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Section VI: Commercialization of Nano-Products for Cancer

Commercialization of Cancer Nanomedicines: Opportunity and Challenges

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Chemotherapeutics in Cancer Therapy

The treatment of cancer remains an ever-growing problem. In developed countries, the most common approach to treating solid tumors, in particular, starts with surgical resection followed by chemotherapy and/or radiotherapy. Such a clinical treatment strategy, requiring sophisticated hospitals with sophisticated staff, equipment and supplies, which are quite costly. For the developing nations of the world, this approach may be an insurmountable economic challenge. And, the efficacy of this approach has not resulted in a dramatic improvement in overall survival rates for most cancers[1].

Using nanoparticles to deliver potent anti-cancer agents to solid tumors, which represent 85% of all cancers reported annually, has the potential to change this paradigm, and potentially change patient outcomes. As solid tumors grow, whether primary or metastatic cancer, new blood vessels grow to support that growth. These new blood vessels are leaky with fenestrations ranging in size from 0.2-1.2 μm^2. This unique biology provides an ideal opportunity for systemically administered nanoparticle-based medicines (nanomedicines), ranging in size from 10-100 nm, to target tumors by exiting the circulation through these fenestrations, potentially resulting in improved biodistribution, bioavailability, safety and efficacy. In effect, the leaky tumor neovasculature argues that solid tumors should only be treated, prior to surgery, *in situ* with nanomedicines, taking advantage of this unique biology and potentially improving the therapeutic index of potent anti-cancer drugs. Recognizing this therapeutic opportunity is the clinical rationale for changing the current cancer treatment paradigm for the vast majority of solid tumors from a surgery first protocol, to medical treatment first.

If nanomedicines are effective in significantly reducing or eliminating cancers, making subsequent surgeries less complex or unnecessary, then this treatment regimen is a clear opportunity for the pharmaceutical industry to help reduce healthcare costs worldwide. Such a public health strategy might effectively improve patient outcomes for the largest number of cancer patients. And, the potential role nanomedicines might play in this paradigm shift, worldwide, represents a major motivating factor for biotechnology

and pharmaceutical companies to seriously explore the clinical development of cancer nanomedicines.

Since the tumor neovasculature is inherently leaky, irrespective of cancer type or disease stage, this biology may be used again and again in its treatment. So, from the perspective of biotechnology and pharmaceutical companies, treating cancer as a chronic medical disease that requires periodic nanomedicine treatments to control/suppress recurrent disease is an added economic incentive to develop nanoparticle-based cancer medicines.

Design of Cancer Nanomedicines

However, the leaky tumor neovasculature is both an opportunity and a challenge for nanoparticle-based medicines. As noted above, the opportunity exists for nanomedicines smaller than 100 nm to passively exit the circulation and remain in the tumor interstitial space, the "enhanced permeability and retention" (EPR) effect. But, is the EPR effect sufficient for the delivery of cancer killing drugs? Comparative data have shown that inclusion of a tumor targeting ligand that binds to a cell surface receptor reduces the time for a nanomedicine to reach a solid tumor from hours to minutes[3]. Consequently, in the design of new nanomedicines for commercialization having a tumor-targeting ligand needs to be considered.

...the opportunity exists for nanomedicines smaller than 100 nm to passively exit the circulation and remain in the tumor interstitial space...

Conversely, a challenge that the leaky tumor neovasculature creates for systemically administered cancer therapeutics, including nanomedicines, is that other similar or smaller-sized blood components also leak into the tumor interstitial space, creating an interstitial pressure gradient in tumors, where the fluid pressure inside the tumor is greater than it is outside the tumor[4]. This high interstitial fluid pressure (IFP) creates a physical barrier, preventing systemic cancer treatments, such as nanomedicines, from reaching their target, the cancer cells.

Clinically, the effect of destroying the high tumor IFP has been most dramatically seen in patients with in-transit melanoma or sarcoma[5]. Using hyperthermic limb perfusion to locally treat these patients first with a vascular disrupting agent, which destroys the high tumor IFP, followed by chemotherapy, has, on average, been reported to result in an 85% complete local response. In effect, this regional limb perfusion protocol eliminates this physical barrier, enabling follow-on chemotherapy to reach its target and kill the cancer cells.

By design, if a nanomedicine is able to destroy tumor blood vessels, then, using the tumor targeting mechanisms noted above, the systemic administration of a nanomedicine to a cancer patient prior to surgery could eliminate the high tumor IFP. With this added mechanism of action, such nanomedicines might have the greatest potential of achieving the high response rates seen with regional limb perfusion. Consequently, incorporating an agent capable of destroying the high tumor IFP should also be considered when creating cancer nanomedicines for systemic treatment of solid tumors.

Looking to the future of creating commercializable cancer nanomedicines, some critical first steps in design and manufacture need to be considered. For example, translation of a nanotechnology-based research concept into a commercial nanomedicine product requires that thought be given to the biocompatibility of the material comprising the nanomedicine platform, the therapeutic payload (ideally a new drug entity), the immunogenicity of the resultant nanomedicine, the ability to actively target tumors and attack cancer cells, the metabolism and elimination of the material comprising the nanomedicine platform, and the ability to scale-up the nanomedicine manufacturing process to commercial lot sizes in a current good manufacturing process (cGMP) facility. And, the resultant product must be stable, with a two-year shelf life at a minimum. Without a clear understanding of these issues, as well as patent protection of the accompanying intellectual property, the translation of a nanotechnology-based drug concept into a nanomedicine product might never be achieved.

Regulatory and Financial Hurdles to Commercialization

Many of the issues noted above must be satisfactorily addressed in the *Investigative New Drug (IND) application* that is required by the Food and Drug Administration (FDA) to initiate human clinical testing. And for nanomedicines specifically, the Chemistry, Manufacturing and Controls (CMC) section of the IND is quite critical in that the Sponsor must fully explain the composition of the new drug, how the nanomedicine is formulated, its stability under various conditions that might approximate its use, and the analytical tests used to interrogate the final drug product and its components. Providing this critical data is a challenge for new nanomedicines, and being sure that the data meet the requirements of the FDA for new product registration and sale is not guaranteed. And, such uncertainty is often perceived as a risk for pharmaceutical companies and for investors, such as venture capital companies that oftentimes provide the necessary capital to develop new technologies.

Such uncertainty stems in part from the fact that the FDA has not issued specific guidance or analytical benchmarks that all nanomedicines must achieve. In fact, the FDA has

maintained that the current procedures for new drug testing and evaluation sufficiently cover the development of nanomedicines[6]. In addition, current FDA policy states that each nanomedicine should be reviewed and evaluated on a case-by-case basis, similar to other drugs in clinical development.

Herein lies the conundrum for the development of new nanomedicines. Developers of nanomedicines typically want as few regulatory hurdles as possible to allow for maximum creativity and flexibility, while large pharmaceutical companies, who usually have the expertise and resources for later stage drug development and commercialization, want as much specificity as possible about the regulatory requirements for final drug product approval to better estimate their financial commitment/exposure in bringing a new nanomedicine to market.

Each element needs to be optimized to create a new nanomedicine product formulation that can be commercialized.

To help overcome this obstacle, nanomedicine stakeholders need to create a nanomedicine development matrix to streamline optimization of the final drug product. For example, to create the ideal ratio of each nanomedicine component to insure that the new formulation has all the functionality needed for optimal safety and efficacy may require that each new nanomedicine formulation be tested directly *in vivo* for pharmacokinetics and biodistribution, looking for longer half-life of the therapeutic payload and specific organ/tissue targeting, respectively, initially skipping over both *in vitro* and *ex vivo* testing. By going from new formulation to in vivo testing, back and forth, might provide the quickest, most cost-effective strategy to define a successful nanomedicine formulation.

The Opportunity

Therefore, to truly improve the outcome of patients with solid tumors, as an example, the ideal cancer nanomedicine needs to: avoid immediate immune detection by the mononuclear phagocyte system (MPS); carry a novel active pharmaceutical ingredient (API), not re-package an already approved drug; target tumors by both passive (EPR) and active (receptor binding) mechanisms; disrupt the high IFP in tumors; and be manufactured using a scalable, robust, reproducible, and cost-effective process. Each element needs to be optimized to create a new nanomedicine product formulation that can be commercialized. And, commercialization most likely requires that patents be issued domestically and internationally to protect the composition of the final drug product, its method of production and its use.

Academia and industry need to seize the opportunity that nanotechnology-based medicines present for changing the cancer treatment paradigm and the outcome for patients with solid tumors; not focusing on perceived challenges and risks, but on the potential to dramatically impact cancer care for the world's population by treating cancer patients with safe and effective cancer nanomedicines prior to surgery, even for resectable tumors.

Manufacturing Challenges of Nano-Products

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Why Bother with a Nanoparticle?

This brief chapter will survey the field of Nano-product manufacturing. First, the term "nano-product" implies that there is some similarity between all things "nano". Outside of the obvious shared dimensional quality, nano-products are actually widely divergent. For this review we will limit ourselves to discussing oncology related nano-particulates and not consider devices fabricated at the nano-scale. Such particles range from simple nano-particulates of pure drug to highly structured multicomponent particles and delivery systems. The term includes solid structures, liquid phases and systems that incorporate small and/or large molecules. Further, "nano" is really nothing new and, on a commercial level, we have been manipulating nanostructures for a very long time. The difference is that now we are more conscious of it and have a much greater ability to measure both what we are doing and its impact.

Because of the many possible nanoparticle structures, they can serve a host of roles in oncology therapeutics and vaccines. On a mechanical level, nano-structures can be biomimetic and engineered to be site selective. Chemically, behaviors such as solubility, reactivity and affinity can be manipulated. Further, nanoparticles can be co-formulated with other technologies imparting even greater flexibility. Ultimately, nanoparticle drug constructs can provide a variety of performance benefits that increase effectiveness: improved pharmacokinetics, improved safety profiles, improved stability, and targeted delivery.

As an indication of the activity in this space, in a Jan 17, 2013 article[7] on nanomedicine products that are approved or in various stages of clinical study by the European Medicines Evaluation Agency were summarized. Of the 247 products noted, there were a total of 33 approved drugs at the time of the study. In the oncology space, **Table 1** gives a list of approved nanotechnology-based oncology products from a publication on cancer nanomedicines[8].

Table 1: Nanotechnology Oncology Products Approved as of 2014				
Product	***Nanoplatform/ agent***	***Indication***	***Status***	***Company***
Doxil	PEGylated liposome/ doxorubicin HCl	Ovarian cancer	Approved 11/17/1995 FDA50718	Ortho Biotech (acquired by JNJ)
Myocet	Non-PEGylated liposome/ doxorubicin HCl	Metastatic breast cancer	Approved in Europe and Canada, in combination with cyclophosphamide	Teva Pharma B.V.
DaunoXome	Lipid encapsulation of daunorubicin citrate	First-line treatment for advanced HIV-associated Kaposi's sarcoma	Approved in USA	Galen Ltd
ThermoDox	Heat activated liposomal encapsulation of doxorubicin	Breast cancer, primary liver cancer	In Phase III in USA	Celsion
Abraxane	Nanoparticulate albumin/paclitaxel	Various cancers	Approved 1/7/2005 FDA21660	Celgene
Rexin-G	Targeting protein tagged phospholipid/ microRNA122	Sarcoma, osteosarcoma, pancreatic cancer, and other solid tumors	Fully approved in Philippines in 2007, Phase III Fast Track Designation, Orphan Drug Status Acquired in USA	Epeius Biotechnologies Corp
Oncaspar	PEGylated asparaginase	Acute lymphoblastic leukemia	Approved 6/24/2006	Sigma-Tau Pharmaceuticals
Resovist	Iron oxide nanoparticles coated with carboxydextran	Liver/spleen lesion imaging	Approved 2001 for European market	Bayer Schering Pharma AG
Feridex	Iron oxide nanoparticles coated with dextran	Liver/spleen lesion imaging	Approved in 1996 by FDA	Berlex Laboratories
Endorem	Iron Oxide nanoparticles coated with dextran	Liver/spleen lesion imaging	Approved in Europe	Guerbet
DepoCyt	Liposome/ cytarabine	Lymphomatous meningitis	Approved in USA	Sigma-Tau Pharmaceuticals

Scale Up Principles

The progression of a formulation manufacturing process from the benchtop to GMP is a critical step for all pharmaceuticals – it is also often very challenging. It involves the simultaneous increase in scale and the maturation of the various unit operations. Even if a formulation is very effective biologically, if it can't be reproducibly scaled to commercially relevant quantities, it is of questionable value. Therefore, from the beginning of the product

development process one needs to keep in mind eventual commercialization, i.e., using off-the-shelf manufacturing equipment if possible, using excipients that are available in the appropriate grade and generally recognized as safe (GRAS), and using processes that have a high probability of being scaled. Deviations from these are of course possible and are, in fact, quite common but their impact needs to be evaluated in real-time. In addition to safety, efficacy and quality, cost needs to be considered. Clearly, the lower the cost the greater number of people that can be potentially helped although subsidies of one kind or another can mitigate even truly expensive therapies. Also one needs to keep in mind that the infrastructure to handle highly potent compounds, as are typically required for oncology agents, is relatively scarce and that this, coupled with the need for GMP and special expertise around nanoparticles, limits the number of available commercial resources. So, early identification and involvement of a scaling partner is key. For academic groups this typically means partnering with a commercial CDMO. For commercial developers, recruitment of internal resources or an appropriate sub-contractor is needed. Either way, early transfer of the product production function will speed development and greatly enhance later chances of success.

The QBD[9] (quality by design) approach is the organizing framework under which the pharmaceutical industry now operates. A review of QBD is not appropriate here but, in brief, it is a proactive scientific approach to pharmaceutical development that pivots around the desired product attributes and provides for the establishment of well-defined processes that result in a reproducible product. During the QBD process, CQA's (critical quality attributes) are defined. CQA's are product properties that are key to safe and effective performance - the amount of drug per dose, the rate of dissolution or the sterility of an injectable are typical examples. Operating by QBD principles and using tools such as DOE (design of experiments), a well-run scale up program will progress in scale generally by increments of 10 fold. Going from mg to grams for instance or 100 mL to the liter scale. Scale up not only considers drug product production, but material acquisition, training, filling, packaging, storage, and administration. As one progresses in scale, greater attention should be paid to the equipment and processes and each weighed against their respective commercial viability.

The QBD approach is the organizing framework under which the pharmaceutical industry now operates.

Production methods and product attributes are intimately linked. Two methods of particle size reduction can yield similar size distributions but different polymorphs as a simple example. All data generated in a drug product development effort is potentially part of

the regulatory submission. This includes details on both active pharmaceutical ingredient (API) and drug product production. Some of the performance data, mainly toxicological, is required and is performed under GLP's (Good Laboratory Procedures). The purpose of this requirement is of course to insure, or at least to be able to assess the risk to, the safety of the clinical trial participants. Thus, the product used in that testing absolutely needs to be identical, in all of its CQAs, to the clinical trial materials. For a product composed purely of API, the manufacturing process used for that API is less important since equivalency of the API from one process to another can be established with some certainty. For complex nanoparticles, the situation is less clear-cut. CQA's are sometimes difficult to define early in development and thus the impact of a manufacturing variation likewise becomes difficult to quantify. For this reason, optimally, by the time legally mandated testing is being performed the manufacturing process should be essentially the same as that which will be used for clinical trial material production. In practical terms, generally speaking, this means that the process should be scaled to a clinically relevant degree no less than 12 months from the estimated first-in-human trial. To accomplish this, process rationalization should start, as a rule of thumb, at least two years prior to the first-in-human target date and, ideally, as early as possible. The more complex the product, the earlier rationalization should begin.

While each product will present its own set of challenges, there are some recurring themes. Perhaps the most frequent shortcoming manufacturers encounter in the advancement of therapeutic nanoparticles is a lack of thorough characterization of the product and the identification, to the extent possible, of the CQA's. This requires, among other things, an early emphasis on the appropriate analytical methods, which is something that is frequently neglected. Other common errors include advancing very low yield processes, failure to identify GMP sources of materials, advancing products based on single batch results, using non-scalable production methods, failure to involve regulatory expertise early on, and inadequate consideration of intellectual property constraints.

Characterization

After a therapeutic nanoparticle is identified, the qualities that enable its benefits should be well understood. Scaling a poorly characterized product is a waste of time. Basic properties should all be well documented and can include, among others, particle size, zeta potential, pH, viscosity, encapsulation efficiency, API assay and related substances, dissolution, solid state, binding efficiency and batch-to-batch variability (i.e., reproducibility). As a rule, one should have a basic idea of stability and use different lots of raw materials, if available, to test potential impact, if any. Raw materials that are themselves variable should be evaluated to establish if that variation impacts product success.

Yield

While many if not most newly developed products will have low yields, a commercially viable product must at least have the promise of adequate yields. At first this can be a paper exercise but should become a focus early on.

Sourcing

All materials used in production of products for human use will be required to be made under cGMPs or, in rare instances where GMP materials are not available and the need is compelling, be controlled to a degree that simulates GMP quality. In development, when possible, all materials used should be from GMP suppliers. This does not mean that the materials need be of GMP quality only that equivalent GMP supplies are available. By their nature however, nano-therapeutics will often incorporate unique excipients that are not available under GMP's. While not inherently bad, and potentially necessary, any such material adds a very significant cost, time and regulatory burden to the drug product development path. Educated assumptions as to their impact should be incorporated into the plan so that rational decisions as to their relative value can be made.

...efficacy should ideally be demonstrated multiple times using multiple batches of the therapeutic with proper controls.

Proof-of-Concept

While not actually a scale up issue, advancing thinly documented therapies wastes finite resources. Great scientific advances don't always make great drug products. Prior to dedicating resources to scale up, efficacy should ideally be demonstrated multiple times using multiple batches of the therapeutic with proper controls. As above, characterization is key.

Processes

After initial proof-of-concept, efforts towards using commercially viable processes should be made whenever possible. At the nano-scale, changes in process invariably result in product changes and these may or may not impact performance in a predictable way. In addition to process driven attribute changes, production methods are evaluated as to practicality. As an example, using a precipitation process at 0.1% solids would mean that for every kg of product one would produce 1,000 kg of waste. For a nanoparticle that might only contain

5% of API that translates to 1 kg of API generating 20,000 kg of waste. While potentially possible, this is certainly less than attractive. Early efforts at practical processes are vital.

Regulatory

This encompasses many aspects including, among others, toxicology and manufacturing conditions. Early developers will benefit from having access to regulatory advice to provide an understanding of the regulatory path for the various kinds of products. As an example, for a sterile product, knowledge of the relative overhead of a terminally sterilized product vs. one aseptically produced will greatly aid the developer in their process choices.

Intellectual Property

As of this writing, the US Patent Office is issuing patents with numbers approaching 9 million. Assessing one's own invention against this pool is hard enough but when one also needs to consider API patents, method of use claims and various manufacturing techniques as part of the intellectual property pool to be considered, the job becomes truly daunting. As a practical matter, developers need to be current at least in their field's literature. When approaching advanced preclinical development, involving an IP professional is advisable if the developer is financially capable of doing so.

Manufacturing

As above, nanoparticles encompass a wide variety of structures so there is no one manufacturing system to review. In general, the caveats for manufacturing include those under scale up with the addition of the necessary Quality and cGMP overhead. Independent of the nuances of a specific nano-product, the steps common to all manufacturing efforts include: technology transfer, analytic method validation and process validation. Each of these involve literally dozens of steps themselves and are intimately linked to each other. Listing them as separate efforts is purely for organizational purposes.

...developers need to be current at least in their field's literature.

Technology transfer involves moving the process from the innovators' lab to the manufacturing site. In this author's experience, this is best done during preclinical development. This allows the manufacturer to gain experience with the process and help it mature along a commercially viable path. Usual practice is that decisions around process improvement, packaging, specifications, labeling and final sourcing have not been made at the time of transfer. In the scheme presented in this chapter much of the process development effort is

effectively shifted to the CDMO making that partnering choice even more important. When possible, it is most efficient to have the same partner do both scale up and manufacturing. This saves time and a great deal of money as transferring methods is costly. A good manufacturer will also help insure that the background information needed in regulatory filings is properly assembled and ready for presentation.

Analytical methods evolve from basic-to-advanced following along with the product itself. The term "phase appropriate" is often used to describe this maturation process. The analytical methods insure the quality of the drug product, its consistent behavior, and ultimately its safety. For in-human studies the analytical methods need to be robust and, most developers will state, validated. Certain methods, sterile filtering, do not vary by development stage and needed to be fully validated even for a Phase I. This is for obvious safety reasons: a microbial contaminate in an injection could have catastrophic results. Clarity on analytical method, stage and purpose is critical. As an example, "stability" has a specific meaning from a regulatory perspective: the product has the same physicochemical properties, within predetermined limits, at some time post-manufacture as it did at the time of manufacture. On the other hand, an innovator often views stability as meaning that the product still works (i.e., has the desired biological activity, after some period of time). Both definitions are valuable and awareness of each is needed for an efficient development process.

Pharmaceutical manufacturing is a unique discipline but should not be separated from the development process.

Once the manufacturing process is locked, each unit operation needs to be refined to the point that the manufacturer has confidence in its repeatability. Ideally there is some way to monitor each unit-op to assess its function in real-time although this, referred to Process Analytic Technology (PAT) in QBD terms, is often not feasible in early stage clinical manufacturing. At a minimum, the process as a whole is demonstrated through engineering runs to produce the desired product, meeting the predetermined specifications. Invariably, because deep product production experience is lacking by definition, early clinical production relies heavily on post-production quality testing. Again, this points to the importance of the proper development of analytical methods. For certain types of products various unit operations are actually validated. This is most evident in sterile processes where the product is either produced under aseptic conditions or terminally sterilized. For aseptic production media fills are required. A media fill is a dry run of the entire process in the clean room with thorough microbial sampling of staff, product and facility to demonstrate the processes ability to

produce a sterile product. For terminally sterilized products, as above, the sterilizing process itself is fully validated.

Future Direction for Manufacturing

Pharmaceutical manufacturing is a unique discipline but should not be separated from the development process. Rather, discovery-to-commercialization should be viewed as a continuum with the handoff from one group to another taking place in phases. The basics of nano-based manufacturing are here and established today. The next 5 to 10 years will see incremental improvement in processing capabilities mostly, we believe, in the areas of aseptic handling and throughput. Why? Simply because that is where the acute need is. Along with this will come standardization and dissemination of procedural operations, again driven by regulatory mandates, not the result of any real innovation. The innovation opportunity lies in the emergence of a disruptive change, not to the nano-products themselves but to the method of manufacture. Among other properties, such a manufacturing advance will be …"cheaper, simpler, smaller and …… more convenient to use"[10] and, if history is any indication, it will be the smaller more nimble companies that champion this change and its adoption.

Regulatory Evaluation of Nanotechnology in Diagnostics for Human Use*

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Background

Nanotechnology is a rapidly evolving field that has tremendous potential to advance human health and medicine. Nanomaterials have already been integrated into medical products designed to treat and diagnose serious and life threatening disease[11]. However, as often is the case, people assume that new is better; or what works well in the laboratory will work well, without modification, in a clinical setting. The zealousness to bring the latest and greatest to market, or be the first to publish on a particular topic can be at the expense of generating a high quality, well characterized, final product, which in the case of medical applications risks injury to the end user, i.e., the patient. It is the role of medical product regulation and regulatory agencies worldwide to both protect and promote the public health. United States Law, in the form of the **Federal Food, Drug, and Cosmetic Act of 1938** (the Act) and the **Public Health Service Act of 1944** (the PHS Act) give primary authority to regulate medical products to FDA.

Introduction to Diagnostic Device Regulation

FDA protects the public health by insuring that medical products are safe and effective for their Intended Use. They promote the public health by guaranteeing that the best and most innovative medical products are available to the public.

Products intended to diagnose a disease or condition, whether implantable (such a heart monitor within a pace maker), *in vivo* (such as an electroencephalogram used on a living person) or *in vitro* (using materials collected from a living person such as blood and urine tests) are considered medical devices. Devices are regulated by FDA's Center for Devices and Radiologic Health (CDRH), with a few exceptions[12]. *In Vitro* diagnostic devices (IVDs) are a special category of device with specific labeling requirements[13]. Whether a product is safe and effective is determined partially by risk classification. Depending upon the classification, an appropriate level of review of the scientific, clinical and manufacturing data for the product is applied[14,15].

While exceptions to each rule exist, generally: *Class I* devices are considered low risk and are therefore exempt from FDA review prior to being placed on the market. Manufacturers of these devices are still required to follow several procedures, referred to as General Controls. These include registration of the company with FDA; listing of all medical products the company sells; following current Good Manufacturing Practices (cGMP, known as the Quality System Regulations for devices); establishing a system for handling customer complaints, establishing a system for preventative actions, corrections and corrective actions (CAPA); performing corrections and removals as necessary (recalls); and providing labeling that is complete, truthful and accurate.

Such nanotechnology-containing devices may still be determined to be substantially equivalent to legally marketed devices or exempted from future premarket notifications and FDA review.

Manufacturers of *Class II* (moderate risk) devices are subject to the same General Control procedures as a Class I product, as well as additional Special Control procedures. The Special Controls are procedures designed to mitigate the moderate risks identified with the device. Special Controls include a submission of pre-market notification for FDA review. This procedure is described in FDA guidance documents and under section 510(k) of the Act. *Such applications are referred to by FDA and industry as, a 510(k) submission*. Review is based on a demonstration of substantial equivalence to another legally marketed Class II device, referred to as the predicate. The idea being that if the clinical value of the predicate is established, the manufacturer of a similar device only needs to show that their device is analytically and technically the same as the predicate. Clinical data is generally not required. If the new is found to be substantially equivalent to the predicate device, the 510(k) device is "cleared" for marketing. Manufacturing facilities are inspected after the device has been cleared.

Class III devices are considered the highest risk. Manufacturers of these devices are required to obtain pre-market approval (PMA). Approval of a PMA application generally requires a clinical study and inspection of both the clinical study sites and the site of manufacturing prior to the device coming on the market. Companies are also required to report all changes to device design or manufacturing[14].

Regulation of New Technologies - Nanotechnology

The Agency does not recognize a formal definition for nanotechnology[16,17], but we ask the same question of any new technology that comes into the Agency: Does it affect the safety or effectiveness of the device for its intended use? In general, the presence of a material that has not previously been used in a medical product may raise additional questions/concerns from regulators. That said, simply adding nanotechnology to a medical device does not necessarily cause it to fall into a different classification than similar marketed Class I or II devices. Such nanotechnology-containing devices may still be determined to be substantially equivalent to legally marketed devices or exempted from future premarket notifications and FDA review.

FDA regulation has evolved over the years and will continue to do so to accommodate new emerging technologies...

If the nanotechnology enables a device to function through different principals than the predicate device, it likely would not be considered substantially equivalent, but the risk of using the new device may still not be considered high. When any new technological characteristic creates a unique device, FDA's *de novo* classification process provides a pathway for a device to be put into Class I or Class II for which general controls or general and special controls provide a reasonable assurance of safety and effectiveness, but for which there is no legally marketed predicate device. For example, special controls for a nanotechnology may reasonably include requirements for well-done physical and physiological characterizations of the new material. Once the nanotechnology-enabled device is classified as Class I or II through the de novo process, similar devices could come to market as exempt devices or by use of the 510(k) pathway, rather than premarket approval.

Combination Products

It has long been a goal of visionaries in the field of nanotechnology to generate a nanomachine that could diagnose, treat and ultimately cure a patient on the cellular level[18,19]. Moving towards such goals, nanotechnology has enabled medical products to develop beyond single mode of action devices into multifunctional platforms performing several functions – such as nanotheranostics that combines therapeutics with diagnostics. Medical products are regulated according to their primary mode of action (PMOA). In the case of products with multiple modes of action, so called combination products, it falls to the FDA's Office of Combination Products to determine whether a product achieves its primary therapeutic benefit from its action as a drug, a biologic product, or a medical device.

Once this determination is made, the regulation of the product will be assigned to the appropriate Center, either CDRH, the Centers for Drug Evaluation and Research (CDER) or Biologics Evaluation and Research (CBER). The Center(s) who have expertise in the additional parts of the combination product are consulted in the review process to insure consistency. For example, contrast agents for MRI are regulated as drugs by CDER while IVD's intended to screen the blood supply are regulated as biologics by CBER. Review of these products may reasonably include consults to MRI and IVD specialists, respectively, and hence involve CDRH. If we envision a potential nanotheranostics product for ex vivo therapy, where tissue may be removed from a patient, manipulated outside of the body, and the re-introduced to the patient, the regulatory framework would likely be related to both the ex vivo biology (regulated by CBER) and the diagnostic device (regulated by CDRH) and potentially CDER depending on the nature of the therapy.

Future Scientific and Clinical Developments

The current regulations, as they stand, provide a sound framework upon which to develop medical products that incorporate nanotechnology. That said, two major factors are found to influence future regulations:

1. The introduction of new technologies in to the medical products realm. FDA has had to deal with smartphones, genetic engineering, personalized medicine and other paradigm shifts in medicine that were precipitated by new scientific discoveries.

2. The behavior of entities marketing medical products. Major shifts in Food and Drug law have occurred because of findings of fraud, corruption, poor quality, false or off-label advertising. These findings, unfortunately, do not usually come to light until after tragedy has struck.

FDA regulation has evolved over the years and will continue to do so to accommodate new emerging technologies, such as nanotechnology, that have the potential to significantly benefit human health and medicine.

Regulatory Evaluation of Nanotechnology in Drug Products*

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In recent years, there has been an increased focus on developing novel drug delivery systems, targeted therapies, and medical devices, including *in vitro* diagnostics, through the use of nanotechnology and nanomaterials. Such focus is translating to an increasing number of submissions for drug products and medical devices to the United States Food and Drug Administration (FDA). Although subject to the same regulatory standards and pathways as any drug or device, unique properties that arise from the small size and large surface area of nanomaterials may lead to additional scientific considerations when following current FDA guidelines and practices.

FDA has not defined the term "nanotechnology" or related terms, given the wide diversity the Agency has seen with these products. FDA has, however, published general guidance on products involving the use of nanotechnology[20]. According to this guidance, when considering whether an FDA-regulated product involves the application of nanotechnology, FDA will ask:

1. 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 (approximately 1 nm to 100 nm), and

2. 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 one micrometer (1,000 nm).

History of Nanotechnology in Drugs and Devices

The Center for Drug Evaluation and Research (CDER) is responsible for reviewing applications for new and generic drugs, new indications for already approved products, and active ingredients and labeling for over-the-counter drugs. CDER reviews each drug product application on its merits, regardless of the presence (or absence) of nanomaterials. CDER has a long history of approving drug products that contain nanomaterials (**Table 2**)[21]. In

recent years, the number of applications to CDER has increased, with over 350 individual applications submitted to date.

Table 2: Representative drug products involving the application of nanotechnology

Platform/Type	*Example*		
	Name	*NDA Approval Year*	*Indication*
Liposome	DOXIL® (Doxorubicin)	1995[a]	Ovarian cancer; AIDS-related Kaposi's Sarcoma; Multiple Myeloma
Inorganic nanoparticle	FERRLECIT® (Sodium ferric gluconate complex)	1999[b]	Iron deficiency anemia in patients with chronic kidney disease (CKD).
Protein nanoparticle	ABRAXANE® (Paclitaxel)	2005	Metastatic breast cancer; Locally advanced or metastatic non-small cell lung cancer (NSCLC); Metastatic adenocarcinoma of the pancreas
Polymer nanoparticle	MACUGEN® (Pegaptanib sodium)	2004	Neovascular (wet) age-related macular degeneration.
Emulsion	RESTASIS® (Cyclosporine)	2002	To increase tear production
Lipid complex	AMPHOTEC® (Amphotericin B)	1996	Invasive aspergillosis
Nanotube	SOMATULINE DEPOT® (Lanreotide acetate)	2007	Acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy
Nanocrystal	TRICOR® (Fenofibrate) 48mg/145mg tabs	2004[c]	Primary hypercholesterolemia or mixed dyslipidemia; Severe hypertriglyceridemia.
Micelle	TAXOTERE® (Docetaxel)	1996	Breast Cancer; Non-Small Cell Lung Cancer; Hormone Refractory Prostate Cancer; Gastric Adenocarcinoma; Squamous Cell Carcinoma of the Head and Neck Cancer

[a] First ANDA approval in 2013.
[b] First ANDA approval in 2011.
[c] First ANDA approval in 2012.

Nanotechnology was first exploited in "first generation" products of nanocrystals or liposomes, where the drug products were typically reformulations of previously known, often poorly water soluble, drug substances. Nanotechnology was used to increase bioavailability, alter biodistribution, or both. In recent years, a "second generation" of products has begun to emerge, which incorporates more complex structures and functions into the drug formulation (example: drug delivery systems with targeting capabilities).

Medical devices are regulated by FDA's Center for Devices and Radiologic Health (CDRH). Products intended to diagnose a disease or condition, whether implantable *in vivo* (such as

a heart monitor within a pace maker), external *in vivo* (such as an electroencephalogram used on a living person) or *in vitro* (using materials collected from a living person such as blood and urine tests) are considered medical devices. CDRH reviews each medical device application, regardless of the presence (or absence) of nanomaterials, by asking the same question: Is this product safe and effective for its Intended Use. Under the Federal Food, Drug and Cosmetic Act, Code of Federal Regulations (CFR) title 21, 860.3, medical devices are classified into three categories based on risk: class I, class II and class III, often referred to as low, moderate and high risk, respectively. Device classification determines the regulatory pathway and the types of controls to which a medical device may be subject. Although CDRH does not have a long history of clearing/approving medical products that contain nanotechnology, there are a limited number of *in vitro* diagnostics that have been cleared/approved and the current regulations, as they stand, provide a sound framework upon which to regulate such devices.

Review Considerations for Drug Products and Devices Containing Nanomaterials

FDA has multiple guidance's for products involving the application of nanotechnology. These guidance's may be Agency-wide, Center-specific, or even product-specific. **Table 3** lists several of the relevant FDA guidance's involving nanotechnology.

Nanotechnology was used to increase bioavailability, alter biodistribution, or both.

In general, drug product applications contain the following information:

- Description and composition
- Physicochemical characterization
- Description of the manufacturing process and packaging
- Specifications needed for product release
- Analytical methods and validation of these methods used to characterize the drug product
- Stability studies to support an expiration date, or shelf life, and in-use conditions.

Table 3: FDA Guidance on Nanotechnology		
Guidance Category	***Name***	***Weblink***
NANOTECHNOLOGY		
General and cross-cutting topics	Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology	http://www.fda.gov/regulatoryinformation/guidances/ucm257698.htm
Food	Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives	http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm300661.htm
Cosmetics	Safety of Nanomaterials in Cosmetic Products	http://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm300886.htm
Animal & Veterinary	Draft Guidance for Industry: Use of Nanomaterials in Food for Animals	http://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm300886.htm
Chemistry, Manufacturing, and Controls (CMC)	Draft Guidance for Industry: Liposome Drug Products Chemistry, Manufacturing and Controls; Human Pharmacokinetics and Bioavailability; and Labelling Documentation	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070570.pdf
GENERIC DRUG PRODUCTS		
Bioequivalence Recommendations	Draft Guidance on Doxorubicin Hydrochloride	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf
Bioequivalence Recommendations	Draft Guidance on Amphotericin B	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384094.pdf
Bioequivalence Recommendations	Draft Guidance on Verteporfin	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384173.pdf
Bioequivalence Recommendations	Draft Guidance on Paclitaxel	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320015.pdf
Bioequivalence Recommendations	Draft Guidance on Sodium Ferric Gluconate Complex	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358142.pdf
Bioequivalence Recommendations	Draft Guidance on Ferumoxytol	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333051.pdf
Bioequivalence Recommendations	Draft Guidance on Iron Sucrose	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM297630.pdf
Bioequivalence Recommendations	Draft Guidance on Sirolimus	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM089640.pdf
Bioequivalence Recommendations	Draft Guidance on Paliperidone Palmitate	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM270384.pdf

The presence of nanomaterials, due to their unique properties, may warrant emphasis on different portions of the review of the drug product. There is a great diversity in drug products containing nanomaterials, ranging from metal colloids to polymeric micelles. Such diversity can make it difficult to apply generalities to all drug products containing nanomaterials. Despite the diversity, some common attributes exist when considering the quality of drug products containing nanomaterials. These include:

- Size and size distribution
- Nanomaterial composition
- Three dimensional structure
- API to nanomaterial ratio
- State of API (e.g., encapsulated, bound, etc.)
- Surface functionalization and state of the surface ligands (if any)
- Surface coating quantitation, density and polydispersity
- Zeta potential or surface charge

In addition, how the characterization of these quality attributes is conducted may vary greatly from one application to another, and is generally more involved than technologies or methods that have been traditionally used for other drug products. Finally, it is generally recognized that orthogonal or complementary methods are needed for key quality attributes of drug products containing nanomaterials due to the high impact of these critical physicochemical properties on the ultimate product performance.

Nanotechnology in medical diagnostics and devices

In general, the presence of a material that has not previously been used in a diagnostic medical device may raise additional questions or concerns from regulators. However, simply adding nanotechnology to a medical device does not necessarily cause it to fall into a different classification than similar marketed Class I or II devices that do not incorporate nanotechnology. Such nanotechnology-containing devices may still be determined to be substantially equivalent to legally marketed devices (called a predicate device) or exempted from future premarket notifications and FDA review.

Nanotechnology may enable medical products to develop beyond a single mode of action into multi-functional platforms performing several functions...

If the nanotechnology enables a device to function through a different principle than the predicate device, it likely would not be considered substantially equivalent to a predicate, but the risk of using the new device may still not be considered high. In such cases, FDA's *de novo* classification process provides a pathway for the device to be put into Class I or Class II. For devices, for which there is no legally marketed predicate device, general controls or general and special controls provide a reasonable assurance of safety and effectiveness. For example, special controls for a nanotechnology may reasonably include requirements for well-done physical and physiological characterizations of the new material. Once the nanotechnology-enabled device is classified as Class I or II through the *de novo* process, it can be used as a predicate for similar devices and these could come to market as exempt devices or by use of the 510(k) pathway, rather than premarket approval (PMA).

Nanotechnology may enable medical products to develop beyond a single mode of action into multi-functional platforms performing several functions – such as nanotheranostics that combines therapeutics with diagnostics. In the case of products with multiple modes of action, so called combination products, it falls to the FDA's Office of Combination Products to determine the primary mode of action (PMOA) of a product. Once this determination is made, the regulation of the product will be assigned to the appropriate Center, either CDRH, CDER or Biologics Evaluation and Research (CBER). The Center(s) who have expertise in the additional parts of the combination product are consulted in the review process to ensure consistency.

Future Regulatory Outlook

The number and complexity of submissions of drug and medical device products containing nanomaterials is expected to increase in the next 5-10 years as the potential of nanotechnology within the medical field is fully realized. Although not treated differently within the regulatory pathway, these drug and medical device products often have different emphasis on parts of the review process due to the specialized properties of the nanomaterials and the product's intended performance (drugs) or use (devices). In either case, an understanding of the scientific basis of the functioning of the nanomaterial within the product, as well as the instrumentation used to characterize it, will assist both applicants and reviewers alike in speeding these products to market.

*Disclaimer: The views presented in these articles do not necessarily reflect those of the Food and Drug Administration.

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