

Chapter 58

The Translational Challenge in Medicine at the Nanoscale¹

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testing, safety and efficacy, clinical trials, phase IV post-market surveillance, basic science, bench-to-bedside, translational medicine, translational science, preclinical research, the Bayh–Dole Act, the Hatch–Waxman Act, current Good Manufacturing Production (cGMP), irreproducible preclinical research, scientific integrity, scientific misconduct, crowd-sourced analysis, National Institutes of Health (NIH), Good Institutional Practice (GIP), Technology Transfer Offices (TTOs), publish-or-perish, trade secrets, physiologically-based pharmacokinetic (PBPK) modelling, pan-assay interference compounds (PAINS), antibodies, FDA's Center for Drug Evaluation and Research (CDER), Biologics License Applications (BLAs), Center for Biologics Evaluation and Research (CBER), Tufts Center for the Study of Drug Development of Clinical Trial, freedom-to-operate, nanopatent land grabs, nomenclature, terminology, nanocharacter, emerging technologies, regulatory guidance, National Center for Advancing Translational Sciences (NCATS)



58.1 Nano Frontiers: Dreams and Reality²

The air is thick with news of nano-breakthroughs. Although nano is a hot topic for discussion in industry, pharma, patent offices and

²This section is derived, with permission, from [29]: Bawa, R. (2016). What's in a name? Defining "nano" in the context of drug delivery. In: Bawa, R., Audette, G., Rubinstein, I., eds. *Handbook of Clinical Nanomedicine: Nanoparticles, Imaging, Therapy and Clinical Applications*, Pan Stanford Publishing, Singapore, Chapter 6, pages 127–168.

regulatory agencies, the average citizen knows very little about what constitutes a nanoproduct, a nanomaterial or a nanodrug. Still, there is no shortage of excitement and hype when it comes to anything “nano.” Optimists tout nano as an enabling technology, a sort of next industrial revolution that could enhance the wealth and health of nations. They promise that in many areas within nanomedicine (nanoscale drug delivery systems, theranostics, nanoimaging, etc.) will soon be a healthcare game-changer by offering patients access to personalized or precision medicine. Pessimists, on the other hand, take a cautionary position, preaching instead a go-slow approach, pointing to a lack of sufficient scientific information on health risks, general failure on the part of regulatory agencies to formulate clearer guidelines and issuance of patents of dubious scope by patent offices. They highlight that nano is burdened with inflated expectations and hype. As usual, the reality is somewhere between such extremes. Like any emerging technology, the whole picture is yet to emerge...and we are just getting started! Whatever your stance, nano has already permeated virtually every sector of the global economy, with potential applications consistently inching their way into the marketplace. But, is nano the driving force behind a new industrial revolution in the making or simply a repackaging of old scientific ideas and terms? Dissecting hope from hype is often difficult.

In reality, nano is the natural continuation of the miniaturization of materials and medical products that have been steadily arriving in the marketplace. It continues to evolve and play a pivotal role in various industry segments, spurring new directions in research, patents, commercialization and technology transfer. Too often though, start-ups, academia and companies exaggerate basic research developments as potentially revolutionary advances and claim these early-stage discoveries as confirmation of downstream novel products and applications to come. Nano’s potential benefits are frequently overstated or inferred to be very close to application when clear bottlenecks to commercial translation exist. Academia, start-ups and companies still exaggerate basic research or project potential downstream applications based on early-stage preclinical discoveries. This issue is quiet serious and often emanates from academic labs perched at distinguished universities like Harvard Medical School, MIT, Johns Hopkins, etc.

Experts continue to highlight this problem where researchers are guilty of promises and exaggerations [1]:

It is essential to identify and translate realistic opportunities offered by understanding the pathophysiological processes for the design and engineering of efficient and safe nanomedicines that can truly enhance benefit-to-risk ratio. This is in contrast to the overwhelming increase in the practice of empirical approaches that tend to find exaggerated in vivo biomedical applications for a broad range of emerging and poorly characterized multifunctional/hybrid entities and often non-biodegradable nanomaterials (e.g., carbon nanotubes, quantum dots, graphene oxide, certain metallic nanoparticles), which have raised toxicity and safety concerns... Materials scientists and the nanotechnology community rarely address these issues; their focus is purely based in extolling the virtues of their own favorite nanosystem for demonstrating the proof-of-concept and often in models irrelevant to the human disease in question. In many attempts a slight selectivity in organ uptake (and an acute pharmacological effect) of a "fancy" nanomaterial is heralded as "targeting" and "therapeutic success" even when less than 1% of the administered dose reaches the desired site..." (citations omitted)

Furthermore, many have desperately tagged or thrown around the "nano" prefix to suit their purpose, whether it is for federal research funding, patent approval of the supposedly novel technologies, raising venture capital funds, running for office or seeking publication of a journal article. All of this is happening while hundreds of over-the-counter products containing silver nanoparticles, nanoscale titanium dioxide and carbon nanoparticles continue to stream into the marketplace without adequate safety testing, labeling or regulatory review.³ Silver nanoparticles are effective antimicrobial agents but their potential toxicity remains a major concern. Similarity, nanoscale titanium dioxide, present in powdered Dunkin' Doughnuts and Hostess Donettes, has been classified as a potential carcinogen by National Institute for Occupational Safety and Health (NIOSH) while the World Health Organization (WHO) has linked it in powder form to cancers.

³A large number of nanomaterials and nanoparticles have been synthesized over the last two decades, yet the EPA and the FDA do not seem to know how to regulate most of them. Obviously, consumers should be cautious about potential exposure but industry workers should be more concerned. See: Bradley, R. (2015). The great big question about nanomaterials. *Fortune*, 171(4), 192–202. Available at: <http://fortune.com/2015/03/06/nanomaterials/> (accessed on January 20, 2016).

Still, there are thousands of nano-related products in the marketplace. While the widespread use of nanomaterials and nanoparticles in consumer products over the years has become pervasive and exposure inescapable, the 1980s and 1990s saw limited applications of these rather than the transformative applications envisioned. Even so, governments across the globe, impressed by “nanopotential,” continued to stake their claims by doling out billions for research and development (R&D).⁴ Boundaries between science, government and industry continue to be blurred. Venture has mostly shied away in recent years, though industry-university alliances have continued to develop. Stakeholders, especially investors and consumer-patients, get nervous about the “known unknown” novel applications, uncertain health risks, industry motives and general lack of governmental transparency. Wall Street’s early interest in nano has been somewhat limited over the years, from cautionary involvement to generally shying away, partly due to these issues. In spite of anemic nanoproduct development, there is no end in sight to publications, press releases, patent filings and patent grants. Universities and small businesses have jumped into the fray with industry with the clear intention of patenting as much nano as they can grab.

Many consider nano to be a repackaging of old terms, ideas and technologies. In this context, the following excerpt pertaining

⁴Nano-developments are often driven by what some of us refer to as “nanopotential.” This is obviously true more for certain sectors of nanotech than others. In this regard, one of the most widely cited predictions was in 2001 when a National Science Foundation (NSF) report was released that forecasted the creation of a trillion dollar industry for nanotech by 2015. This report, now proven false, was often quoted in articles, business plans, conference presentations and grant applications. See: National Science Foundation (2001). *Societal Implications of Nanoscience and Nanotechnology*. Available at: <http://www.wtec.org/loyola/nano/NSET.Societal.Implications/nanosi.pdf> (accessed on February 1, 2016). Given such flawed projections, Michael Berger of Nanowerk accurately pointed out: “*These trillion dollar forecasts for an artificially constructed “market” are an irritating, sensationalist and unfortunate way of saying that sooner or later nanotechnologies will have a deeply transformative impact on more or less all aspects of our lives.*” See: Nanowerk Spotlight. (2007). Debunking the trillion dollar nanotechnology market size hype. Available at: <http://www.nanowerk.com/spotlight/spotid=1792.php> (accessed on February 1, 2016). There are also various technical reports highlighting the potential market for nanotech. Again, one must take all such predictions with caution and not draw too many conclusions therefrom (“*A good decision is based on knowledge and not on numbers.*”—Plato).

to nanomedicine and nanopharmaceuticals accurately traces the evolution of terminology while highlighting the issue that various “nano” terms are indeed a relabeling of earlier terminology [2]:

The new concept of nanomedicine arose from merging nanoscience and nanotechnology with medicine. Pharmaceutical scientists quickly adopted nanoscience terminology, thus “creating” “nanopharmaceuticals”. Moreover, just using the term “nano” intuitively implied state-of-the-art research and became very fashionable within the pharmaceutical science community. Colloidal systems reemerged as nanosystems. Colloidal gold, a traditional alchemical preparation, was turned into a suspension of gold nanoparticles, and colloidal drug-delivery systems became nanodrug delivery systems. The exploration of colloidal systems, i.e., systems containing nanometer sized components, for biomedical research was, however, launched already more than 50 years ago and efforts to explore colloidal (nano) particles for drug delivery date back about 40 years. For example, efforts to reduce the cardiotoxicity of anthracyclines via encapsulation into nanosized phospholipid vesicles (liposomes) began at the end of the 1970s. During the 1980s, three liposome-dedicated US start-up companies (Vestar in Pasadena, CA, USA, The Liposome Company in Princeton, NJ, USA, and Liposome Technology Inc., in Menlo Park, CA, USA) were competing with each other in developing three different liposomal anthracycline formulations. Liposome technology research culminated in 1995 in the US Food and Drug Administration (FDA) approval of Doxil[®], “the first FDA-approved nanodrug”. Notwithstanding, it should be noted that in the liposome literature the term “nano” was essentially absent until the year 2000. (Citations omitted)

This current decade has witnessed relatively more advances and product development in nanomedicine.⁵ In this context, many point to the influence of nanomedicine on the pharmaceutical, device and biotechnology industries. One can now say that R&D is in full swing and novel nanomedical products, especially in the drug delivery sector (Fig. 58.1), are starting to arrive in the

⁵There is no standard definition for nanomedicine. We define it as the science and technology of diagnosing, treating and preventing disease and improving human health via nanoscale tools, devices, interventions and procedures. It is driven by collaborative research, patenting, commercialization, business development and technology transfer within diverse areas such as biomedical sciences, chemical engineering, biotechnology, physical sciences, and information technology.

marketplace.⁶ Still, revolutionary nanotech breakthroughs are just promises at this stage. Whether nanomedicine eventually blossoms into a robust industry, or it continues to influence medicine and healthcare, one thing is certain: The die is cast and it is here to stay. In the meantime, tempered expectations are in order. Giant technological leaps can leave giant scientific, ethical and regulatory gaps. Extraordinary claims and paradigm shifting advances necessitate extraordinary proof and verification.

⁶Obviously, the Holy Grail of any drug delivery system, whether it is nanoscale or not, is to deliver to a patient the correct dose of a particular active agent to a specific disease or tissue site while simultaneously minimizing toxic side effects and optimizing therapeutic benefit. This is often not achievable via conventional formulations and drug delivery systems. However, the potential to do so may be greater now via nanoscale drug delivery systems or NDDS (sometimes referred to as “nanodrugs” or “nanotherapeutics”). The prototype of targeted drug delivery can be traced back to the concept of a “magic bullet” that was postulated by Nobel Laureate Paul Ehrlich in 1908 (*magische Kugel*, his term for an ideal therapeutic agent) wherein a pathogenic organism or diseased tissue could be selectively targeted by a drug while leaving healthy cells unharmed. See: Ehrlich, P. (1913). Address in pathology. On chemotherapy. Delivered before the 17th International Congress of Medicine. *Br. Med. J.*, **16**, 353–359; Witkop, B. (1999). This concept of a “magic bullet” was realized by the development of antibody-drug conjugates (ADCs) when in 1958 methotrexate was linked to an antibody targeting leukemia cells wherein the antibody component provides specificity for a target antigen and an active agent confers cytotoxicity.

A century later, various classes of nanoscale “magic bullets” have been designed (nanoscale drug delivery systems or NDDS), some in development while others commercialized. Obviously, the truly revolutionary ones will be those that can specifically deliver therapeutics to target tissue and even specific cells or organelles. It should be noted that, technically, ADCs are NDDS. The NDDS that have already reached the marketplace have been approved by the FDA, EMA or foreign equivalent. Data from industry and the FDA shows that most of the approved or pending NDDS are oncology-related and based on protein-polymer conjugates or liposomes. The first FDA-approved nanotherapeutic was Doxil while Ambisome was the first one approved by EMA. It should be noted, however, that a nanoparticulate iron oxide intravenous solution in the market since the 1960s and certain nanoliposomal products approved in the 1950s and later should, in fact, be considered true first nanomedicines.

In October 2011, drug shortages were such a pressing issue in the US that an executive order from the President was issued directing the FDA to streamline the approval process for new therapeutics that could fill the voids. One of the major drugs whose supply was deficient in the US was Doxil, and to curb this shortage, the FDA authorized the temporary importation of Lipodox in February 2012. Following this, the FDA evaluated and approved the drug formulation within a year, roughly one-third of the time it takes for an average generic to receive premarket regulatory approval. As a result, Lipodox became the first generic nanodrug approved in the US.

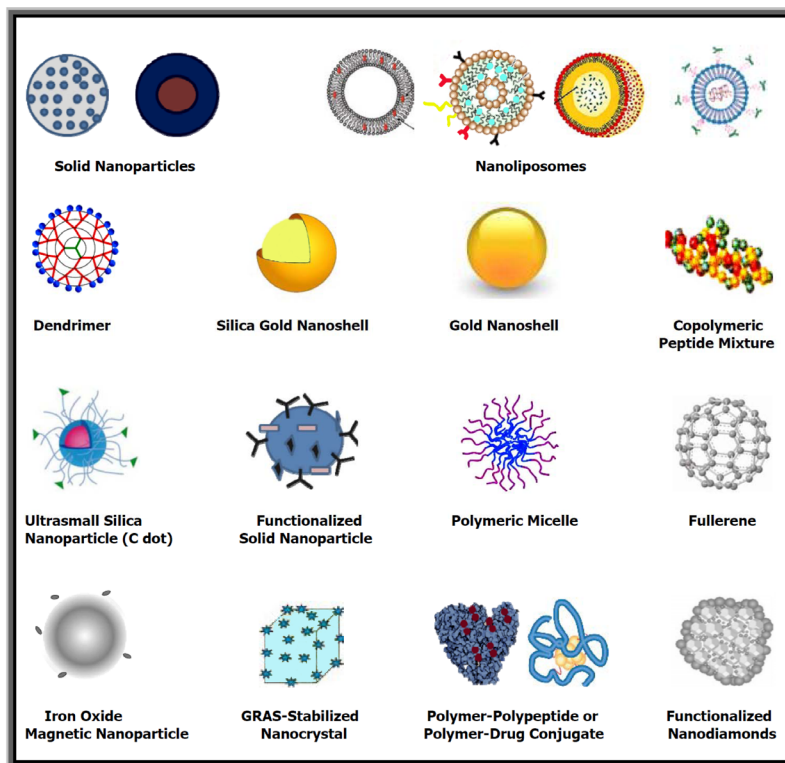


Figure 58.1 Schematic Illustrations of Nanoscale Drug Delivery System Platforms (Nanotherapeutics or Nanodrug Products). Shown are nanoparticles (NPs) used in drug delivery that are either approved, are in preclinical development or are in clinical trials. They are generally considered as first or second generation multifunctional engineered NPs, generally ranging in diameters from a few nanometers to a micron. Active biotargeting is frequently achieved by conjugating ligands (antibodies, peptides, aptamers, folate, hyaluronic acid) tagged to the NP surface via spacers or linkers like PEG, or by altering the NP surface characteristics. NPs such as carbon nanotubes and quantum dots, although extensively advertised for drug delivery, are specifically excluded from the figure as this author considers them commercially unfeasible for drug delivery. Non-engineered antibodies and naturally occurring NPs are also excluded. Antibody-drug conjugates (ADCs) are encompassed by the cartoon labelled “Polymer-Polypeptide or Polymer-Drug Conjugate.” This list of NPs is not meant to be exhaustive, the illustrations are not meant to reflect three dimensional shape or configuration and the NPs are not drawn to scale. Abbreviations: NPs: nanoparticles; PEG: polyethylene glycol; GRAS: Generally Recognized As Safe; C dot: Cornell dot; ADCs: Antibody-drug conjugates.

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58.2 Basic Science in the Era of Clinical Translation

In the past six decades, great strides have been made in basic science and research. This is obviously critical to any advanced society. However, the enormous medical advances that should have come from the large public and private investment in biomedical research have not translated into many clinical products. All stakeholders—pharma, patients, academia, regulators, patent offices, NIH—have suffered and are to blame for the so-called “valley of death” (Section 58.4). Each needs to re-examine its role and become an active, full partner in the biomedical ecosystem so that translational activities are more fruitful. Similarly, although great strides have been made in nanomedicine generally at the “science” level, especially with respect to drug delivery and nanoimaging, the field continues to be dogged by challenges and bottlenecks at the “translational” level. Barriers to nanomedicine commercialization persist (Table 58.1).

It is well established that moving basic scientific ideas to practice and health impacts is a long, expensive and challenging path. However, the relatively long time from discovery to clinical use and the relatively low proportion of discoveries that survived that journey is a problem. Given this, the aim of translational medicine (TM) or translational research is to take innovations developed within the research context into clinical practice. There is no denying that TM is the term of the moment (see Table 58.2). TM appears everywhere, from grants proposals to media to medical school curricula. But, what exactly is TM? Here is one definition [3]: *“Ask ten people what translational research means and you’re likely to get ten different answers. For basic researchers clutching a new prospective drug, it might involve medicinal chemistry along with the animal tests and reams of paperwork required to enter a first clinical trial. For groups wanting to develop diagnostics, imaging tools, or screening and prevention methods the route would be different...In some sense much translational research is just rebranding—clinical R&D by a different name. But it also involves investing in training, research and infrastructure to help researchers engage in clinical research—and cross the valley of death. Funding agencies hope that this will break down barriers in*

Table 58.1 Common Barriers to Nanomedicine Translation

Nomenclature and Terminology
imprecise definition for nanomedicines and related terms
lack of technical specifications, standards, guidelines, best practices and measurements regarding “nano”
different terms refer to identical nanomaterials and nanoparticles
failure of standard-setting organizations (ISO, ASTM, etc.) to produce technical specifications that clarify the issue
Manufacturing and Quality Control
issues pertaining to separation of undesirables (byproducts, catalysts, starting materials, etc.) during manufacturing
lack of precise control over nanoparticle/nanomaterial manufacturing parameters and control assays
many currently used compounds/components for synthesis pose problems for large scale current Good Manufacturing Practice (cGMP)
scalability complexities regarding enhancing production rate to increase yield
complexities and high fabrication costs of various nanomaterials, nanoparticles and nanomedicines
reproducibility issues like control of size distribution and mass
batch-to-batch variability
Toxicity
lack of <i>in vivo</i> knowledge regarding the interaction between nanomedical products and complex biosurfaces/tissues
lack of rational pre-clinical characterization strategies via multiple techniques
limited knowledge on biocompatibility and biodistribution of diverse nanomaterials and nanoparticles
limited prior experience with toxicity assessment of nanoscale therapeutics
mixed messages emanate from various federal agencies and transnational regulatory bodies regarding safety and toxicity issues on similar/identical nanomaterials and nanoparticles
unpredictable toxicity with respect to the diverse population of nanomaterials and nanoparticles
limited advanced tools, technologies and characterization efforts regarding nanomedical products providing potential clarity
adsorption, distribution, metabolism and excretion (ADME) studies regarding nanomedicines either lacking altogether or limited in scope
Consumer Confidence
public’s general reluctance to embrace innovative or emerging medical technologies without clearer safety or regulatory guidelines

perception that many nanoproducts are inherently unsafe

government and industry suspicion

media hype and misinformation not effectively countered by academia, government and industry

ethical challenges and societal issues not addressed by stakeholders

Funding Challenges

relative scarcity of venture funds due to the perception that most medical nanoproducts lack a good return on investment (ROI)

prolonged time scale is a detriment to funders and investors

funders and venture capitalists often not experienced or versed in technological aspects and cannot fully gauge potential for translation

barriers more steep for nanomedicine with respect to procuring funds to initiate a first-in-human (FIH) clinical trial

big pharma's continued reluctance to seriously invest in nanomedicine, specially early-stage preclinical research lacking "proof-of-concept" in man

lack of industry support limits potential to reach FIH clinical trials in any research setting (academic, start-up, small company, etc.)

due diligence and peer review regarding translational potential of projects or research proposals often lacking while projects being funded

Clinical Research and Trials

cost, time and effort required for clinical trials is a deterrent

general lack of knowledge about the FDA drug or device review process and limited understanding of the various aspects of FDA law

challenges in patient recruitment is more acute in nanomedicine due to factors like strict inclusion/exclusion criterion and delay by ethics committees

lack of consensus on the different procedures, assays and protocols to be employed during pre-clinical development and characterization of nanomedicines; this can also impact clinical trial design

Patents and Intellectual Property

patent review delays, spotty examination and access to relevant "prior art" at patent offices

issuance of invalid patents or patents of unduly broad legal scope by patent offices

emerging patent thickets due to a "patent prospector" mentality

a general lack of understanding of the patent process by stakeholders

limited knowledge regarding the basics of intellectual property law in academic circles

(Continued)

Table 58.1 (Continued)

Support for Small Businesses and Start-ups
few unique financial incentives favoring longer-term nanomedicine investments
limited tax-free bonds for financing, tax credits for capital investments, reduced capital gains tax rates, investment-specific loan guarantees, etc.
lack of mentorship and business planning assistance
little assistance in attracting private and public funds
the Small Business Innovation Research (SBIR) process in the US is more focused on research and less on commercialization
lack of centralized audit system from the federal government is costly and slows down work at small businesses
more nano tools needed in academia and small businesses
Academia and the University Professor
overhyped press releases from eminent university labs
professors behaves more like “celebrity-politicians” than basic researchers
research often focused on poorly characterized and non-biodegradable nanomaterial-based platforms
fancy animations on lab websites exaggerate preclinical data and clinical partnerships with pharma project false hope of translational potential
irreproducibility of basic, preclinical research at universities
awards and research activities that generate publications (<i>l’art pour l’art</i>) rather than patents are valued
focus is often on impact factors and attending conferences
focus is on research and publications rather than commercialization; some academics even shun commercialization
inability or lack of willingness to conform to translational activities; few incentives for translational activities compound the problem
lack of coherent technology transfer policy from universities to startups
lack of communication between clinical researchers and basic scientists
evidence of clinical validity and clinical utility is often lacking
lack of interdisciplinary research; lack of a collaborative spirit between industry and academia or between clinical and basic science researchers
a deficit in cross-disciplinary or hybrid scientific training at educational institutions
Regulatory Uncertainty
confusion due to “baby steps” undertaken by federal regulatory bodies like the FDA and EMA

a lack of clear regulatory or safety guidelines

governmental regulatory bodies lack technical and scientific knowledge to support risk-based regulation, thereby leaving a significant regulatory void

issuance of too many nonbinding “draft” guidance documents by the FDA and “position papers” by EMA to make substantive policy changes

product classification issues blur the regulatory boundaries between various product classes given that many are multimodal hybrid structures

precautionary stance by regulatory agencies reflects their lack of expertise and experience with nanoscale formulations

national differences in regulatory requirements pose challenges for clinical trials involving international multicenters

bureaucracy and a conservative, insular attitude among government regulators hinders translation

rise of diverse nano-specific regulatory arrangements and systems contribute to a dense global nanoregulatory landscape, full of gaps and devoid of central coordination

Technology Transfer Offices (TTOs)

TTOs at universities and institutes lack in-depth technical and business expertise

decisions made in a vacuum or on imperfect analysis and there are no informed gatekeepers to do valuation or proper audit of “true” licensing royalties

issues like insular nature and high employee turnover indirectly impedes translation

Other

key technology benefits not identified early on in product development or research project

limited infrastructure that becomes outdated quickly due to advances in technology

relative scarcity of workers trained for product development; need for foreign workers poses problems

crisis of reproducibility in antibody performance due to shortcuts taken by manufacturers and researchers

quality assurance (QA) guidelines for basic research lacking or not properly implemented

plans lack ability for tracing data, including which equipment the experiment was conducted on and where the source data is stored

the transformation of basic-science breakthroughs into clinical applications ('bench to bedside') and enable more research on human subjects and samples to generate hypotheses that are more relevant to people than to animal models..." The European Society for Translational Medicine [4] defines "TM as an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and community. The goal of TM is to combine disciplines, resources, expertise, and techniques within these pillars to promote enhancements in prevention, diagnosis, and therapies. Accordingly, TM is a highly interdisciplinary field, the primary goal of which is to coalesce assets of various natures within the individual pillars in order to improve the global healthcare system significantly." TM invariably involves multidisciplinary, collaboration and networking along with novel models, modes of communication and regulatory systems—all features being the hallmark of nanomedicine. The National Institutes of Health (NIH) has made TM a central piece of its so-called "NIH Roadmap for Medical Research" [5a] while the FDA launched a similar "Critical Path Initiative" to address the growing crisis in moving basic discoveries to the market where they can be available to patients [5b]. Both of these governmental initiatives were launched in 2004 with a lot of fanfare. However, in the decade since then, these bureaucracies have little to show for with respect to dramatically improving the availability of new diagnostic/therapeutic modalities due to their inability in addressing key blocks in translational research.

In summary, translational medicine focuses on facilitating the transition of preclinical or basic research into clinical or medical application, generally via a faster, easier, cheaper and more efficient route. This allows realizing the social value of science, i.e., the production of medical products, applications and methods that help improve human health. The primary impetus for TM is that there are better ways to move preclinical biomedical research to medical practice more quickly without sacrificing quality or increasing costs. However, in spite of significant investments by the public and private sectors, major issues that led to the emergence of TM in the first place have continued to dog TM and persist along the research-practice continuum (Table 58.1).

Table 58.2 Key Terms Related to Translational Medicine

Basic Research
Basic research involves scientific exploration that can reveal fundamental mechanisms of biology, disease or behavior. Every stage of the translational research spectrum builds upon and informs basic research.
Pre-Clinical Research
Pre-clinical research connects basic science and human medicine. During this stage, scientists apply fundamental discoveries made in the laboratory or the clinic to further understand the basis of a disease or disorder and find ways to treat it. Hypothesis testing is carried out using cell or animal models; samples of human or animal tissues; or computer-assisted simulations of drug, device or diagnostic interactions within living systems.
Clinical Research
Clinical research includes clinical trials with human subjects to test intervention safety and effectiveness, behavioral and observational studies, outcomes and health services research, and the testing and refinement of new technologies. The goal of many clinical trials is to obtain regulatory approval for an intervention.
Clinical Implementation
The clinical implementation stage of translation involves the adoption of interventions into routine clinical care for the general population. This stage also includes implementation research to evaluate clinical trial results and identify new clinical questions and gaps in care.
Public Health
In this stage of translation, researchers study health outcomes at the population level to determine the effects of diseases and efforts to prevent, diagnose and treat them. Findings help guide scientists working to improve interventions or develop new ones.
Translation
This is the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public — from diagnostics and therapeutics to medical procedures and behavioral changes.
Translational Science
This is the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process.

Courtesy of the National Center for Advancing Translational Sciences, NIH.

As mentioned above, in pharma, translational research involves the many elements that contribute to the successful conversion of an idea into a drug. Translation of drug products is a challenge faced by pharma at various levels. Bridging the chasm between *drug discovery research activities* and the *successful translation of a drug to the market* is a daunting task that requires varying degree of participation from key players—pharma, academia, nonprofit and for-profit institutions, federal agencies and regulatory bodies (FDA, NIH, EMA, Patent Offices), diseases foundations and patients. The growth of translational research, in general, has coincided with an ever-changing drug development landscape. For example, unlike in past decades, numerous other stakeholders who play a vital role in the drug discovery and development process—biopharma, start-ups, academic institutions and venture firms—surround big pharma. In the distant past, big pharma had carried the torch alone: It had been the sole source of inventing, manufacturing and distributing new drugs. In the decades that followed, the large, unwieldy companies could no longer rely solely on their own internal ideas for innovation and had to compete with more than just a few other pharma companies. More recently, as the boundaries between big pharma and biotech companies have further blurred,⁷ big pharma has adapted its operational strategy, employing outside collaborations with respect to research, technology, workforce and marketing. Obviously, big pharma's evolving role has resulted partly from the "biotech boom," and the "genomics boom," where enormous advances resulted from molecular biology and DNA technology, but also from advances in information and computer technology. In addition, two important pieces of legislation have had a major

⁷The demarcations between pharmaceutical and biotechnology companies (and between branded and generics) are no longer that clear. For example, Genentech (owned by Roche) and Medimmune (owned by AstraZeneca), although operate independently, are technically part of big pharma. Many biotechs are developing therapeutics that are traditional small molecule drugs rather than biotech products. Conversely, big pharma is developing biotech products along with traditional small molecules. Furthermore, often, branded companies are developing generics and *vice versa*. Currently, there is a symbiotic relationship between all these diverse players. For example, pharma (which is well versed in clinical trials and commercialization expertise) frequently turns to biotech companies (which are generally low on funds, lack a robust sales force or lack regulatory expertise) to license compounds or to develop platform technologies with the promise to yield multiple molecules.

impact on the drug industry in the US: (a) the Bayh-Dole (or Patent and Trademark Law Amendments) Act of 1980, which allowed universities, hospitals, nonprofit organizations and small businesses to patent and retain ownership arising from federally funded research [6]⁸; and (b) the Hatch-Waxman (or Drug Price Competition and Patent Term Restoration) Act of 1984, that defined patent exclusivity for both generic and brand name drugs [7].

58.3 Chaos in Academia: Irreproducible Preclinical Research

There is a problem in the research world. And, it is no longer a silent crisis. The rush to celebrate “eureka” moments is overshadowing a rather mundane activity on which the science enterprise deeply depends: reproducibility. Some blame the current pervasive culture of science that focuses on rewarding eye-catching and positive findings. Others point to an increased emphasis on making provocative statements rather than presenting technical details or reporting basic elements of experimental design. While these may be some of the factors that have resulted in major bodies of biomedical knowledge that cannot be reproduced, data irreproducibility is a serious concern for the research enterprise in general. The battle for the soul of science is on. However, there is no evidence to suggest that irreproducibility is caused by scientific misconduct [8].

⁸Also see: Fang, F. C., Casadevall, A. (2010). Lost in Translation—Basic science in the era of translational research. *Infect. Immun.*, **78**(2), 563–566: “The consensus forged after the Second World War that basic and applied research were the domains of academia and industry, respectively, began to fade in the 1980s when the Bayh-Dole act allowed universities to patent knowledge obtained with federal funding. Universities ascertained that certain discoveries were enormously lucrative, and academic scientists began to emerge in a new role: that of the discoverer-entrepreneur. Within a decade, all major universities developed offices specializing in intellectual property to promote the protection and commercialization of scientific discoveries. Whatever the merits of this approach, one outcome was the blurring of the intellectual boundaries between academia and industry. Hence, scientists that formerly worked solely on basic biological mechanisms found greater freedom to develop their research along more practical lines, with the encouragement of their institutions. Furthermore, universities learned that it was much easier to connect with the public as well as with potential benefactors by highlighting their translational advances rather than their basic science discoveries. Translational research generated revenue, brought publicity, and enhanced public relations. In the evolving zeitgeist, academia is no longer viewed as an impartial champion for basic research.”

This widespread reproducibility crisis is seen in all disciplines of biomedical research [9–11].⁹ It appears that even the NIH is concerned and plans significant interventions to enhance preclinical reproducibility [8].¹⁰ The area most susceptible pertains to work that employs animal models [9]. Various proposals and recommendations, including crowd-sourced analysis of research [12], are being considered as viable options to stem this tide of irreproducible biomedical research.

Frankly, research institution administrators, faculty members and trainees all share blame. They must do far more for reproducibility of biomedical research data [13]:

Irreproducible research poses an enormous burden: it delays treatments, wastes patients' and scientists' time, and squanders billions of research dollars. It is also widespread. An unpublished 2015

⁹Baker, M. (2016). Quality time. *Nature*, **529**, 456–458: “Scientific rigour has taken a drubbing in the past few years, with reports that fewer than one-third of biomedical papers can be reproduced (see *Nature* <http://doi.org/477>; 2015). Scientific culture, training and incentives have all been blamed for promoting sloppy work; a common refrain is that the status quo values publication counts over careful experimentation and documentation.”

Bertuzzi, S. The sensational vs. the useful in the quest for reproducibility in research. American Society for Cell Biology, Available at: <http://www.ascb.org/the-sensational-vs-the-useful-in-the-quest-for-reproducibility-in-research/> (accessed on January 18, 2016): “A core concept in scientific research is that empirical results must be replicable. This concept dates back to the birth of the experimental method itself. The *Accademia del Cimento* (Academy of Experiment) was founded in Florence in 1657 by Galileo's students and it published the first manual of scientific experimentation, a guide for data collection and methodological standardization. The society's motto was *provando e riprovando* (trying and trying again), emphasizing the importance of replication of scientific experiments. Fast forward to the present day where scientific discovery proceeds at an impressive pace and yet we find that in many instances research findings cannot be replicated. The causes for the lack of replication have been examined, revealing a complex scenario with multiple determinants ranging from sheer sloppiness (which is inexcusable) to the almost Twitter-length restrictions imposed on the materials and methods sections of many glamorous journals. Other culprits implicated include selection bias in publishing only positive results and the hypercompetitive quest for scientific discoveries that forces scientists toward sensationalism in presenting their results. It is important to note here that I am not talking about fraud. That is a wholly different issue.”

¹⁰From [8]: “However, human clinical trials seem to be less at risk because they are already governed by various regulations that stipulate rigorous design and independent oversight including randomization, blinding, power estimates, pre-registration of outcome measures in standardized, public databases such as *ClinicalTrials.gov* and oversight by institutional review boards and data safety monitoring boards. Furthermore, the clinical trials community has taken important steps towards adopting standard reporting elements...”

survey by the American Society for Cell Biology found that more than two-thirds of respondents had on at least one occasion been unable to reproduce published results. Biomedical researchers from drug companies have reported that one-quarter or fewer of high-profile papers are reproducible. Many parties are addressing the problem. Funding bodies such as the US National Institutes of Health (NIH) have announced training initiatives and explicitly instructed grant reviewers to consider whether experimental plans ensure rigor. New methods of data analysis and peer review have been proposed to deflate bias. Several journals, including *Nature* and *Science*, have updated their guidelines and introduced checklists. These ask scientists whether they followed practices such as randomizing, blinding and calculating appropriate sample size. *Science* has also added statisticians to its panel of reviewing editors. Philanthropic and non-profit organizations have sponsored projects to improve robustness. Funders' policies, journal guidelines and widespread soul-searching are necessary. But they are not sufficient. Conspicuous by their absence from these efforts are the places in which science is done: universities, hospitals, government-supported labs and independent research institutes. This has to change. Institutions must support and reward researchers who do solid—not just flashy—science and hold to account those whose methods are questionable...Although researchers want to produce work of long-term value, multiple pressures and prejudices discourage good scientific practices. In many laboratories, the incentives to be first can be stronger than the incentives to be right...Data-dredging is used to find statistically significant results that justify a publication. Sound practices such as blinding, multiple repeats, validated reagents and appropriate controls are dismissed as luxuries or nuisances... Research institutions contribute to and benefit from these perverse incentives. They bathe in the reflected glory of their faculty; they trumpet breakthroughs published in top-tier journals, lauding achievements to the media and donors. Some even pay investigators for publications. Many require that investigators generate their salary from research grants...few institutions have strong, transparent processes in place to discourage poor-quality science or to foster objectivity... The scientific community should come up with a similar system for research, which we term good institutional practice (GIP). If funding depended on a certified record of compliance with GIP, robust research would get due recognition... The systems needed to promote reproducible research must come from institutions—scientists, funders and journals cannot build them on their own... Still, most institutions will not make the

necessary moves unless forced. Funding bodies should make GIP a prerequisite for receiving a grant... (citations omitted)

In the past, drug-screening was mainly performed at pharma and supported internally by outstanding teams of chemists. Over the years, there has been a growing reliance on academia for this upstream drug R&D.¹¹ In fact, this collaborative innovation between pharma and the academic community is credited with producing key enabling discoveries underlying many marketed blockbusters. Today, preclinical drug discovery research is still primarily conducted and managed by pharma. But, academia now contributes to this effort by conducting basic research into fundamental and mechanistic aspects of human disease biology and discovery of targets whose modulation could have therapeutic potential. The resultant “gold nuggets” that are thus generated by academia are then selected by pharma to discover and develop drugs that modulate those targets, thereby driving the drug discovery engine (though no longer *roaring* as in the past).

However, this common arrangement is in trouble and the collaborative paradigm is breaking down because of irreproducibility of basic research at universities [14]: *“Much of the innovation landscape involves breakthroughs made in academia—but much of the research published in academia has proven not to be reproducible in pharma companies’ hands.”* Basically, academic target discovery research reproducibility has become suspect [9, 15]. Some of the reasons for this crisis are inherent to the two entities. Academia and drug industry have differing expertise and incentives with respect to drug discovery targets, lead discovery programs, hit discovery, lead optimization strategies, interpretation of complex data and production of high quality probes. The mission and focus of academia versus the drug industry is distinct, though overlapping in a few areas. Academics are obligated to educate students, create and disseminate

¹¹Academia is increasingly involved in upstream drug development as is evident from the formation of the international, non-profit, Academic Drug Discovery Consortium (ADDC) in 2012 whose goal is *“to build a collaborative network among the growing number of university-led drug discovery centers and programs.”* The ADDC currently has 141 academic centers as members with most interested in translating targets towards conventional small molecules or biologics. See: Academic Drug Discovery Consortium. Available at: <http://addconsortium.org/> (accessed on March 3, 2016).

knowledge, obtain grants and live by the “publish-or-perish” mantra to succeed. For industry, the focus is on cutting-edge research that translates clinically into effective products to the marketplace, justifying their R&D costs to their shareholders, obtaining a substantial return on investments and competitive expansion of the start-of-the-art. Obviously, pharma is more in tune with issues like trade secrets, intellectual property strategy, filing patent applications, drafting license agreements, engaging in litigation and pursuing commercialization.

Another important factor for the failed marriage between academia and industry with respect to drug R&D is the absence of outstanding support structure from academic drug researchers who are typically not trained to separate “hits” into compounds good, bad and ugly [16]. Many contend that, as a result, naivety about promiscuous, assay-duping molecules is polluting the literature and wasting resources [17]:

Academic researchers, drawn into drug discovery without appropriate guidance, are doing muddled science. When biologists identify a protein that contributes to disease, they hunt for chemical compounds that bind to the protein and affect its activity. A typical assay screens many thousands of chemicals. ‘Hits’ become tools for studying the disease, as well as starting points in the hunt for treatments. But many hits are artefacts—their activity does not depend on a specific, drug-like interaction between molecule and protein. A true drug inhibits or activates a protein by fitting into a binding site on the protein. Artefacts have subversive reactivity that masquerades as drug-like binding and yields false signals across a variety of assays...These molecules—pan-assay interference compounds, or PAINS—have defined structures, covering several classes of compound...But biologists and inexperienced chemists rarely recognize them. Instead, such compounds are reported as having promising activity against a wide variety of proteins. Time and research money are consequently wasted in attempts to optimize the activity of these compounds. Chemists make multiple analogues of apparent hits hoping to improve the ‘fit’ between protein and compound. Meanwhile, true hits with real potential are neglected. Publications falsely revalidate molecules as good drug leads and feed Sisyphean cycles of ‘screen, publish, flounder’. Chemical companies include these artefacts in their sales catalogues as published protein inhibitors, and other biologists start using them in their own studies...

It is also worth highlighting here that shortcuts taken by antibody manufacturers and researchers alike have resulted in a crisis of reproducibility in antibody performance, thereby contributing to the reproducibility crisis in biomedical research [18, 19]. Obviously, this greatly affects preclinical research, including identification of drug targets [19]:

Antibodies are among the most commonly used tools in the biological sciences—put to work in many experiments to identify and isolate other molecules. But it is now clear that they are among the most common causes of problems, too. The batch-to-batch variability... can produce dramatically differing results. Even more problematic is that antibodies often recognize extra proteins in addition to the ones they are sold to detect. This can cause projects to be abandoned, and waste time, money and samples. Many think that antibodies are a major driver of what has been deemed a 'reproducibility crisis', a growing realization that the results of many biomedical experiments cannot be reproduced and that the conclusions based on them may be unfounded. Poorly characterized antibodies probably contribute more to the problem than any other laboratory tool... Researchers ideally should check that an antibody has been tested for use in particular applications and tissue types, but the quality of information supplied by vendors can vary tremendously. A common complaint from scientists is that companies do not provide the data required to evaluate a given antibody's specificity or its lot-to-lot variability. Companies might ship a batch of antibodies with characterization information derived from a previous batch. And the data are often derived under ideal conditions that do not reflect typical experiments... Many academics use Google to find products, so optimizing search results can sometimes matter more to a company than optimizing the actual reagents...

This discontent has spurred action, with advanced technologies and characterization efforts promising clarity [20]. In the meantime, it may be best that researchers hold back using commercial antibodies rather than further muddy up preclinical research data with the subsequent negative consequences for translational medicine.

Unfortunately, the reproducibility crisis has coincided with major changes in pharma's productivity¹² as numerous market

¹²Falling productivity is often defined as the cost per new molecular entity (NME) and is often due to drawbacks with methods for target discovery and validation, project scrutiny, data evaluation, pharma internal decisions at key junctures (such as "go-or-no-go" decisions) and internal reward systems (such as monetary awards for number of patents).

forces and drivers have continued to dictate a change in its quest for discovering, developing and delivering novel therapeutics. These include downsizing, mergers and acquisitions (M&A),¹³ revenue losses due to patent expirations on blockbusters, enhanced regulatory oversight, high cost of clinical trials, ANDA challenges from generic manufacturers,¹⁴ and relative scarcity of novel new chemical entities (NCEs) due to an innovation crisis. In the process, these forces are altering the drug landscape and affecting healthcare delivery. All of this is cause for concern. Clearly, new ground rules, flexible business models, strategic collaborative partnerships and competitive business strategies

¹³Today's pharma landscape is the result of the "era of mergers" in the 1990s when numerous consolidations in big pharma took place: (i) Bristol-Myers merged with the Squibb Corporation forming Bristol-Myers Squibb Co. (1989); (ii) SmithKline Beckman and The Beecham Group plc merged to form SmithKline Beecham plc (1989), which in turn merged with Glaxo Wellcome plc to form GlaxoSmith Kline plc or GSK (2000); (iii) Ciba-Geigy Ltd. merged with Sandoz Ltd. to form Novartis AG (1996); (iv) Sweden-based Astra AB merged with the UK-based Zeneca group to form Astra Zeneca plc or AZ (1999); (v) Pharmacia & Upjohn, Inc. merged with Monsanto Co. to form Pharmacia Corp. (1999) (its agricultural chemical division was spun off in 2000 under the name Monsanto). In November 2015, US-based Pfizer Inc. and Ireland-based Allergan PLC (which previously merged with Actavis) announced they would merge in a massive, \$155 billion deal that will create the world's largest drugmaker called Pfizer plc via an "inversion," where US companies are bought by or merge with foreign firms in order to reduce US corporate tax burdens. According to Pfizer, the combined company would generate more than \$2 billion in savings over the first three years and would enjoy a tax rate of 17–18% that is far less than Pfizer's current corporate tax rate of roughly 25% because corporate taxes in Ireland are lower than in the US. Also, see: U.S. unveils rules to make corporate inversions more difficult. *The Wall Street Journal*. Available at: <http://www.wsj.com/articles/u-s-unveils-rules-to-make-corporate-inversions-more-difficult-1447970935> (accessed on January 20, 2016).

In addition, numerous pharma companies took the acquisition route: (i) Pfizer Inc. acquired Warner-Lambert Co. (2000), Pharmacia Corp. (2003) and Wyeth (2009); (ii) Sanofi-Synthelabo S.A. (Sanofi since 2011) acquired Aventis S.A. (2004); (iii) Bayer AG acquired Schering AG (2006); (iv) Merck & Co. Inc. acquired Schering-Plough Corp. (2009).

¹⁴For example, in 2012 alone, branded drugs valued at over \$30 billion lost patent protection. A recent report from London-based GlobalData predicts that the drug industry will lose roughly \$65 billion in revenue through the end of 2019. See: Drug makers face another \$65 billion patent cliff. Available at: <http://www.marketwatch.com/story/drug-makers-face-another-65-billion-patent-cliff-2014-12-10> (accessed on January 20, 2016).

are in order in this post-blockbuster era. In fact, pharma is frequently turning to high throughput screening¹⁵ and miniaturization technologies like “nano” to enhance or supplement aspects of drug target discovery and drug development. Also, in spite of pharma’s strategy of M&A, in-licensing and an enormous capital investment in R&D, the pharmaceutical industry has been unsuccessful in replacing drugs coming off patent with sufficient new molecular entities (NMEs)¹⁶ and the number of

¹⁵High (or ultra-high) throughput screening technologies often favor the selection of drug candidates with higher lipophilicity. As a result, the drug formulation specialist is often faced with challenges developing a variety of drug products that are poorly water-soluble. In fact, there are few ultimate solutions, in spite of advertisements of a variety of unique excipients, methods and technologies (including encapsulation techniques).

¹⁶See: New drugs at FDA: CDER’s New Molecular Entities and New Therapeutic Biological Products. Available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM481709.pdf> (accessed on January 20, 2016). *“Each year, CDER approves hundreds of new medications, most of which are variations of previously existing products, such as important new dosage forms of already-approved products, or cost-saving generic formulations... Novel drugs are often innovative products that serve previously unmet medical needs or otherwise significantly help to advance patient care and public health. NMEs have chemical structures that have never been approved before. However, in some cases an NME may have actions similar to earlier drugs and may not necessarily offer unique clinical advantages over existing therapies...In rare instances, it may be necessary for FDA to change a drug’s new molecular entity (NME) designation or the status of its application as a novel new biologics license application (BLA). For instance, new information may become available which could lead to a reconsideration of the original designation or status. If changes must be made to a drug’s designation or the status of an application as a novel BLA, the Agency intends to communicate the nature of, and the reason for, any revisions as appropriate.”*

According to the FDA code, certain drugs are classified as NMEs for purposes of FDA review. Many of these products contain active moieties that have not been approved by FDA previously, either as a single ingredient drug or as part of a combination product. Some drugs are characterized as NMEs for administrative purposes, but nonetheless contain active moieties that are closely related to active moieties in products that have been previously approved by the FDA. For example, CDER classifies biological products submitted in an application under section 351(a) of the Public Health Service Act as NMEs for purposes of FDA review, regardless of whether the FDA previously has approved a related active moiety in a different product. Note that the FDA’s classification of a drug as an NME for review purposes is distinct from FDA’s determination of whether a drug product is a “new chemical entity (NCE)” within the meaning of the Federal Food, Drug, and

NMEs reaching the market have not increased in any dramatic way in the past decade (Fig. 58.2). For the past two years in a row, the FDA drug approvals set new records as far as the number of drugs approved. Although 2015 marks a 19-year high in total drugs approved (45) by FDA's CDER, according to Boston Consulting Group (BCG), the commercial potential is not stellar: The average peak sales forecast for a 2015 approval is \$900 million compared to \$1.4 billion in 2014. Surprisingly, the regulatory rejection rates at the FDA were at an all-time low in 2015: Only two complete letters that denied drug approvals were issued by CDER by November-end. Based on this, it is hard for these authors not to ask the FDA the obvious: Has the FDA lowered its regulatory approval standards, or does this low rejection rate simply indicate better submissions from drug sponsors? Also, from our perspective, the bounty of drugs approved in 2015 are more impressive in their steep price tags and rapid approval rate than their quality of therapy.

Cosmetic Act. According to the Code of Federal Regulations, Title 21 (April 2015), an "active moiety" means *"the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance."* See: New chemical entity. Available at: https://en.wikipedia.org/wiki/New_chemical_entity (accessed on December 1, 2015): *"An NCE is a molecule developed by the innovator company in the early drug discovery stage, which after undergoing clinical trials could translate into a drug that could be a cure for some disease. Synthesis of an NCE is the first step in the process of drug development. Once the synthesis of the NCE has been completed, companies have two options before them. They can either go for clinical trials on their own or license the NCE to another company. In the latter option, companies can avoid the expensive and lengthy process of clinical trials, as the licensee company would be conducting further clinical trials and subsequently launching the drug. Companies adopting this model of business would be able to generate high margins as they get a huge one-time payment for the NCE apart from entering into a revenue sharing agreement with the licensee company. Under the Food and Drug Administration Amendments Act of 2007, all new chemical entities must first be reviewed by an advisory committee before FDA can approve these products."*

Also, see: Branch, S. K., Agranat, I. (2014). "New Drug" designations for new therapeutic entities: New active substance, new chemical entity, new biological entity, new molecular entity. *J. Med. Chem.*, **57**(21), 8729–8765.

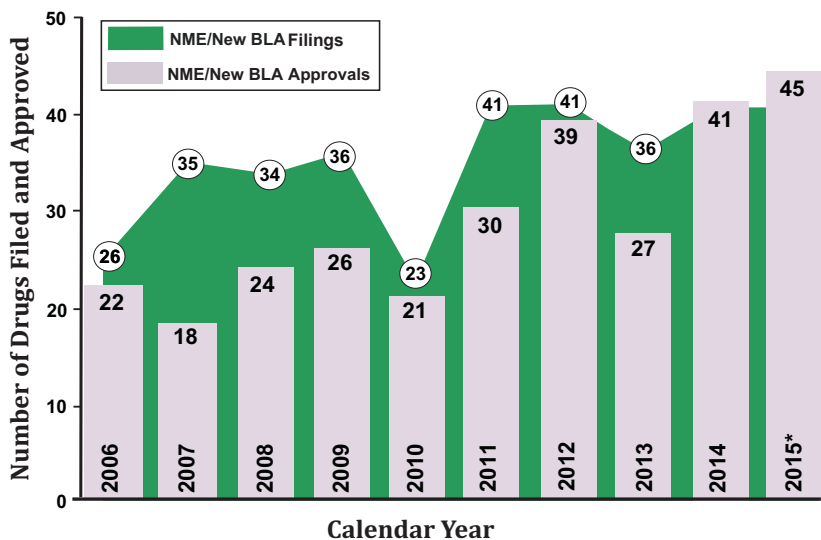


Figure 58.2 Ten Year Historic Comparison of Drug Approvals by FDA's Center for Drug Evaluation and Research (CDER). New drugs approved by the FDA have risen sharply in recent years with the 2015 bounty being the most productive since 1996. However, in 2015 big innovations were in short supply, rejection letters issued by the FDA were surprisingly down, and few drugs stood out as breakthroughs. In fact, many products were more known for their breathtaking price tags and rapidity of approval. The gray vertical bars indicate the number of novel drugs approved by CDER in each year of the past decade. CDER approved 45 novel drugs in 2015 (new molecular entities (NMEs) and new biologic license applications (BLAs)), up from the previous recent record in 2014 of 41 drugs approved. Of these, 10 (22%) represented breakthrough-designated drugs, 14 (31%) were cancer drugs, about 30% were biologics, 21 (47%) were orphan-designated drugs, and 16 were drugs with a novel mechanism of action. From 2006 through 2014, CDER has averaged about 28 novel drug approvals per year. The green portion of the graph with the circled numbers indicates the number of new NDAs for NMEs plus BLAs for new therapeutic biologics received by CDER for approval during the last 10 years. Note that approvals by the Center for Biologics Evaluation and Research (CBER) are excluded in this drug count. The data in this figure are current as of December 31, 2015.

*The 2015 filed numbers include those filed in calendar year 2015 plus those currently pending filing (i.e., within their 60-day filing period) in calendar year 2015. Data courtesy of Drugs@FDA, the FDA and various drug companies.

58.4 Overcoming the Valley of Death in Drug Commercialization

Although chemistry, molecular and cellular biology, omics and related technologies have come a long way in the past 70–75 years, searching for novel drugs and testing candidates remains an elusive task. Drug development is time-consuming, expensive and enormously challenging.¹⁷ *De novo* drug discovery and development is often a 10–17-year process from idea to marketed drug. It may take up to a decade just for a drug candidate to enter clinical trials with less than 10% of the tested candidates in trials arriving in the clinic (Fig. 58.3a, Fig. 58.3b and Table 58.3). In fact, more drugs come off patent each year than approved by the FDA. According to a 2014 study by the Tufts Center for the Study of Drug Development, developing a new prescription medicine that gains marketing approval is estimated to cost nearly \$2.6 billion.¹⁸

¹⁷See: Bruno, J. R. (2015). Improving the bio-availability of drugs through their chemistry. *Am. Pharm. Rev.*, **15**(4), 34–39: “The development of new drugs is a complex process that requires a multiple of scientific disciplines. As drugs become even more complex, the ability of companies to get products to market has become even more difficult. Today, many potential drugs can fail early during the development process. Inherent in the complexity of the molecules is low solubility and poor bio-availability. While clinically they appear to be good targets, the inability to get them into the body destines them to failure. In addition, with the cost of drug development escalating, companies are often forced to drop products quickly in favor of potentially more active compounds.”

¹⁸See: Tufts Center for the Study of Drug Development. Available at: http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study (accessed on January 12, 2016): “The \$2,558 million figure per approved compound is based on estimated average out-of-pocket cost of \$1,395 million and time costs (expected returns that investors forego while a drug is in development) of \$1,163 million. Estimated average cost of post-approval R&D—studies to test new indications, new formulations, new dosage strengths and regimens, and to monitor safety and long-term side effects in patients required by the U.S. Food and Drug Administration as a condition of approval—of \$312 million boosts the full product lifecycle cost per approved drug to \$2,870 million. All figures are expressed in 2013 dollars. The new analysis, which updates similar Tufts CSDD analyses, was developed from information provided by 10 pharmaceutical companies on 106 randomly selected drugs that were first tested in human subjects anywhere in the world from 1995 to 2007. “Drug development remains a costly undertaking despite ongoing efforts across the full spectrum of pharmaceutical and biotech companies to rein in growing R&D costs,” said Joseph A. DiMasi, director of economic analysis at Tufts CSDD and principal investigator for the study. He added, “Because the R&D process is marked by substantial technical risks, with expenditures incurred for many development projects that fail to result in a marketed product, our estimate links the costs of unsuccessful projects to those that are successful in

Alternatives to this lengthy and expensive pathway have been proposed. For example, drug repositioning [21–22] offers the possibility of reduced time and risk as several phases common to drug R&D can be bypassed by repositioning candidates that have been through several phases of development for their original indication. Alternatively, more drug companies are reassessing their failed candidates in an effort to alter/increase their solubility and dissolution rates to improve overall bioavailability via tweaking chemistry or reformulating.

Regardless of the industry or the origin of technology, for a product to become successful it must endure and traverse a most difficult period in its lifetime, the so-called “valley of death” (Fig. 58.4).¹⁹ It is a graveyard for many “good” scientific ideas, technologies, new products and processes, representing the transition from basic research activities to product development.

obtaining marketing approval from regulatory authorities.” In a study published in 2003, Tufts CSDD estimated the cost per approved new drug to be \$802 million (in 2000 dollars) for drugs first tested in human subjects from 1983 to 1994, based on average out-of-pocket costs of \$403 million and capital costs of \$401 million. The \$802 million, equal to \$1,044 million in 2013 dollars, indicates that the cost to develop and win marketing approval for a new drug has increased by 145% between the two study periods, or at a compound annual growth rate of 8.5%. According to DiMasi, rising drug development costs have been driven mainly by increases in out-of-pocket costs for individual drugs and higher failure rates for drugs tested in human subjects. Factors that likely have boosted out-of-pocket clinical costs include increased clinical trial complexity, larger clinical trial sizes, higher cost of inputs from the medical sector used for development, greater focus on targeting chronic and degenerative diseases, changes in protocol design to include efforts to gather health technology assessment information, and testing on comparator drugs to accommodate payer demands for comparative effectiveness data. Lengthening development and approval times were not responsible for driving up development costs, according to DiMasi. “In fact,” DiMasi said, “changes in the overall time profile for development and regulatory approval phases had a modest moderating effect on the increase in R&D costs. As a result, the time cost share of total cost declined from approximately 50% in previous studies to 45% for this study.”

Also see: A billion here, a billion there: The cost of making a drug revisited. Available at: <http://www.forbes.com/sites/brucebooth/2014/11/21/a-billion-here-a-billion-there-the-cost-of-making-a-drug-revisited/> (accessed on January 21, 2016).

¹⁹The “valleys of death” model has replaced the old paradigms of B² (“bench to bedside”) and C³ (“cell to clinic to community”). The NIH has proposed one valley (basic science vs. clinical science) while the Canadian Institutes of Health Research has proposed two valleys (between basic biomedical research vs. clinical science vs. clinical practice and health decision making). A four-valley model has also been proposed (between discovery vs. candidate health vs. evidence based guidelines vs. health practice vs. population health impact). See: Meslin, E. M. (2007). *Genet. Med.*, 9, 665–674.

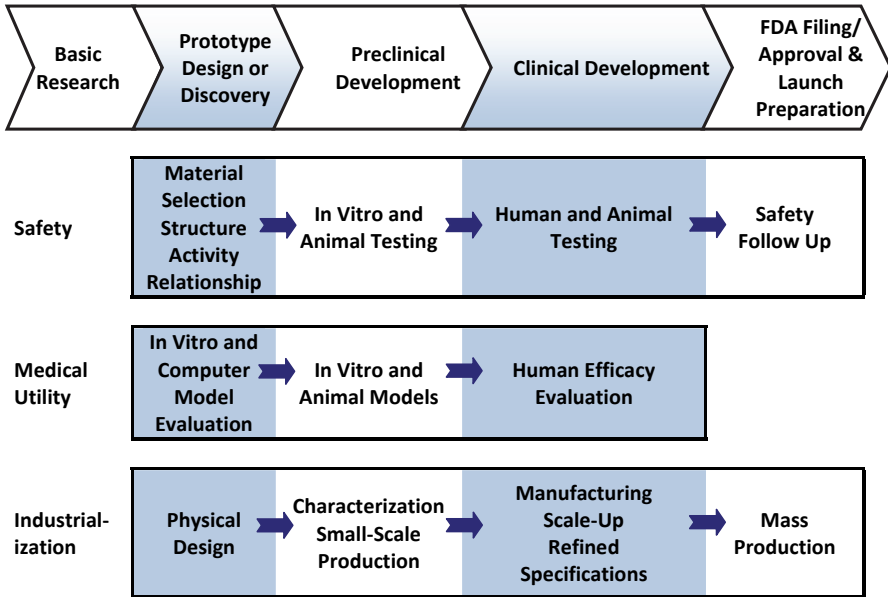


Figure 58.3a An Overview of the Drug Development Pathway. This figure represents a highly generalized description of activities involving drug development that must be successfully completed at different points. Drug development can be conceptualized as a process leading from basic research through a series of developmental steps to a commercial product. First, a candidate drug emerges from a drug discovery program. Then, the candidate must successfully complete a series of evaluations of its potential safety and efficacy and must be amenable to mass production. For each candidate finishing the pathway, thousands of candidates are evaluated in the discovery phase. Many of activities involving drug development are highly complex and whole industries are devoted to supporting them. Not all are performed for every candidate and many activities are omitted from the figure.

Adapted from the FDA.

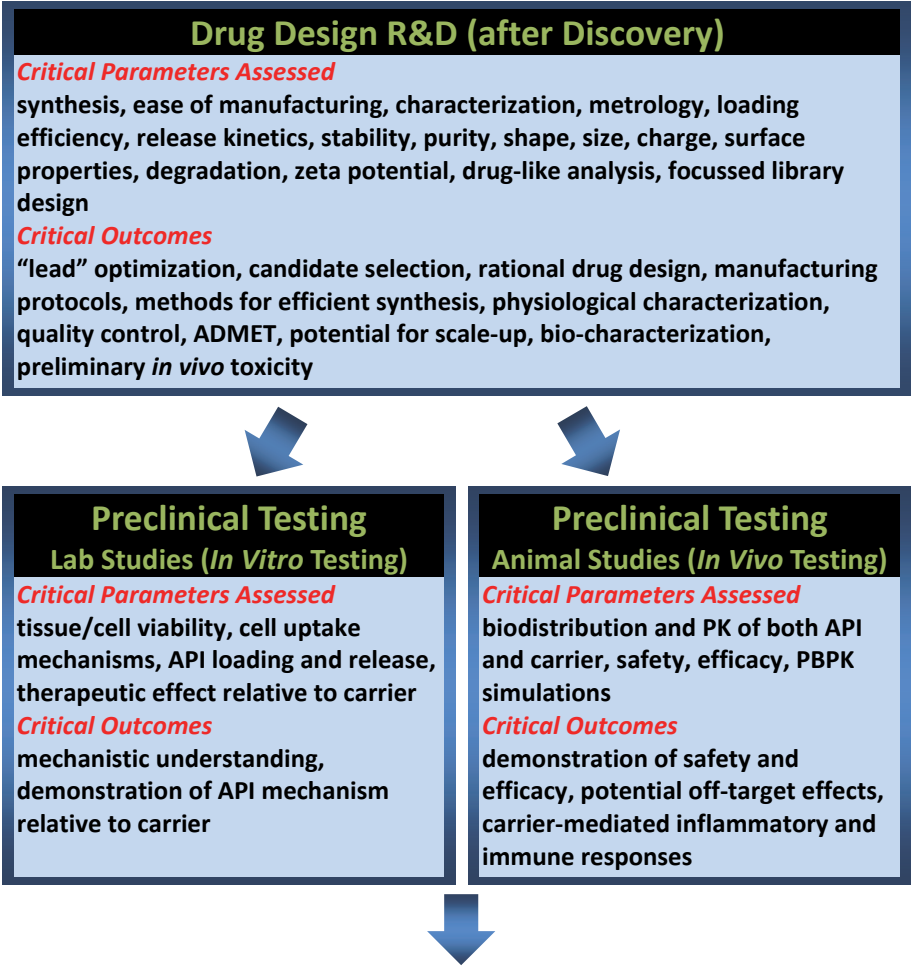


Figure 58.3b (Continued)

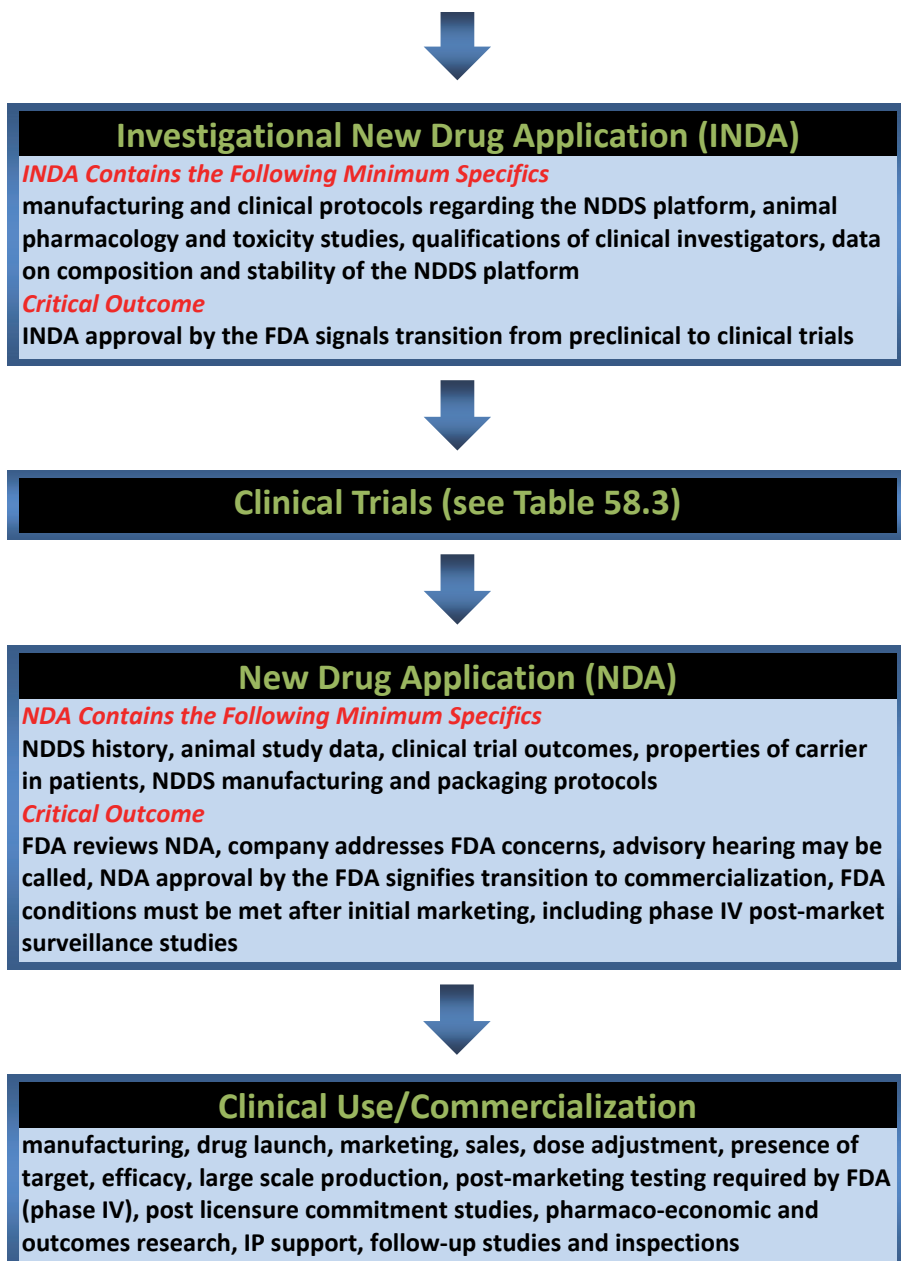


Figure 58.3b Translation of a Nanoscale Drug Delivery System (NDDS) Platform. ADMET: absorption, distribution, metabolism, excretion and toxicity; API: active pharmaceutical ingredient; PK: pharmacokinetic; PBPK: physiologically based pharmacokinetic; IP: intellectual property; NDDS: nanoscale drug delivery system.

Table 58.3 Comparison of Clinical Trial Phases

	Phase 1	Phase 2	Phase 3	Phase 4
Objectives	Determine the metabolic and pharmacological actions and the maximally tolerated dose	Evaluate effectiveness, select dose for Phase 3, determine the short-term side effects and identify common risks for a specific population and disease	Obtain additional information about the effectiveness on clinical outcomes and evaluate the overall risk–benefit ratio in a demographically diverse sample	Monitor ongoing safety in large populations and identify additional uses of the agent that might be approved following another marketing authorization application
Factors	Bioavailability–bioequivalence–dose proportionality Metabolism Pharmacodynamics–pharmacokinetics	Bioavailability; drug–disease interactions; drug–drug interactions; efficacy at various doses; pharmacodynamics–pharmacokinetics; and patient safety	Drug–disease interactions; drug–drug interactions; dosage intervals; risk–benefit information; and efficacy and safety for subgroups	Epidemiological data Efficacy and safety within large, diverse populations Pharmacoeconomics
Data	Vital signs Plasma and serum levels Adverse events	Dose response and tolerance Biomarkers Adverse events Efficacy	Laboratory data Efficacy Adverse events	Efficacy Pharmacoeconomics Epidemiology Adverse events

	Phase 1	Phase 2	Phase 3	Phase 4
Design	Single, ascending dose tiers Uncontrolled	Placebo controlled comparisons Active controlled comparisons Well-defined entry criteria	Randomized Controlled Two to three treatment arms Broader eligibility criteria	Uncontrolled Observational
Duration of study	Up to 1 month	Several months	Several years	Ongoing (following marketing authorization)
Population	Healthy volunteers or individuals with the target disease, e.g., cancer	Individuals with target disease	Individuals with target disease	Individuals with target disease, as well as new age groups, genders, etc.
Number of test subjects	15–100	25–300	Hundreds to thousands	Thousands
Example	Study of a single dose of Drug X in normal subjects	Double-blind study evaluating safety and efficacy of Drug X vs. placebo in patients with Alzheimer’s disease	Study of Drug X vs. standard treatment in an antidepressant	Study of economic benefit of newly approved Drug X vs. standard treatment for hypertension

Source: Reprinted from University of Pittsburgh, open access: https://www.clinicalresearch.pitt.edu/Content/docs/Comparison_of_Clinical_Trial_Phases.pdf (accessed on January 20, 2016).

In biomedicine, it represents the gap that exists between R&D breakthroughs made at the cellular and molecular biology levels on one end and the static levels of new treatments, diagnostics and preventative tools reaching the market on the other [3, 23]. This is the time prior to market entry where decisions need to be made whether to proceed or terminate product development. This is the time when ideas and inventions must undergo technical feasibility review, manufacturing optimization, market demand evaluation, reduction in production costs, commercialization potential studies. The *upstream* side of the valley of death (the science side) represents basic research inherently fraught with uncertainty while *downstream* (the business side) represents the more regimented process of product development characterized by manufacturing, marketing, deliverables, deadlines, budgets. Commercialization is about the translation crossing these two distinct paradigms.

According to NIH, its “mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.” However, the NIH has not been that successful in this mission. There is a growing perception that it has neglected its mandate to apply knowledge generated in basic research towards improving health. It has failed at translating advances at the preclinical stage in the lab into clinical applications in the practice of medicine (“bench-to-bedside”). In fact, in recent decades a research gap has developed between basic and clinical sciences that threatens to stall translation [3]: *“The barriers to translational research are relatively recent. Back in the 1950s and 60s, basic and clinical research were fairly tightly linked in agencies such as the NIH. Medical research was largely done by physician-scientists who also treated patients. That changed with the explosion of molecular biology in the 1970s. Clinical and basic research started to separate, and biomedical research emerged as a discipline in its own right, with its own training. The bulk of biomedical research is now done by highly specialized PhD scientists, and physician-scientists are a minority.”*

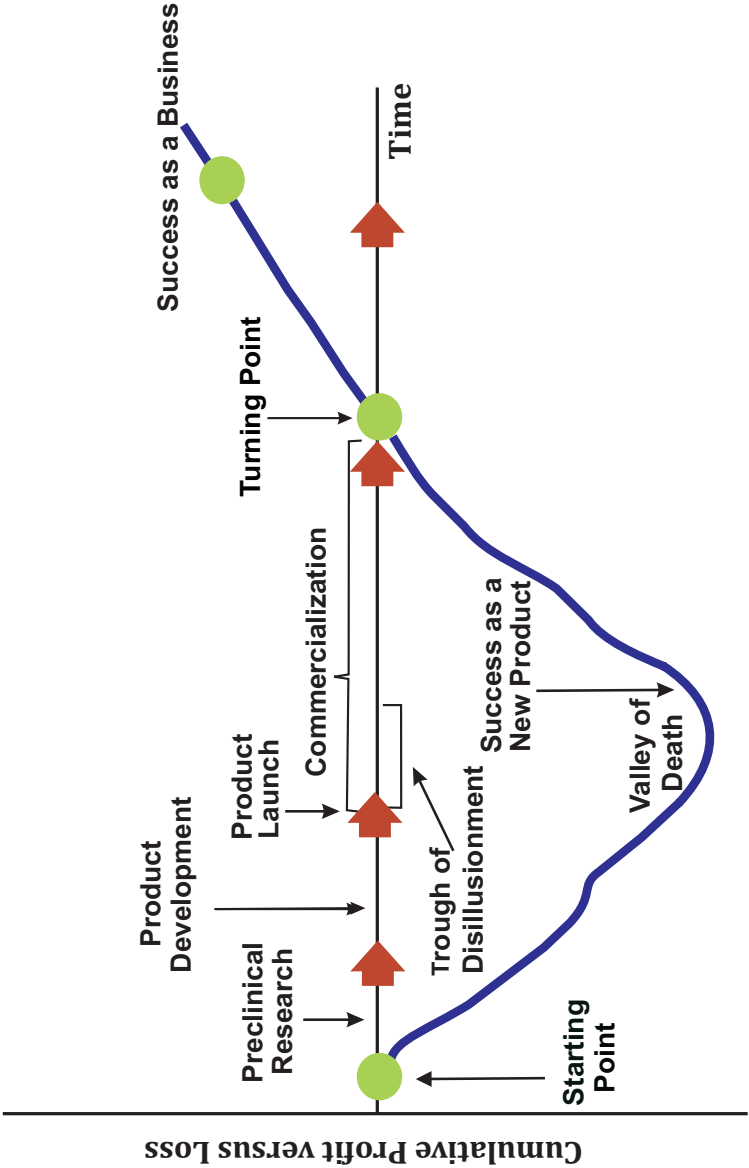


Figure 58.4 Mapping the Valley of Death in Commercialization.
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58.5 Scientific Innovation in a Culture of Conformity

In our publish-or-perish culture, is scientific innovation being smothered by a culture of conformity? Looks like we are becoming more conservative and risk-averse in our choice of research problems [24]. Painstaking characterization work or collection of fine-grained data are slowly disappearing in a publish-or-perish (or patent-or-perish) culture. Risk is essential for ground breaking work and creativity to fully flourish. We must also broaden our horizons beyond historical boundaries between disciplines, embrace global scientific collaboration and leverage interconnected global networks to address grand challenges in biomedicine. In any case, biomedicine is trending in the direction of cross-disciplinary research and interdisciplinary education. In order to drive science, innovation and the economy, we need doctorates and medical scientists trained in a variety of fields and disciplines. Although the number of science doctorates is rising, graduate programs should be revamped further to incorporate workplace skills and select courses in management, communication, commercialization and business. In this regard, nano has an inherent edge over other fields: Interdisciplinarity and international collaboration are the hallmarks of nano.²⁰ These are also two key aspects for effective

²⁰See: Jackson, S. A. New vantage points. Available at: <http://www.rpi.edu/president/speeches/ps102915-falltownmeeting.html> (accessed on March 6, 2016): "...[F]irst, humanity faces global and interconnected challenges surrounding our supplies of food, water, energy, and a changing climate; human health and the mitigation of disease; national and global security; the allocation of valuable natural resources; and our need for a sustainable infrastructure. Clearly, such challenges cannot be addressed by a single discipline, sector, nation, or geography working alone...The second factor encompasses the advanced tools and technologies that are affording us new insights into our world, and new ways to navigate and manage that world...These challenges and opportunities demand that we educate the next generation of leaders for depth in their specific domains, since you have to know something to do something—as well as for the breadth that allows them to perceive the connections among domains that initially appear unrelated. These connections cross disciplinary boundaries that link ever more strongly the humanities, arts, and social sciences, architecture, and business, with our roots in science and engineering..."

translation. And, we need risk-takers in biomedicine and nanomedicine. There is evidence that increased risk-taking and the publication of experimental failures would substantially improve the speed of discovery [24]. This, in turn, would enhance the rate of translation.

58.6 Patents and Translational Research

The protection of intellectual property (IP) of inventions, within which patents fall, is increasingly important. So far, the process of converting basic research in nanomedicine into commercially viable products has been difficult. Intellectual property, obviously, is the life-blood of this enterprise, both as an enablers of translation and sometime as a barrier. Understanding the patent process, the patent landscape and white-space opportunities are essential to translational research and the development of innovations for clinical use. Patents can have an impact at all stages in translation, from the preclinical or research stage to clinical trial stage, at the point of commercialization, and also when the product is in the clinic. Freedom-to-operate is another important concept that researchers should become fluent with so that they are aware of the patents in existence when developing novel technologies in the first place. This will help (i) identify technology in development that could potentially infringe valid patents and lead to enforcement action on the part of the patent holder (a time-consuming and expensive process for both parties); and (ii) assist researchers protect their own IP by assessing their inventions and the scope of protecting them via patents relative to other art in their field of research. Details on nanopatents, including the legal criterion necessary to obtain a US patent (Fig. 58.5) and the process for obtaining a US patent (Fig. 58.6), can be found elsewhere [25].

The protection of inventions via patents provides an opportunity for pharma to recoup the high cost of discovery by preventing competitors from entering the marketplace while the patent is in force. Patents and the protection that they afford are the lifeblood of big pharma. Securing valid and defensible patent protection

from the PTO is critical to any commercialization effort. Valid patents stimulate market growth and innovation, generate revenue, prevent unnecessary licensing and reduce infringement lawsuits. In spite of anemic product development, nanopatent filings and grants have continued unabated. However, it is no secret that nanopatents of dubious scope and breath, especially on foundational nanomaterials and upstream nanotechnologies,

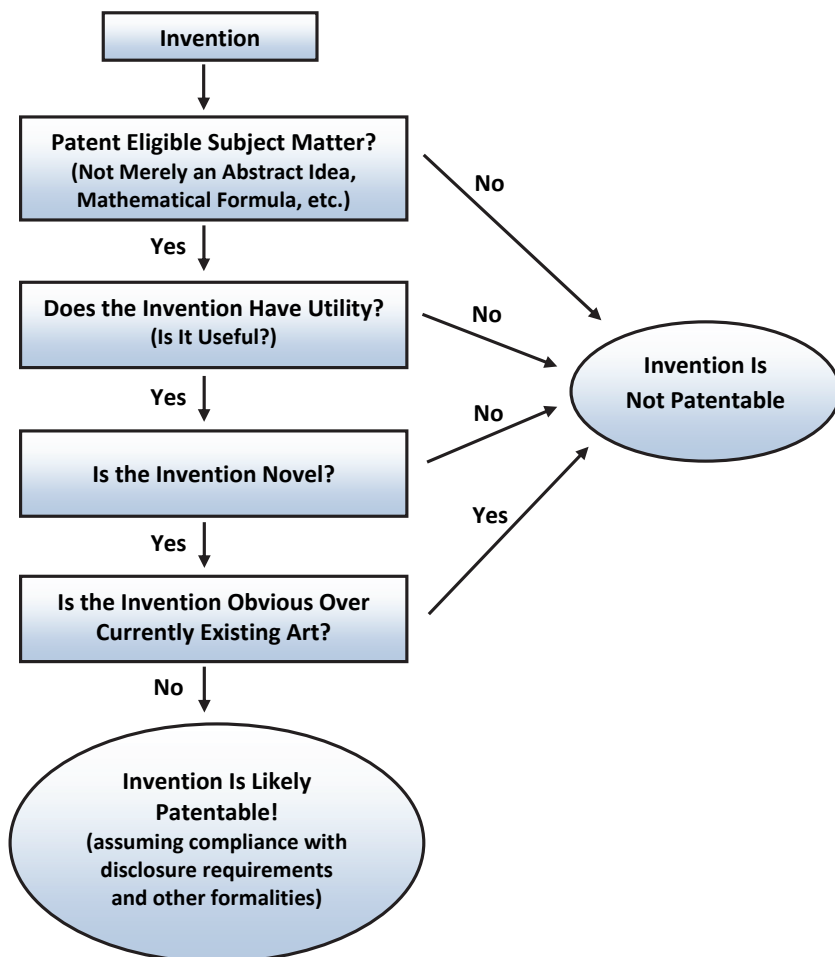


Figure 58.5 Legal Criterion to Obtain a US Patent.

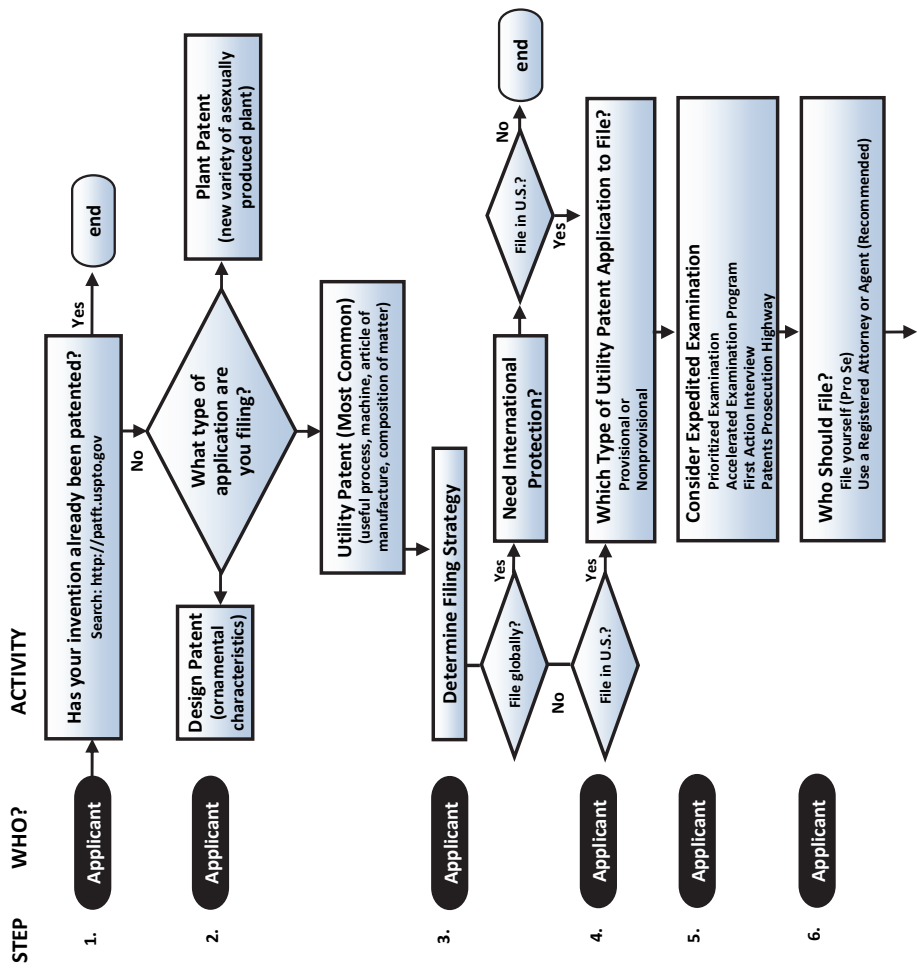
Courtesy of Dr. Brian E. Reese, Choate, Hall & Stewart LLP, Boston, MA.

have been granted by patent offices. In fact, “patent prospectors” have been on a global quest for “nanopatent land grabs” since the early to mid-1980s [26–28]. As a result, patent thickets in certain sectors of nanotechnology have arisen that could have a chilling impact on commercialization activities.²¹ The PTO continues to be under enormous strain and scrutiny. Issues ranging from poor patent quality, questionable examination practices, inadequate search capabilities, rising attrition, poor examiner morale and an enormous patent backlog are just a few issues that need reform. The nomenclature issue (Section 58.7 below) is also affecting patent drafting and prosecution.

58.7 Lost in Translation: The Issue of Nomenclature

It is true that in the heady days of any new, emerging technology, definitions tend to abound and are only gradually documented via reports, journals, books and dictionaries. Ultimately, standard-setting organizations like the International Organization for Standardization (ISO) and American Society for Testing and Materials (ASTM) International produce technical specifications. This evolution is typical and essential, as the development of terminology is a prerequisite for creating a common language for effective communication in any field. Similarly, an internationally

²¹For example, the carbon nanotube (CNT) patent landscape is a tangled mess, mainly due to issuance of multiple US patents in error by the PTO. Also, to blame is the fact that there is a lack of nano-nomenclature because of which inventors and scientists have employed distinct terms to refer to CNTs. As a result, contrary to the foundation of US patent law, various US patents on CNTs have been granted with legally identical claims. See: Harris, D., Bawa, R. (2007). The carbon nanotube patent landscape in nanomedicine: an expert opinion. *Expert Opin. Ther. Patents*, **17**(9), 1165–1174. The expected negative impact on commercialization and patent litigation has not (yet) arrived because CNTs have failed to deliver on the hype. Fabrication of affordable and high-quality CNTs has (yet) not materialized and scientists are now pursuing other exciting materials such as graphene instead. Hype and technology often evolve together and, in this case, the “peak of inflated expectations” of the 1990s was replaced by the “trough of disillusionment” in the early 2000s. See: Davenport, M. (2015). Much ado about small things. *Chem. Eng. News*, **93**(23), 10–15.



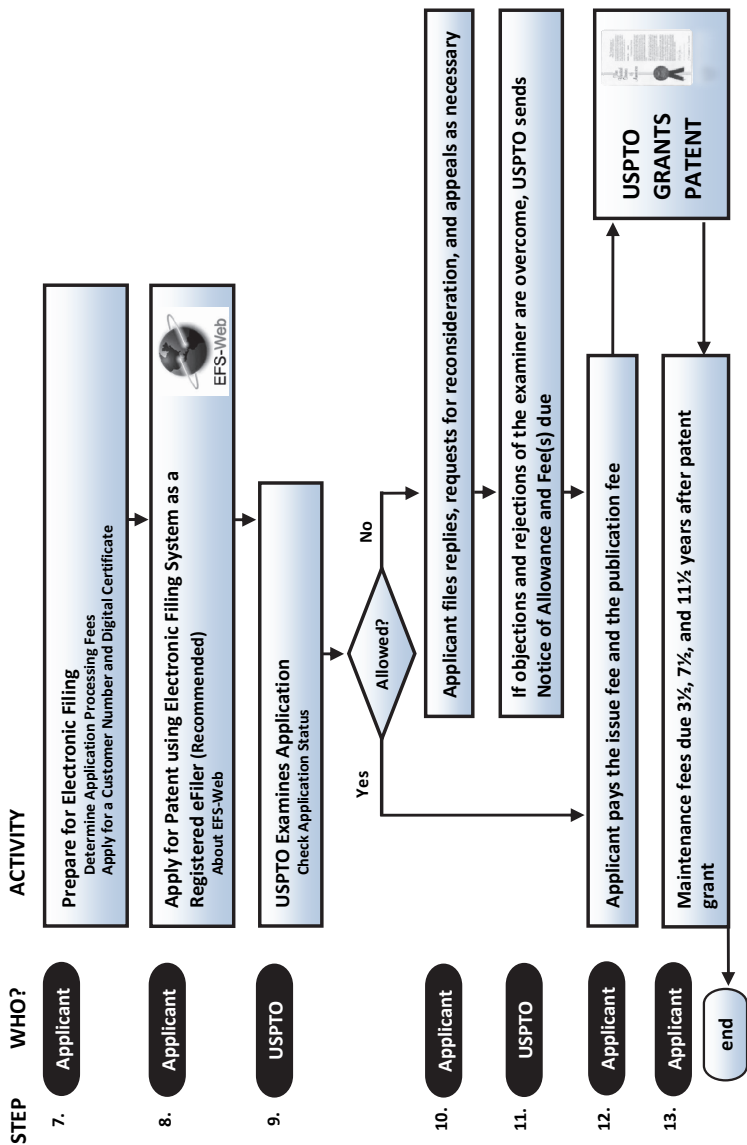


Figure 58.6 Process for Obtaining a US Utility Patent.
Courtesy of the US Patent & Trademark Office.

agreed definition for key terms like nanotechnology, nanoscience, nanomedicine, nanobiotechnology, nanodrug, nanotherapeutic, nanopharmaceutical and nanomaterial, has gained urgency.²² Nomenclature, technical specifications, standards, guidelines and best practices are critical to advancing nanotechnologies in a safe and responsible manner. Contrary to some commentators, terminology does matter because it prevents misinterpretation and confusion. It is essential for research activities, harmonized regulatory governance, accurate patent searching and prosecution, standardization of procedures, manufacturing and quality control, assay protocols, decisions by granting agencies, effective review by policymakers, ethical analysis, public dialogue, safety assessment, and more. Also, nomenclature is critical to any translational and commercialization efforts. Definitions of nanotechnology based on size or dimensions should be dismissed, especially in the context of nanomedicine and nanodrugs for reasons well-articulated elsewhere recently [29]. There is simply no scientific basis or logic to limiting all nanotechnology to a sub-100 nm limitation; it is illogical, random and foolish [29]. Moreover, “nano” is not simply a metric of length and nanoscale research does not accept such rigid limitations on dimensionality. It can be summarized that nanoscale therapeutics may have unique properties (nanocharacter) that can be beneficial for drug delivery and other applications but there is no specific size range or dimensional limit where superior properties are found [29–31]. Hence, the size limitation below 100 nm cannot be touted as the basis of novel properties of nanotherapeutics. The arbitrary sub-nano cutoff from the NNI has been correctly criticized over the years [31]:

²²Similar disagreements over terminology and nomenclature are seen in other fields as well. For example, the term “super resolution microscopy,” the subject of the 2014 Nobel Prize, is considered an inaccurate description of the technique. Since electron microscopes and scanning probe microscopes can resolve features at the nanometer, it is a misnomer to affix the “nano” prefix to these terms. Therefore, it may be more appropriate to refer to these “scopes” as “nanoscopes” instead. Inaccurate terminology often becomes the norm with time. It is hoped that such is not the case for “nano” where the prefix gets too entrenched for a corrective change to be made.

The 100 nm size boundary used in these definitions, however, only loosely refers to the nano-scale around which the properties of materials are likely to change significantly from conventional equivalents. In reality, there is no clear size cut-off for this phenomenon, and the 100 nm boundary appears to have no solid scientific basis. A change in properties of particulate materials in relation to particle size is essentially a continuum, which although more likely to happen below 100 nm size range, does not preclude this happening for some materials at sizes above 100 nm...

There are concerns regarding this definitional issue that could clearly pose a roadblock to translational efforts in nanomedicine. This is echoed by various commentators [32]:

The definition of nanomedicine has implications for many aspects of translational research including fund allocation, patents, drug regulatory review processes and approvals, ethical review processes, clinical trials and public acceptance. Given the interdisciplinary nature of the field and common interest in developing effective clinical applications, it is important to have honest and transparent communication about nanomedicine, its benefits and potential harm. A clear and consistent definition of nanomedicine would significantly facilitate trust among various stakeholders including the general public while minimizing the risk of miscommunication and undue fear of nanotechnology and nanomedicine.

If translation of nanomedicine is to fully succeed, it is important that some order, central coordination and uniformity be introduced at the transnational level to address the rise of diverse nano terms seen in the patent literature, journals and the press. This is also critical to prevent a significant scientific, legal and regulatory void from developing, all of which will further negatively affect translational efforts [33]:

Nomenclature, technical specifications, standards, guidelines and best practices are critically needed to advance nanotechnologies in a safe and responsible manner...However, defining nanotechnology, from any perspective (scientific, regulatory, patent law, ethics, policy), is no easy task. So far, no real consensus has been reached on basic "nano" terms such as nanotechnology, nanodrug, nanomedicine, nanomaterial, nanotherapeutic, nanoparticle, nanoscale, etc. In fact, finding a consensus on nano-nomenclature is a challenge, especially with the diversity and scope of scientific disciplines, voices and technologies encompassed by the nanotechnology umbrella.

An official, scientifically credible and legally workable definition of nanotechnology as applied to nanoparticle drug delivery systems or nanoformulations does not currently exist. ...viable sui generis definition of nano having a bright-line size range as applied to nanodrugs blurs with respect to what is truly nanoscale; it is unnecessary, misleading, and in fact, may never be feasible. ... this has contributed to the evolving patent thicket in certain sectors along with a lack of specific protocols for preclinical development, slower nano-characterization and confusion in the scientific literature. In the near future, stakeholders ranging from patent professionals, scientists, drug regulatory community, pharmaceutical companies, policy-makers and governmental agencies must come together on a global platform to address, define and formulate formal definitions and nomenclature for various “nano” terms.

58.8 Regulatory Guidance: Critical for Translation

Emerging technologies are particularly problematic for governmental regulatory agencies, given their independent nature, slow response rate, significant inertia and a general mistrust of industry. Major global regulatory systems, bodies and regimes regarding nanomedicines are not fully mature, hampered in part by a lack of specific protocols for preclinical development and characterization. Additionally, in spite of numerous harmonization talks and meetings, there is lack of consensus on procedures, assays and protocols to be employed during pre-clinical development and characterization of nanomedicines. On the other hand, there is a rise of diverse nano-specific regulatory arrangements and systems, contributing to a dense global nanotechnology regulatory landscape, full of gaps and devoid of central coordination [33–39]. It is often observed that governmental regulatory bodies lack technical and scientific knowledge to support risk-based regulation, thereby leaving a significant regulatory void. In fact, the “baby steps” the FDA has undertaken over the past decade have led to regulatory uncertainty. The bumpy ride is expected to continue [33]:

Internationally, robust regulatory guidance for nanotechnology is also lacking. In fact, regulatory agencies around the world continue to struggle in their efforts to develop, meaningful regulatory

definitions and balance them with policies that are already in place. However, guidance is critically needed to provide clarity and legal certainty to manufacturers, policy-makers, healthcare providers, and the consumer-patients. Common sense warrants that some sort of guidance, oversight, or regulation by the FDA is in order, at least on a case-by-case basis. But, so far, it has chosen to regulate nanomedicines and nanoproducts solely via laws and regulations that are already on the books. There are hundreds, if not thousands, of nanoproducts in the market for human use, but little is known of their health risks, safety data, or toxicity profiles. Even less is known of nanoproducts that are released into the environment that can potentially contact humans. Then, there are products such as cosmetics that are flooding the market but are not even subject to any pre-market review by the FDA. Under the current regulatory regime, it continues to be the FDA's position that nano-ingredients (e.g., nanoparticles) are presumed to be "bioequivalent" to their bulk counterparts. Thus, manufacturers of nanoproducts are neither required to obtain pre-market approval from the FDA nor required to list nano-ingredients on product labels at this time. These nanoproducts, whether they are a drug, device, biologic, or combination of any of these, are creating challenges for the FDA regulators as they struggle to accumulate data and formulate testing criteria to ensure the development of safe and efficacious nanoproducts.

In order to move the translational process along, we provide various recommendations with respect to FDA regulation of nanomedicine (Table 58.4).

It is worth quoting a recent publication [31] that highlights some of the challenges confronting regulatory agencies like the FDA and EMA regarding nanotech:

There are potentially serious and inhibitory consequences if nanodrugs are overregulated, and a balanced approach is required, at least on a case-by-case basis, that addresses the needs of commercialization against mitigation of inadvertent harm to patients or the environment. Obviously, not every nanotherapeutic or nano-enabled product needs to be regulated. However, more is clearly needed from regulatory agencies like the FDA and EMA than a stream of guidance documents that are in draft format, position papers that lack any legal implication, presentations that fail to identify key regulatory issues and policy papers that are often short on specifics. There is a very real need for regulatory guidelines

that follow a science based approach that are responsive to the associated shifts in knowledge and risks.

Table 58.4 Recommendations for the FDA Regarding Nanomedicine Regulation

Safety and Risk
<ul style="list-style-type: none"> • On a case-by-case basis and in conjunction with industry, identify unique safety issues associated with nanoparticles and nanomedical products. FDA should meet its regulatory and statutory obligations by offering technical advice and guidance to industry beyond what its track record currently reflects. • Actively seek product safety data from industry where FDA statutory authority exists for pre-market review. • Incentivize and encourage voluntary industry submissions of safety data on nanomaterials or products that incorporate nanotechnology prior to market launch, especially in cases (e.g., cosmetics) where the FDA lacks statutory authority for pre-market review. • Correlate physiochemical properties with <i>in vivo</i> biological behavior and therapeutic outcome. • Since there are few protocols to characterize nanomedicines at the physicochemical, biological and physiological levels, it is essential to develop a research strategy that involves adsorption, distribution, metabolism, and excretion (ADME) studies. A holistic approach to understanding ADME can be realized through the integration of mechanistic ADME data through the mathematical algorithms that underpin physiologically-based pharmacokinetic (PBPK) modelling, routinely utilized to support regulatory submissions for conventional medicines in the US by the FDA and in Europe by the EMA. • Develop toxicology tests and conduct physico-chemical characterization (PCC) studies for nanomaterials. Although complexity and diversity of nanomedicines poses a problem, biocompatibility and immunotoxicity must be taken into consideration during preclinical assessment. • Understand mass transport across biomembranes and body compartments as well as biodistribution profiles following administration via a specific route. • Develop standards that correlate the biodistribution of various nanomaterials with safety/efficacy by using parameters such as size, surface charge, stability, surface characteristics, solubility, crystallinity and density. • With industry input, create a comprehensive public databank relating to the biological interactions of engineered nanomaterials (ENMs).
Data
<ul style="list-style-type: none"> • Adapt existing methodologies, as well as develop new paradigms for evaluating <i>in vivo</i> animal and clinical data pertaining to safety and efficacy of nanomedical products before and during the product life cycle. • Develop guidance that provides specifics as to what kind of data is required at each step of the nanomedical translational process.

- Share data in a transparent and harmonized manner. Seek additional data on safety or effectiveness during premarket review process when warranted. FDA's excessive reliance on publicly available or voluntarily submitted information, adverse-event reporting and on post-market surveillance activities may not be ideal in the case of ENMs for human use.

Standardization and Nomenclature

- Create reference classes for ENMs that are synthesized and characterized.
- Develop consensus testing protocols to provide benchmarks for the creation of classes of nanoscale materials, both engineered and native.
- Create uniform nomenclature for and/or working definitions of nanomaterials. Refine the current definitions of nanomaterial, nanotechnology, nanodrug, nanopharmaceutical, nanoscale and nanomedicine for regulatory purposes.
- Further explore international regulatory harmonization efforts and formal treaties with relevant stakeholders.
- In addition to governmental bodies, involve various standard-setting organizations such as the ISO and ASTM International.
- Consult and collaborate with other federal agencies in a more effective, transparent and science-based manner. FDA's current engagement in policy dialogue with other federal agencies (via the Emerging Technologies Interagency Policy Coordination Committee and other forums) has not produced any important guidelines for industry. FDA should limit the number of non-binding draft guidance and policy papers that it periodically issues.

Tools and Techniques

- Assist in developing unique tools and techniques to characterize nanoscale materials.
- Develop imaging modalities for visualizing tissue biodistribution.
- Develop mathematical and computer models for risk/benefit analysis that can monitor quality, safety and effectiveness vis-à-vis standard ENMs.

Classification Scheme

- Reevaluate the current FDA classification scheme, including the Primary Mode of Action (PMOA) criteria for combination products.
- Develop a classification system that is based on (a) function or (b) risk of potential harm.
- Reevaluate the system of differing legal standards for different product classes that may result in divergent regulatory outcomes for different product classes.
- Place more effort in tailoring relevant guidances governing various product classes and address interpretation of relevant statutory/regulatory standards relative to these classes.

58.9 Final Thoughts: Streamlining Translational Medicine at the Nanoscale

It is clear to these authors that the seemingly intractable problems between the clinic and the lab persist in spite of enormous infusion of funds by governments and private entities. Therefore, it is important to optimally integrate health care, academia and industry to achieve changes at various levels along the translational path. These are critical to transform nanomedicine and improve the performance of its supply chain for the benefit of all stakeholders (Fig. 58.7 and Table 58.5). We believe that issues such as effective patent reform, adaptive regulatory guidance, robust governmental efforts and consumer health are all intertwined and require special attention while addressing nanomedicine

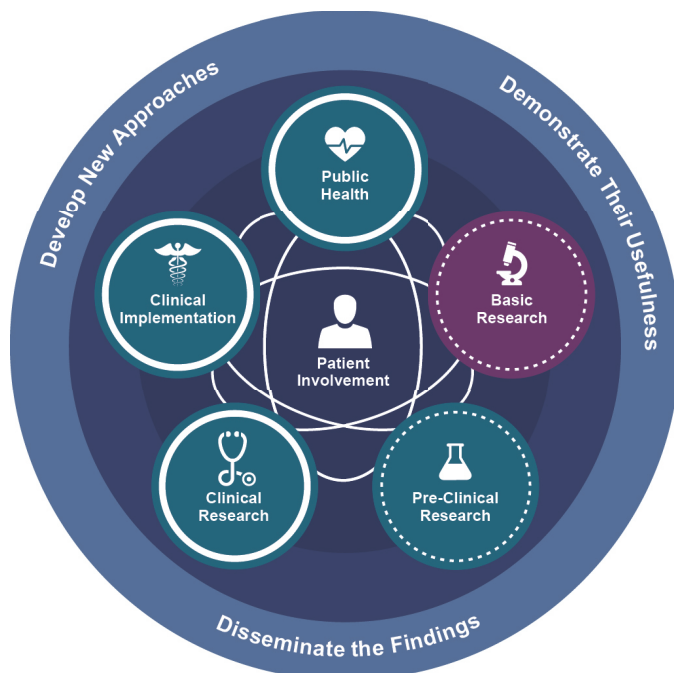


Figure 58.7 Interrelated Stages Along the Path of Translational Medicine. The central position of the patient in the figure highlights patient involvement as being a critical feature of all stages in translation. The various stages shown are not linear or unidirectional but instead each stage builds upon and informs the others.

Courtesy of the National Center for Advancing Translational Sciences, NIH.

translation from the bench to the bedside. In this regard, science-based governance that promotes translation on one hand and balances consumer health on the other is crucial. Further efforts are being made to streamline the research approval process and reduce regulatory burdens. For example, in the US, the National Center for Advancing Translational Sciences (NCATS) was established in 2012 with its mission to *“catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions”* [41].

We hope that a “translational turn” within biomedicine, at least in the US, can be seen in the years ahead instead of the long-standing problems in clinical research and between the clinic and the lab. This will obviously percolate into nanomedicine. The “gaps” and “roadblocks” in translation can only be addressed by closer integration between the various constituencies with a stake in the process: the US government, academia, the NIH, regulatory and patent agencies, the pharmaceutical industry, the public and patients. The long-term prognosis of translational medicine at the nanoscale hinges on these key players. They must endure and traverse the valley of death together.

Table 58.5 Improving Translational Nanomedicine: General Points to Consider

Research scientists in academia should understand the entire supply chain from research to development, including basic concepts relevant to commercialization.
Granting agencies and peer reviewers that review grants should have expertise in translational medicine, industrial portfolio management and commercialization of research to properly access feasibility of proposals that have a greater potential for patient application. Proposals and submissions should seek/include criteria to evaluate whether the research is capable of clinical application. Funding projects should be evaluated in terms of realistic potential of making it to the clinic rather than specific disease targets.
Educational institutions and universities should offer more interdisciplinary/hybrid courses and graduate training modules where applied research, business landscaping, intellectual property law, FDA regulatory issues and the patent process are emphasized.
Academic researchers should be encouraged to develop innovative translatable products. Academic research that is advertised as being applied or translational should have to demonstrate a minimum threshold requirement on realistic chances to help patients prior to funding. Portfolios and projects should be developed and evaluated with an eye on applied research; even basic research should be analyzed to determine such potential.

(Continued)

Table 58.5 (Continued)

Matrices and stringent evaluation criteria should be employed throughout a funded applied academic project to see how successful it is with respect to translation and whether it merits further funding.

Academia and industry must enhance collaborative efforts to address the non-reproducibility of preclinical research that primarily emanates from academic research labs.

Labs that focus on clinical applications should implement quality assurance systems such as Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP), especially if submitting data to regulatory agencies.

Key questions should be asked early on during the development phase of the project: is the idea patentable, will it help patients in a clinical-setting, is the clinical hypothesis backed by generated preclinical data, is there freedom-to-operate with respect to the patent estate and commercial landscape, is it likely to be reimbursed by insurance companies, is there a need commercially, is there a significant market size, are safety issues addressed, is the immunology and pharmacology well studied, are all components (active, carrier, excipient, etc.) well characterized, are there unique safety concerns due to nanoscale, are there fabrication costs and complexities, etc.

Science policy-makers should subsidize more risky research strategies, incentivize strategy diversity and encourage publication of failed experiments—all activities known to increase the speed of discovery.

University Technology Transfer Offices (TTOs) should be revamped and required to disclose the return-on-investment (ROI) in terms of funds expended on patent prosecution versus licensing royalties generated.

Quality assurance (QA) guidelines for basic research published by the WHO or RQA should be implemented by labs to safeguard data and ensure scientific rigor. Digital manipulation or errors can be minimized or prevented via “read-only files” stored on lab instruments. Granting agencies should require proof that instruments have been calibrated and that plans exist for tracing data, including which equipment the experiment was conducted on and where the source data is stored.

Recognizing genuine requests for scrutiny from harassment in a climate of research transparency is essential to safeguarding the research community and driving translational efforts.

Early sponsor interaction with the FDA in the development process to identify appropriate pathways to be navigated. File patent applications at an early stage to capture upstream aspects of nanomedical products; employ an interdisciplinary team of patent attorneys or patent agents to draft applications. The regulatory review process, patent prosecution at patent offices and business developments should all be coordinated throughout translation.

Allow greater patient input into drug development, regulatory processes and clinical trial design. Manufacturers should seek patient perspective early on in product development. Furthermore, patient information and data should be more readily shared for research especially with respect to chronic diseases. However, for these recommendations to become a reality, clearer policies and guidelines may be needed via governmental action so that companies do not risk legal issues, patient privacy is safeguarded and data security is ensured.

Enhance and streamline institutional review board (IRB) approval process to minimize unnecessary delays and redundancy.

Editor's Note

The American Statistical Association (ASA) recently issued principles to guide use of the p -value and warned that the p -value cannot be used to determine whether a hypothesis is true or whether the results are important. According to the ASA, misuse of p -values is contributing to the irreproducibility crisis currently plaguing preclinical biomedical research (discussed in detail in Section 58.3). See: Baker, M. (2016). Statisticians issue warning on P values. *Nature*, **531**, 151; Wasserstein, R. L., Lazar, N. A. (2016). The ASA's statement on p -values: Context, process, and purpose. *The American Statistician*, doi:10.1080/00031305.2016.1154108.

According to estimates, about \$28 billion annually is wasted on irreproducible preclinical research in the US. In this regard, because errors in study design and biological reagents and materials contribute to a majority spent, implementing steps to improve preclinical reproducibility should be a priority in these two areas. See: Freedman, L. P., Cockburn, I. M., Simcoe, T. S. (2015). The economics of reproducibility in preclinical research. *PLoS Biol.*, **13**, e1002165.

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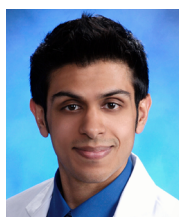
Raj Bawa is president of Bawa Biotech LLC, a biotech/pharma consultancy and patent law firm based in Ashburn, Virginia that he founded in 2002. He is an inventor, entrepreneur, professor and registered patent agent licensed to practice before the US Patent & Trademark Office. Trained as a biochemist and microbiologist, he has been an active researcher for over two decades. Since 1999, he has held various adjunct faculty positions at Rensselaer Polytechnic Institute in Troy, NY, where he is currently an adjunct professor of biological sciences and where he received his doctoral degree in three years (biophysics/biochemistry). Since 2004, he has been an adjunct professor of natural and applied sciences at NVCC in Annandale, VA. He is a scientific advisor to Teva Pharmaceutical

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