Meeting Report

Theme: Nanotechnology in Drug Development
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Nanomedicine Drug Development: A Scientific Symposium Entitled “Charting a Roadmap to Commercialization”

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Abstract The use of nanotechnology in medicine holds great promise for revolutionizing a variety of therapies. The past decade witnessed dramatic advancements in scientific research in nanomedicines, although significant challenges still exist in nanomedicine design, characterization, development, and manufacturing. In March 2013, a two-day symposium “Nanomedicines: Charting a Roadmap to Commercialization,” sponsored and organized by the Nanomedicines Alliance, was held to facilitate better understanding of the current science and investigative approaches and to identify and discuss challenges and knowledge gaps in nanomedicine development programs. The symposium provided a forum for constructive dialogue among key stakeholders in five distinct areas: nanomedicine design, preclinical pharmacology, toxicology, CMC (chemistry, manufacturing, and control), and clinical development. In this meeting synopsis, we highlight key points from plenary presentations and focus on discussions and recommendations from breakout sessions of the symposium.

INTRODUCTION

The inaugural Nanomedicines Alliance Symposium, *Nanomedicines: Charting a Roadmap to Commercialization* was held on March 6–7, 2013 in Rockville, MD. Through plenary presentations, breakout discussions, and poster sessions, about 70 attendees representing government (e.g., FDA, NIH, EPA, etc.), academia, and the pharmaceutical industry shared recent experiences, discussed challenges, and debated best practices in five distinct sessions: design, preclinical pharmacology, toxicology, CMC (chemistry, manufacturing, and control), and clinical development of nanomedicine products. Key scientists from these disciplines presented their work during the platform portion of each session. The presentations were followed by interactive breakout discussions for each session. In each breakout, authors of this paper facilitated a discussion focused on a set

of questions prepared in advance (see Table I), along with follow-up discussion from the talks. This paper briefly highlights the content from the platform presentations and cites references where more information on the presentation topics is available. The main focus of this paper is on key discussion points and recommendations arising from the breakout discussions following the platform sessions. The symposium provided a platform for drug developers and other stakeholders to have constructive dialogue which will facilitate the design, development, and regulatory approval of nanotechnology-based drug products.

KEYNOTE SPEECH “NANOPARTICLE THERAPEUTICS: FROM CONCEPT FOR CLINIC”

In his keynote presentation, Dr. Mark Davis from California Institute of Technology provided a historical overview of the development of nanoparticle therapeutics. Nanotechnology came to the forefront in the USA in 2001 after the federal government announced funding for the National Nanotechnology Initiative in 2000. The past decade witnessed dramatic advancements in scientific research in this area. “Nanomedicine” has evolved from a concept to a well-structured approach to designing drugs with many different desirable properties. A number of nanoparticle-based medicinal products have reached clinical development or are about to reach this status. The availability of innovative instrumentation and methods for nanoparticle characterization, along with an increased knowledge on how colloidal particles and

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Table I. Questions Provided to Breakout Session Participants

Session I: designing nanomedicines: principles, premises, myths, and facts	<p>Passive vs. active targeting: how important is active targeting? How effective is “passive targeting (e.g. enhanced permeability and retention effect)”?</p> <p>Immunoavoidance vs. immunorecognition: when is immunorecognition beneficial? How important is immunoavoidance?</p> <p>Biodegradability vs. non-biodegradability: is biodegradability an absolute must? Where do non-biodegradable materials find uses?</p> <p>What are some of the strategies to implement factors discussed above?</p>
Session II: preclinical pharmacology	<p>What are the implications of the MPS system on nanoparticle clearance <i>in vivo</i>?</p> <p>Is the EPR effect real and how do <i>in vivo</i> results translate to human clinical data?</p> <p>What are some of the preclinical study pitfalls that are unique to testing nanomedicines?</p>
Session III: chemistry, manufacturing, and control	<p>What are the biggest challenges yet to be met regarding the characterization and manufacture of nanomedicines?</p> <p>What advancement(s) are imminent that will revolutionize the characterization and manufacture of nanomedicines?</p> <p>How do you plan to assure comparability of nanomaterials (e.g., those used in toxicology vs. clinical testing)?</p> <p>How will Quality by Design be executed for nanomedicines?</p>
Session IV: toxicology/ADME	<p>What are the unique ADME/toxicity challenges posed by nanomedicine drug development, as compared to more conventional drug candidates?</p> <p>What research approaches are needed to address these challenges?</p> <p>What are the differences in data requirements to enable first-in-human evaluation, as compared to product registration?</p>
Session V: clinical studies	<p>Are there opportunities to better leverage available clinical data from published results including non-industry sponsored trial data related to the efficacy of approved active pharmaceutical ingredients to support regulatory submission for nanopharmaceuticals with the FDA and other international agencies?</p> <p>What novel clinical trial designs may be appropriate to support the efficacy evaluation of nanopharmaceuticals with known approved active pharmaceutical ingredients that can accelerate identification of efficacy signals in phase 2 and/or registration trials?</p> <p>Are there challenges and opportunities to assessing safety and risk-benefit evaluation unique to nanopharmaceuticals for phase 0 or phase 1 clinical trials?</p>

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biological systems interact, has accelerated and will likely continue to accelerate the progress in this field (1–3).

Dr. Davis also presented a few examples of nanoparticle therapeutics which, due to nanoparticle properties such as specific targeting to tissues (e.g., tumors) and active intracellular delivery, show enhanced efficacy while dramatically reducing side effects. Dr. Davis highlighted a few important issues for the development and regulatory approval of nanoparticle therapeutics, including, among others, a better understanding of the vasculature structure associated with human tumors, acceptable variation in nanoparticle properties for commercial products, and interspecies scaling to enable preclinical to clinical translation. Continued advancement in these important areas will be critical to the future success of nanotechnology-based drug products.

SESSION I: DESIGNING NANOMEDICINES: PRINCIPLES, PREMISES, MYTHS, AND FACTS

Advances in the field of nanoparticle-mediated drug delivery promise to enable tailoring of a drug's absorption, distribution, metabolism, and excretion (ADME) properties, as well as the specific locations where a drug is delivered—at specific tissue, cell or subcellular systems, directly onto a pathogen, such as a bacterium, a virus particle, or even beta-

amyloid plaque or other debris. Such control also enables using as drugs hitherto extremely difficult molecules such as hydrophobic small chemicals, proteins, enzymes, catalytic antibodies, immunoconjugates, antibodies, mi-si-RNA, dsRNA, ssDNA, dsDNA, and their modifications. Such precise control could also revolutionize vaccines as they exist today. Designing nanomedicines will require significant collaborative efforts that span fields from biology to chemistry to physics to engineering.

This session focused on active targeting, biodegradability, immune-avoidance vs. immune-recognition, and the enhanced permeability and retention (EPR) effect for nanomedicines. Philip Low, Purdue University, demonstrated that active targeting of drugs by nanotechnology increases drug delivery (4,5). Anil Diwan, NanoViricides, showed that active targeting of viruses using biomimetic virus-binding ligands produced effective drug candidates. Edith Mathiowitz, Brown University, presented advantages bioadhesive nano-encapsulation offers as a delivery system, particularly for complex drugs such as proteins and genes (6). Justin Hanes, Johns Hopkins University, described how mucus-penetrating particles can deliver drugs to specific sites in the body, such as lungs and the brain (7). Lastly, Uma Prabhakar, Office of Cancer Nanotechnology Research, NCI-NIH, introduced the TONIC (Translation of Nanotechnology in Cancer) initiative, a public/private consortium to accelerate the development of

nanotechnology for cancer by accelerating the translation from academic research to the clinic (8).

During the breakout session, participants discussed the following major topics:

1. Benefits of active targeting of drugs

Active targeting of drugs to specific cells and tissues by nanotechnology can result in increased drug accumulation and efficacy. Depending on the design, active targeting can result in minimal or dramatic improvement in drug efficacy. The advantage of active targeting is dependent on where the drug is intended to be released and the specific cargo. For example, active targeting may offer significant advantages when a cargo which cannot diffuse efficiently across cell membranes needs to be delivered into cells. The benefit of active targeting also depends on whether the receptor is (a) substantially and (b) differentially expressed on the targeted cells. "Substantially" can be viewed in terms of the proportion of target cell surface covered by the receptor, whereas "differentially" refers to the ratio by which the receptor expression on target cells exceeds the receptor expression on nontarget cells. Some drugs, such as the ones designed for direct neutralization of a virus particle or a cell surface receptor (e.g., hERG), inherently require active targeting. It was raised that some event-driven drug release, such as pH-dependent, or enzyme-dependent (e.g., protease, oxidase, etc.) drug release, can be regarded as another class of active targeting.

Several small companies raised a practical concern that for them, designing "active targeting" nanomedicines might be too risky due to the added level of complexity associated with this approach, especially since the therapeutic efficacy of "active targeting" nanomedicine may only be slightly (e.g., twofold) higher than passive targeting. This clearly demonstrates a need for further elucidation of parameters that need to be optimized for successful active targeting.

2. Immune-avoidance *versus* immune-targeting

Specific targeting of immune system cells by cell type is feasible and can be advantageous. For example, some tumor-associated macrophages secrete factors to promote the growth of the tumor. Targeting delivery of drugs to these macrophages, and thereby killing them, may be an effective way to stop tumor growth. Macrophages can take up large nanoparticles and can become vectors that distribute the drug payload into the organs to which they circulate. This may be a way to cross the blood-brain barrier. However, for drugs that do not require immune-mediated mechanism, immune-avoidance is generally a good strategy.

3. PEGylation

PEGylation (therapeutic molecules covalently bound to polyethylene glycol [PEG]) of drugs and therapeutic proteins is a technology widely used to avoid immune-recognition, prolong circulatory time, and provide water solubility to hydrophobic drugs and therapeutic proteins.

However, vacuolation induced by relatively high doses of proteins bound to PEG may present toxicological concerns (9), and immunogenicity of PEG-containing

therapeutics may also present concerns. In general, polymers and nanoparticles can lead to vacuolation. Due to the wide use of PEG in the food and pharmaceutical industry, an increasing number of patients appear to have detectable level of anti-PEG antibodies before they enter a clinical trial for PEGylated products, although it should be noted that in a separate section of this symposium, it was discussed that all of the so called anti-PEG antibodies studied by the Nanotechnology Characterization Laboratory of NCI have been against the methoxy- or ethoxy- terminal group of the chain and not against the PEG backbone.

The utility of PEGylation technology in the future was discussed. There is considerable scientific and commercial interest in developing alternatives to PEGylation that would confer acceptable avoidance and half-life extension properties of nanomedicine constructs.

4. Other design issues

Size, shape, and charge of a nanoparticle are all critical parameters affecting its mobility in tissues. Some guidelines for optimizing these parameters can be found in the literature (for example, see reference 10). However, many additional parameters need to be accounted for during nanoparticle design and optimization to achieve desired drug distribution and pharmacokinetics.

Other interesting questions discussed include the importance of mechanical flexibility of nanoparticle materials and heterogeneity of nanoparticles. Polymeric micelles are inherently flexible and have shown advantages in nanomedicine drug development. Heterogeneity of nanomaterials may enable modulation of the drug release profile, as the smaller particles release the drug first and the larger particles continue to release until much later; however, batch to batch consistency of the product must be considered to ensure its safety and efficacy.

The nanomedicine approach is well established in cancer and is making headway in viral diseases. However, there are many disease areas where this approach may have benefits, such as tau and amyloid pathologies including Alzheimer's disease, synucleinopathies including Parkinson's disease, diabetes, and many other diseases. Each disease and pathology will require further innovations in nanomedicine design.

SESSION II: PRECLINICAL PHARMACOLOGY

There are more than 300 nanoparticle formulations of anticancer agents in development. The transition of these agents from the preclinical stage to safe and effective human medicines requires appropriate tools and model systems that can evaluate nanoparticle therapeutic agents in sensitive and specific ways.

In this session, William Zamboni from the University of North Carolina at Chapel Hill presented data indicating the bidirectional interaction between PEGylated liposomal anticancer agents and the mononuclear phagocyte system (MPS). This bidirectional interaction clearly plays a key role in the release and clearance of anticancer agents encapsulated in the

nanoparticle. Thus, the MPS has important influences on the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of nanoparticle therapeutic agents (10,11).

Kevin Chu from Joseph DeSimone's lab at the University of North Carolina at Chapel Hill introduced the particle replication in non-wetting templates (PRINT) technology as a novel platform to fabricate uniform, size-, and shape-specific particles with precise control over their spatiochemical composition to evaluate the relationship between single formulation variables and particle biodistribution. Studies demonstrated that decreased particle diameter decreased accumulation into liver and spleen, which led to improved tumor accumulation (12). Additionally, increased PEG density improved blood circulation half-life and potentially boosted particle tumor accumulation, leading to enhanced efficacy (13).

During the breakout session, participants discussed the following key topics:

1. Mononuclear phagocyte system

The mechanisms of nanoparticle clearance and the ultimate fate of the "payload" in macrophages remain unclear with some studies showing that particles remain in macrophages for their lifetime. It is important to note that different cancers have different effects on MPS activities. Clearance of drugs is different when comparing breast, ovarian, male prostate, and male lung cancers.

2. Enhanced permeability and retention effect

A better understanding of the mechanisms of the EPR effect that is characteristic of nanoparticles in tumors is essential. EPR effects are based on the assumption that tumors possess abnormal vascularization. However, there is a range of vascularization phenotypes displayed in tumors, e.g., compromised vascularization with no active blood supply; uniform, "normal" vascularization; and vascularization at the periphery of the tumor but not in the core. It is not known if and how the EPR effect occurs in all of these situations nor is the role that the lymphatic system plays in the EPR effect known. Understanding the mechanisms of the EPR effect is critical to understanding efficacy in animal and human tumors.

3. Other hurdles for preclinical pharmacology studies

Participants discussed other hurdles for studying preclinical PD/efficacy of nanomedicines. Establishing predictive animal models remains a key challenge. It is also critical to understand the specific indication, target tissue, and payload as well as the route of administration in order to design the nanoparticle and adjust its physicochemical properties as needed. Uniform particle shape, hydrodynamic properties, and rapid transport through the extracellular matrix are all important.

4. A specific case

In phase I dose escalation studies for small molecules, the number of dose levels is typically 3–5, whereas for nanomedicines it can be as high as 14. This is because in phase I human trials, the starting dose may be based on dog toxicology study results, and dogs may be hypersensitive to nanoparticle therapeutic agents (14). As a result, the typical starting doses in humans show no effect which leads to a large number of doses

in an ascending dose study. Participants recommended that the industry should compile and organize this information and share it with the FDA in order for the industry to better design phase I studies of nanoparticle therapeutic agents. This could result in phase I studies that have a similar number of dose levels as those of typical small molecules.

SESSION III: CHEMISTRY, MANUFACTURING, AND CONTROL

Chemistry, manufacturing, and control (CMC) requirements are an integral part of any drug's approval process. For nanomedicines, unique challenges exist due to the nature of nanoscaled materials, the wide diversity of nanomaterial platforms, and the currently limited experience with both formulation development and scale up of nanomedicine manufacturing. The CMC session started with an overview of analytical tools by Jennifer Grossman from the Nanotechnology Characterization Laboratory. Participants learned about innovative analytical techniques that have been developed for the physicochemical characterization of components and finished formulations. The advantages, limitations, and application of various techniques were described including precautionary points for avoiding common pitfalls (15). This talk was followed by presentations describing considerations for product development and manufacturing steps for nanomedicines by Jeff Hrkach of BIND Therapeutics and Marc Wolfgang of Cerulean Pharma. Unique manufacturing and scale up challenges were discussed, covering polymer considerations, drug entrapment, and chemical conjugation (both drug and targeting ligands). Insights on third party manufacture and cost of goods were also presented.

During the breakout session, major topics of discussion included the following:

1. The importance of applying *in vitro* product performance testing

The need to consider product-specific attributes was a common theme throughout all the discussions. Nanomedicines are quite diverse, and each product will have unique attributes that must be taken into consideration when designing testing protocols for product characterization, quality evaluation, and change control. In particular, robust performance-based *in vitro* tests could play key roles in demonstrating product comparability and consistency over the product life cycle and supporting CMC aspects of regulatory filings such as manufacturing site changes.

2. Particle size testing

Particle size measurements deserve particular attention when developing a control strategy for a nanomedicine product. It was recognized that analytical technique and specific instrumentation can significantly influence particle size and distribution results and that care must be taken in defining the methods used to characterize and control particle size for nanomedicine products.

3. Application of quality by design

Due to the complex nature of nanomedicines and their manufacture, quality by design was generally viewed as an area of opportunity for the CMC

development of nanopharmaceuticals. In particular, the concepts of design space and in process controls were discussed and it was mentioned that these elements were being utilized by some of the participants in early process development.

4. CMC investment during drug development

The attendees also reflected on the resources and investments required to sustain a successful nanomedicine development program. During early development when clinical success is uncertain, CMC investment is relatively modest with the primary focus on supplying cGMP clinical supplies. However, once clinical readouts appear promising, there is often a knowledge gap that needs to be filled quickly to meet aggressive registration strategies. CMC leadership must be able to articulate choices and consequences to corporate decision makers, especially in small, cash-strapped biotechnology organizations.

SESSION IV: TOXICOLOGY/ADME

Nonclinical studies to evaluate the toxicological properties and ADME patterns of nanomedicines are required to support safe clinical development and product registration. While the basic principles of these studies apply equally to nanomedicines and more traditional investigative drugs, special issues may exist with nanomedicines. Depending on the specific nanomedicine, these may include challenges of tracking *in vivo* ADME properties and interactions with the immune and/or hematological systems.

This session covered current experiences and case studies in nanomedicine toxicology/ADME, with a focus on the immune and hematologic systems, stability and deposition, and comparison of *in vitro* and *in vivo* outcomes. Stephan Stern from the Nanotechnology Characterization Laboratory (NCL) provided a comprehensive presentation on a number of observations and case studies investigated at the NCL (15). He addressed how the physicochemical characteristics of nanoparticles, such as size, hydrophobicity, and charge affect *in vivo* behavior. Marina Dobrovolskaia from the NCL presented experiences and case studies related to nanoparticles and immunotoxicity and discussed other potential areas for nanoparticle toxicity such as hemolysis, thrombogenicity, complement activation, effects related to protein corona, and antigenicity (16). Michael Mirsky from Pfizer presented a case study on the preclinical safety evaluation of hydrophobically modified dextran nanoparticles for delivery of insoluble therapeutics, covering the correlation between *in vitro* and *in vivo* safety findings and some of the challenges and learnings from the research (17).

The breakout session covered many of these topics in more detail:

1. Regulatory considerations

The current status of understanding of these issues was discussed. Regulatory authorities view nanomedicines on a case-by-case basis and are continuing to gather safety data. Similarly, research organizations such as the NCL are assembling a “critical mass” of learnings based on their many collaborations that may help guide nanomedicine development and potential ADME/

safety issues that nanomedicine sponsors should be aware of. This increased level of understanding may at some future point lead to useful points to consider or guidance documents. Any potential mechanisms by which the nonclinical ADME/safety data sharing could occur would help facilitate and inform research and development. This would be useful, for example, in further understanding of the data suggesting a heightened sensitivity of dogs to nanomaterial toxicity as discussed in session 2. Another point of discussion centered on when nanomedicine drug developers should engage regulatory authorities before entry into clinical development and the amount and type of data that should be available for those meetings.

2. Study design/interpretation issues

The potential value of having two control groups in toxicity studies was discussed, as was the potentially longer timelines for nonclinical development (compared to “conventional” therapeutics) due to a need for additional studies addressing the heterogeneous nature of many nanomedicines. Quality attributes are very important to understand during development, and the need for toxicology and CMC collaboration was underscored. Issues such as endotoxin contamination that might interfere with detecting nanomedicine-induced toxicity, the role of nanomedicine size in safety evaluation, and the influence of changes in quality attributes (as they relate to available ADME and safety information) were highlighted.

3. *In vivo* behavior of nanomedicines

Other topics focused on the *in vivo* ADME behavior of nanomedicines. Release of a drug payload is incompletely understood; for example, the specific properties that optimize a nanomedicine construct for delivery to the desired anatomic compartment and how drug release kinetics may impact safety. It was further noted that some fraction of a nanomedicine (or components thereof) might circulate in macrophages. There is a need for better understanding of interactions of nanomedicines and coagulation factors; specific factors may be preferentially involved, the entire cascade may be involved, or in some cases, complement activation may be dose-limiting. Also, the physiological state of the target anatomic compartment needs to be understood in relation to nanomedicine delivery; for example, the potential influence of hypoxic regions within tumors is uncertain.

The utility and limitations of modeling were discussed. The NCL experience of compartmental and noncompartmental modeling was discussed, as was the potential utility of other approaches such as population-based PK modeling. Incomplete understanding of ADME-specific mechanisms limits the utility of modeling, for example, the role of macrophages impacting stable liposomes. Overall, it is difficult to model and predict efficacious doses early in development and more work in this area is needed.

SESSION V: CLINICAL STUDIES

Whether nanomedicines are based on reformulation of previously approved molecular entities as API, or vehicle/

carrier enhanced new chemical entities (NCEs), or hybrid NCEs, designing clinical trials has to take into consideration traditional drug development factors as well as constraints unique to nanomedicines.

Due to the substantial investment in and competition for patients in clinical trials, the FDA and the industry have recognized the importance of innovation in study design to improve the efficiency and effectiveness of clinical trials. In this session, Edward Garmey from Cerulean Pharma discussed a type of trial, termed phase 0 studies (18), which are conducted at about 1/100th of the dose expected to produce pharmacologic effect in a small number of patients (e.g., fewer than 10) over a short period of time (e.g., less than 7 days). The purpose is to establish baseline pharmacokinetic profile, bioavailability, and other pharmacologic or metabolic endpoints when animal model studies are inconsistent or may not be predictive of the human experience. Phase 0 studies could be helpful in determining the best options for nanomedicine development programs, such as to help select the optimal linkers, vehicles, or carriers.

Dirk Reitsma and Austin Combest of PPD and Neil Desai of Celgene presented an overview of clinical trial designs used for nanoscaled reformulations of well-studied products (19). They highlighted the benefits of adaptive trial design, especially when the active agent has a known efficacy and safety profile. Adaptive designs can provide robust answers to study questions and in the meantime reduce the total number of patients required, resulting in potentially reduced costs and shorter timelines than traditional trials. The session concluded with Iulian Bohe from NanoCarrier sharing his company's experience in clinical development program for nanomedicines (20).

The breakout session primarily focused on the following topics:

1. The appropriateness of phase 1 trial starting dose selection based on current preclinical models
The same case example in which a very low starting dose was selected based on studies on dogs—a very sensitive species—for phase 1 trials (see session II) was discussed. Participants agreed that this could have significantly increased cost and time for those trials and may bear an ethical concern because more patients are exposed to low non-efficacious doses of drugs.
2. Phase 0 studies
The group discussed whether phase 0 studies are an appropriate tool to acquire data to speed up early decision-making for a nanomedicine drug development program. Human PK data generated from phase 0 studies could facilitate decision-making about nanoparticle design, such as which linker to use. Participants also debated whether using phase 0 studies in place of or in addition to the preclinical models to establish pharmacokinetic profile would enable a higher starting dose in phase 1. Participants agreed that phase 0 trials may be beneficial for certain drugs, but not for all drug programs.
3. A need for early engagement of regulatory authorities
It is important for sponsors to start thinking about clinical trial design and consulting regulatory authorities early, as regulatory requirements for clinical trials for any drug, especially for a nanomedicine, could be

complicated. The group also suggested that more regulatory consideration of alternative strategies for preclinical and clinical studies would be needed. For example, fewer preclinical studies could be sufficient for nanomedicines that incorporate approved active agents, and there is a need to consider alternative preclinical models for the establishment of phase 1 trial starting doses. In addition, due to differences in regulations from different countries, additional or different early phase and late phase studies for nanomedicines may be required.

4. Biomarkers

Participants also discussed the role of biomarkers and their integration into study design and clinical endpoint evaluation. Biomarkers could play an important role, but face a challenge because of a scarcity of accepted validated biomarkers. In addition, product-specific and mechanism-specific biomarkers may need to be used to evaluate different nanomedicines.

In conclusion, it is difficult to generalize clinical trial designs, biomarkers, or animal model recommendations for nanomedicines. Assessment on a case-by-case basis is the most prudent and practical approach at the moment.

CONCLUSION

The application of nanotechnology to the design of pharmaceuticals is expanding due to rapid technological advances and an increased appreciation of the value of precisely targeted biodistribution, particularly in oncology. While scientific advancement has been substantial over the past decade, as evidenced by the number of nanomedicine agents in clinical development, the number of marketed nanopharmaceuticals is small compared to traditional drug products. The symposium highlighted questions regarding how best to design nanomedicines to improve efficacy while minimizing safety issues, providing a favorable benefit-to-risk ratio for an intended medical indication. Two areas stand out as being important for continued nanomedicine advancement:

1. Greater understanding of nanomedicine biodistribution, including the EPR effect and clearance mechanisms, in animals and humans should enable more accurate translation of preclinical results to clinical application; and
2. Generation of predictive *in vitro* performance tests to help identify and control key parameters in nanomedicine manufacturing processes

With a wide variety of approaches being explored, case-by-case evaluation of nanomedicine candidates becomes necessary—as has been recognized for biotherapeutic drug development. Design, development, and registration require close working relationships between a broad range of drug development scientists and key stakeholders such as regulatory authorities. This symposium and others like it have provided and will continue to provide platforms for all involved parties to define, debate, and eventually resolve the complex issues involved, thus leading to commercialization of a new wave of safe and effective nanomedicines.

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