the best aptitude to integrate pharmaceutical science, regulatory evaluation, and clinical data to lead decision making regarding the use of nanomedicines for patient care. Given the application of nanomedicines to a wide and diverse array of disease states, pharmacy educators should be forward thinking in their approach to including and expanding the coverage of nanomedicines in the pharmacy curriculum. Given the density of material already covered in the PharmD program, innovative techniques, such as cocurricular electives, student organization initiatives, and certificate programs, could effectively provide didactic education in key nanomedicine concepts.

REFERENCES

1. Ventola CL. Progress in nanomedicine: approved and investigational nanodrugs. *P T*. 2017;42(12):742-755.
2. Taniguchi N. On the Basic Concept of Nanotechnology. *Proc Int Conf Prod Engin.* Vol Part 1974:18-23.
3. Nano 101: Nanotechnology, what it is and how it works. *The United States National Nanotechnology Initiative*. www.nano.gov/nanotech-101/what. Accessed July 1, 2020.
4. Nanotechnology–Over a Decade of Progress and Innovation: A Report by the U.S. Food and Drug Administration. *U.S. Department of Health and Human Services*. July 2020. www.fda.gov/media/140395/download. Accessed October 23, 2020.
5. Drug Products, Including Biological Products, That Contain Nanomaterials - Draft Guidance for Industry issued by: Center for Drug Evaluation and Research, *U.S. Food and Drug Administration*, Docket Number: FDA-2017-D-0759. In: Federal Register NA, ed. Vol 82. Rockville, MD: Office of the Federal Register; 2017:60019.
6. Weissig V, Guzman-Villanueva D. Nanopharmaceuticals (part 2): products in the pipeline. *Int J Nanomedicine*. 2015;10:1245-1257.
7. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov.* December 4, 2020.
8. Nanomedicine and the COVID-19 vaccines. *Nat Nanotechnol*. 2020;15(12):963.
9. Liposomal Doxorubicin Market Size, Share, Industry Report, 2013-2024. *Grand View Research Inc.* https://www.grandviewresearch.com/industry-analysis/liposomal-doxorubicin-market. Accessed January 4, 2021.
10. El-Kilani Z FK, Mulcahy A, and Bosworth, A. Medicare FFSPart B and International Drug Prices: A Comparison of the Top 50 Drugs. Washington, DC: Office of the Assistant Secretary for Planning and Evaluation, *U.S. Department of Health and Human Services*; 2020:1-29.

11. Barenholz Y. Doxil(R)–the first FDA-approved nano-drug: lessons learned. *J Control Release.* 2012;160(2):117-134.
12. Lawrie TA, Rabbie R, Thoma C, Morrison J. Pegylated liposomal doxorubicin for first-line treatment of epithelial ovarian cancer. *Cochrane Database Syst Rev.* October 21, 2013(10): CD010482.
13. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis*. 2019;19(12):e405-e21.
14. Nikravesh N, Borchard G, Hofmann H, Philipp E, Fluhmann B, Wick P. Factors influencing safety and efficacy of intravenous iron-carbohydrate nanomedicines: from production to clinical practice. *Nanomedicine.* 2020;26:102178.
15. Tyner KM, Zheng N, Choi S, et al. How has CDER prepared for the nano revolution? A review of risk assessment, regulatory research, and guidance activities. *AAPS J.* 2017;19(4):1071-83.
16. Pai AB. Evaluating plasma pharmacokinetics of intravenous iron formulations: judging books by their covers? *Clin Pharmacokinet*. 2015;54(4):323-324.
17. Muhlebach S. Regulatory challenges of nanomedicines and their follow-on versions: a generic or similar approach? *Adv Drug Deliv Rev.* 2018;131:122-131.
18. Smith JA, Mathew L, Burney M, Nyshadham P, Coleman RL. Equivalency challenge: evaluation of Lipodox(R) as the generic equivalent for Doxil(R) in a human ovarian cancer orthotropic mouse model. *Gynecol Oncol*. 2016;141(2):357-363.
19. Smith JA, Costales AB, Jaffari M, et al. Is it equivalent? Evaluation of the clinical activity of single agent Lipodox(R) compared to single agent Doxil(R) in ovarian cancer treatment. *J Oncol Pharm Pract.* 2016;22(4):599-604.
20. Al-Nemrawi NK, AbuAlSamen MM, Alzoubi KH. Awareness about nanotechnology and its applications in drug industry among pharmacy students. *Curr Pharm Teach Learn*. 2020;12(3):274-280.
21. Piascik P. CAPE outcomes 2013: building on two decades of advances to guide the future of pharmacy education. *Am J Pharm Educ.* 2013;77(8):160.
22. Greene JM, Fuller KA, Persky AM. Practical tips for integrating clinical relevance into foundational science courses. *Am J Pharm Educ*. 2018;82(5):6603.
23. Maerten-Rivera JL, Chen AMH, Augustine J, et al. Co-curriculum implementation and assessment in accredited doctor of pharmacy programs. *Am J Pharm Educ*. 2020;84(3):7569.
24. Sinko PJ. Drug delivery systems and drug product design. In: Sinko PJ, ed. *Martin's Physical Pharmacy and Pharmaceutical Sciences.* 7 ed. Philadelphia: Lippincott Williams & Wilkins; 2016: 642-692.
25. Allen LV. Novel dosage forms and drug delivery technologies. In: Allen LV, ed. *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems.* 11 ed. Philadelphia: Wolters Kluwer; 2017: 550-568.