J Nanopart Res (2011) 13:1513–1520
DOI 10.1007/s11051-011-0260-z

SPECIAL FOCUS: GOVERNANCE OF NANOBIOTECHNOLOGY

Regulatory uncertainty and the associated business risk for emerging technologies

Robert A. Hoerr

Received: 18 January 2011 / Accepted: 25 January 2011 / Published online: 5 March 2011

Abstract An oversight system specifically concerned with nanomaterials should be flexible enough to take into account the unique aspects of individual novel materials and the settings in which they might be used, while recognizing that heretofore unrecognized safety issues may require future modifications. This article considers a question not explicitly considered by the project team: what is the risk that uncertainty over how regulatory oversight will be applied to nanomaterials will delay or block the development of this emerging technology, thereby depriving human health of potential and substantial benefits? An ambiguous regulatory environment could delay the availability of valuable new technology and therapeutics for human health by reducing access to investment capital. Venture capitalists list regulatory uncertainty as a major reason not to invest at all in certain areas. Uncertainty is far more difficult to evaluate than risk, which lends itself to quantitative models and can be factored into projections of return on possible investments. Loss of time has a large impact on investment return. An examination of regulatory case histories suggests that an increase in regulatory resting requirement, where the path is well-defined, is far less costly than a delay of a year or more in achieving product approval and market launch.

Keywords Development cost · Emerging technology · Investment risk · Nanotechnology · Regulatory oversight · Regulatory uncertainty · Venture capital · Governance

R. A. Hoerr (✉)
Nanocopoeia, Inc., 1246 University Avenue West, Suite 463, St. Paul, MN 55104, USA
e-mail: bob.hoerr@nanocopoeia.com

Introduction

The project that is the focus of this symposium issue began with the premise that establishing a proactive regulatory oversight system is desirable for the emerging technology of active nanostructures and nanosystems, particularly given the uncertain nature of the risks to human health and the environment represented by these novel materials (Ramachandran et al. 2011). While the project team learned important lessons from the case histories detailing how regulatory systems have interacted with other emerging technologies, a key challenge we faced in applying these lessons to nanotechnology-related products is the diversity of materials represented and the rapid pace of development. We considered a broad range of product categories, from truly novel material forms, such as carbon nanotubes or cadmium selenide quantum dots, to new composite materials, such as drugs coupled to tissue-targeting ligands and imaging

materials, to more conventional materials processed to nanoscale dimensions, such as sunscreen components, to nanoscale drug particles with improved bioavailability. It became clear that risks from the production or use of these materials are not inherently linked to nanoscale dimensions, but rather to a complex matrix that recognizes the interactions among size, composition, route, and duration of exposure, fate of distribution in the body, and other factors that are part of any toxicological evaluation.

Risk of regulatory uncertainty

This article supports the view that any oversight system specifically concerned with nanomaterials should be flexible enough to take into account the unique aspects of individual novel materials and the settings in which they might be used, while recognizing that heretofore unrecognized safety issues may require future modifications. The goal here is to extend the analysis by posing a balancing question that the project team did not explicitly consider: what is the risk that uncertainty over how regulatory oversight will be applied to nanomaterials will delay or block the development of this emerging technology, thereby depriving human health of potential and substantial benefits? Said more directly, what is the risk for human health that an ambiguous regulatory environment will make this emerging technology unavailable? As a physician who is also co-founder of a company using nanoscale processing to improve drug delivery, the author appreciates both sides of the debate and is, without doubt, an interested party. The purpose here is to illustrate the tensions involved in bringing new therapeutic options to patients in an environment which is costly, always changing, and which carries a high risk of failure and financial loss.

Prolonged regulatory ambiguity is a cause for concern because markets place a high value on risk mitigation and predictability of outcomes. Developing innovation technology requires capital from venture capital investors who are comfortable with the risk of complete failure in exchange for the substantial rewards of success. Uncertainty in the regulatory environment has the potential to increase both the costs and time needed for development, thereby making the commercialization process unpredictable and, in the worst case, incapable of being financed. Therein lies the risk. To focus this discussion, the point of view will be from the perspective of a small early-stage company developing products regulated by the Food and Drug Administration (FDA).

Impact of evolving regulations on venture investment

Examples supporting the contention that an ambiguous regulatory environment has blocked products on their path to market are difficult to document, though a web search provides multiple examples where venture capitalists list regulatory uncertainty as a major reason for not investing in certain areas (e.g., Baeyens et al. 2006). This may be because uncertainty is far more difficult to evaluate than risk, which lends itself to quantitative models and can be factored into projections of return on possible investments (see, e.g., Alesandri et al. 2004; Sjöö 2008). The halt in gene therapy trials after the unexpected death of a research subject and the recent court action halting embryonic stem cell research connected to federal funding demonstrate the pervasive and immediate impact that external forces can have on a research field and its associated development stage companies. These incidents could not have been predicted; however, neither of these examples arose due to regulatory uncertainty. It is more likely that, instead of a complete halt, regulatory uncertainty will result in a delay or drag on the development of innovative technologies through a variety of factors, most of which are predicated on a lack of access to capital.

The free market perspective assumes that a disruptive technology will find its way to the market as the opportunity it presents is matched with appropriate investors and capital. In the United States, if the disruptive technology has application to human health, then it is highly likely that it will encounter a strong system of oversight by the FDA that is well-established in the Code of Federal Regulations (CFR) for drugs, biologics, medical devices, and diagnostics, principally embodied in CFR Title 21: Food and Drugs. Because the approval process for these categories of technology is reasonably predictable and prescribes a systematic path of nonclinical safety testing (cell-based assays, animal toxicology studies, etc.) and both safety and efficacy

testing in normal and diseased human subjects, the costs of a development program can be estimated in advance. This process is further predictable because of the so-called pre-IND meeting, where a product sponsor meets with FDA before submitting an Investigational New Drug exemption application (IND) to solicit input by the regulators into key development decisions.

If the market for a product or product class is substantial, say on the order of a half billion to a billion dollars a year, the likelihood that the development costs will be financed by private or public capital is extremely high. Adams and Brantner (2006) from the Federal Trade Commission estimated that the cost of new drug development averaged $868 million in 2000 dollars, with a range from $500 million to $2 billion. The bulk of the expense is incurred during the clinical testing phases. Adams and Brantner estimate that Phase 3 testing is more than three times as expensive as Phase 1, and the duration of clinical testing phases is over 6 years on average. For drug products with a large market opportunity, the questions then get reduced not to whether the development will be financed, but to under what terms will it be financed. Typically, as a product or technology makes its way through the regulatory system, the risks associated with its development are reduced, even though the costs associated with its clinical testing increase dramatically, particularly if the population that will be exposed to and potentially benefit from the product is large. As a result, investors and large company licensing partners are willing to put up larger sums of money under terms that become more favorable as the product advances. A product that generates unexpected toxicity or shows inadequate efficacy is washed out of the development process. The earlier this occurs, the better. Financing products in the later stages of development is generally straightforward and affected more by predictions of market size and penetration rather than by unexpected health risks.

Challenge of financing early stages of development

The central challenge for emerging technologies is financing them adequately at the earliest stages of development, when the technologies' applications are still being defined and their risks are poorly understood. In the United States, research and development (R&D) financing derives from several key sources. At academic institutions, the bulk of funding comes from government grants. Total R&D expenditures at universities and colleges were over $50 billion in 2008, with about $30 billion of that coming from federal sources (National Science Foundation (NSF) 2008). This was dwarfed by industry's R&D expenditures of over $260 billion, a figure that does not include almost $26 billion in additional funding from federal sources (National Science Foundation (NSF) 2008). In early-stage companies, the funding may come from government grants, especially the Small Business Innovation Research grant program, but is far more likely to come from the private sector, from individual investors, from venture capital firms representing pools of individuals and institutions, or from industrial partners.

Many technologies have been "hot" for limited periods of time, when they are perceived as having tremendous upside and the risks of development failure are not well-defined. These technologies have little trouble attracting venture capital under favorable terms during these "hot" windows. Examples of such technologies include recent technical innovations like alternative energy, personalized medicine, and molecular diagnostics. Favored investment sectors change as enthusiasm cools, and capital may become more expensive as a field falls out of favor.

Modeling impact of delay on investment return

The classic models used by investors to determine the value of an investment in the regulated product sector rely on internal rate of return (IRR), modified internal rate of return, or the net present value (NPV) of a future revenue stream. In their simplest form, these can easily be modeled by anyone familiar with Microsoft Excel financial functions. Because regulated products do not generate a regular revenue stream, the first liquidity event (when the investment first yields a return to the investor) is delayed. It may come in the form of a lump-sum, if the company in which the investment is made is acquired, or spread over a period of time, if the company goes public through an initial public offering (IPO) and the equity owned by the investor is sold in one or more stages

after the initial "lock-up" period has expired, typically several months after the IPO. In a sense, the value attributable to these investments is linked to future earnings from an approved product, because the valuation of the company at the time of IPO is established by Wall Street analysts and initial purchasers based on projections of future earnings modified by a discount factor that adjusts for market and regulatory risks.

Early-stage companies are typically valued by the first one or two products in development. Valuing products rather than processes or services is easier because products follow the established rules and predictable path to market, while valuing the impact of a process is more difficult. The process may represent enabling technology without which a product cannot be developed. In this case, the value of the process may be primarily determined by the breadth of its applicability and number of licensing deals it can generate. The process may provide improvements in manufacturing efficiency, resulting in lower cost of goods and translating into greater profitability or expanded market size. In such a case, value is established by the net increases in revenue and profitability over the lifecycle of the products that are generated.

Variations from the expected path introduce unknowns into the valuation process. Consider, as an example, the case of an investigational new drug in nanoparticle form. If FDA were to decide that additional environmental impact testing and toxicology studies based on particle size were necessary for any product and those tests were precisely delineated and negotiated at the time of the pre-IND meeting, the added costs of development would be reasonably known and added to the size of investment needed to move the product into clinical trials and to approval. Similarly, the overall development project could be designed for optimal efficiency and cost, with studies being run in parallel rather than serially, thus having minimal impact on the time to approval. FDA could also take the position that its current policy statements on nanotechnology-related products are sufficient, with each product being evaluated on its own unique circumstances (Food and Drug Administration (FDA) 2007a). While this does not provide a clear road map, it does anticipate that any testing needed due to unique circumstances will be discussed and advice offered during the pre-IND meeting. Companies can mitigate the possibility of additional requests by anticipating possible questions related to the product they are developing. For example, the author's company assumed that the issue of workplace safety was a given for a spray process that created nanoparticles and, therefore, designed containment systems into its production equipment (Hoerr et al. 2009).

On the other hand, suppose that FDA were to take an ambiguous position, promising regulatory guidance at some point in the future. In an attempt to influence that position, groups opposed to or concerned about potential special risks posed by nanotechnology-related products in general might lobby government officials or seek to influence other stakeholders. Likewise, industry trade groups would begin counter-efforts to minimize any special regulatory changes. While neither side may be successful in influencing FDA, the tone of the public discourse may discourage venture investors from considering investments in nanotechnology-related companies or increase the discount factors they assign to such investments significantly to account for the uncertainty, thus diluting the value of the company to its founders or earliest investors.

This scenario is currently playing out in the debate on personalized medicine and molecular diagnostics, related and rapidly growing market sectors currently receiving significant venture capital investment. For example, the market for molecular diagnostics is expected to reach $12.2 billion by 2015, more than doubling the current year's estimate of $5 billion. This market intersects with nanobiomedicine because nanotechnology advances enable some of the new diagnostic testing methods. It also intersects with another policy debate on direct-to-consumer genetic testing and the need for more stringent regulatory oversight. In 2007, FDA issued draft guidance on in vitro diagnostic multivariate index assays (IVD MIAs), proposing to extend oversight and approval of these laboratory-developed tests as medical devices (Food and Drug Administration (FDA) 2007b). Representatives of the venture capital industry, including the National Venture Capital Association, have been opposing the draft guidance on the grounds that it is ambiguous and creates regulatory uncertainty, thereby making it difficult for companies to know whether their products will fall under the regulations, what the regulations will require, and

what the cost of compliance will be, while concurrently not improving the quality of the tests (Heesen 2010).

Identifying difficult-to-quantify risk in emerging technology development

The tension between constructive regulatory oversight of a rapidly developing field and encouraging technical or medical innovation was a common theme to the project team's case studies. Potential changes in the regulatory framework create investment risk that can come in many forms. Examples of risks that are difficult to quantify, but that may accompany an uncertain regulatory path include:

- inadequate financing to reach approval (cost overruns);
- delays due to unanticipated testing, such as toxicology testing;
- delays due to a mismatch between current toxicological models and their relevance to the product/technology being developed (i.e., a test adequate to evaluate the perceived risk may be unavailable);
- delays in onset of clinical trials;
- extensions in the period of monitoring for unanticipated adverse responses after clinical trials (much more costly than post-market surveillance); and
- unanticipated litigation to block certain aspects of development.

It should be noted that this list does not include risks due to unanticipated safety issues—all new drugs in development run the risk that adverse reactions may occur in late stage clinical testing that were not be predicted by earlier nonclinical or clinical testing. This uncertainty is separate from an ambiguous regulatory environment.

Impact of delay on cost of development and investment return

Delays are expensive. Suppose, for example, that FDA requested an additional, unexpected, nonclinical toxicology test after the IND was filed, effectively placing the investigational product on clinical hold. An FDA review team can request additional testing for a given product based on questions of safety at any stage of development. This additional testing does not require regulatory change. For a routine small molecule drug or biologic, this may add a delay of several months, including time for designing the study, possibly manufacturing the product, negotiating a contract with a contract research laboratory, and conducting the study under Good Laboratory Practices. Further delays are possible if the animal model or analytical tools have not been fully validated. For example, animal studies on the impact of inhaled nanoscale products could be designed, but the methodology is still a research tool (Oberdörster 2010). The final report for submission of the toxicological study may not be available for six months or longer. During this period, the company will also have to meet payroll and all other operating expenses, adding costs beyond those associated with the additional study. For extended delays, companies may be forced to cutback staff and reduce spending on other development projects in order to conserve cash.

The following example demonstrate the impact that a delay might have on the financial return for an investor in an early-stage, private company developing a pharmaceutical product perhaps two years out from licensing the technology from a university, and embarking upon a reasonably aggressive development program to seek FDA approval. The figures used in the example shown are for illustration only, but are not far from the four to fivefold return that might be experienced by an early-stage investor in such a company (see, e.g., Price 2007). For an investor to commit to this company, the expected rate of return should meet certain targets that are much higher than an individual might expect from a retirement account. Investors predict what the return on investment might be when the company is successful based on the product being developed, the market size, and the likelihood that the product will interest a larger company in either acquiring the company or licensing the product. Investors model the investment to evaluate its possible IRR or the NPV of the future payoff.

The impact of a year's delay on the investment return can be seen in Fig. 1, where a hypothetical initial investment of $1 million results in a $5 million return at four or more years. The impact

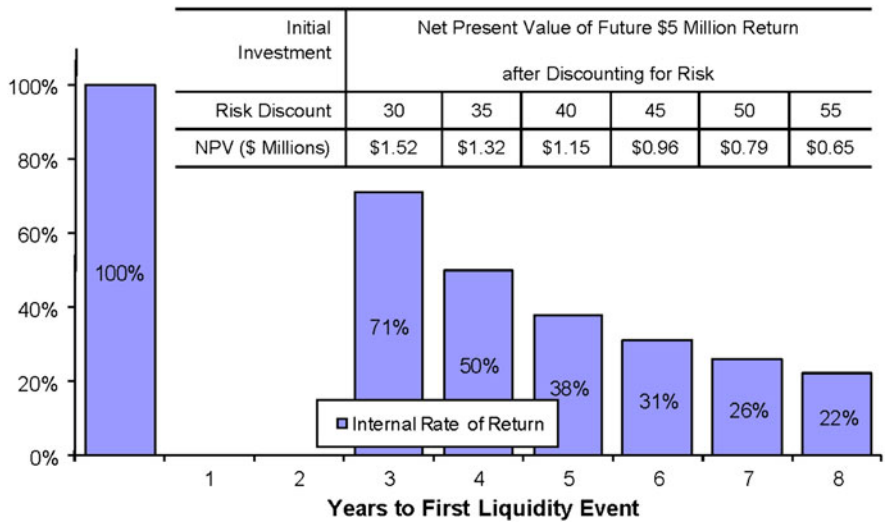

Fig. 1 Impact of a year's delay in the timing of an investment's first liquidity event (acquisition or public offering) on the IRR, where initial investment in the first year is $1 million and return at exit is $5 million (net return of $4 million). Values in the table above *bars* are the NPV of the future investment return, with values discounted beginning at 30% in year 3, increasing 5% per year to a maximum discount of 55% in year 8. Calculated using Microsoft Excel 2003

is particularly large in the initial year, where the IRR drops from 71 to 50%. In contrast, if the required investment was increased by 25% to $1.25 million, the initial IRR would be 59%, still substantially better than the drop to 50% due to the year's delay. The cost is reflected merely not only in a lower IRR, but also in the overall dilution to early-stage investors that results when the delay requires additional financing rounds and dilution, often under terms that are not optimal because the delay may also signal weakness and/or desperation to the investors providing the additional funds. While these rates of return may seem inordinately high to those more accustomed to single-digit returns on their personal investments, one must keep in mind the high risks associated with these endeavors, in which only one of ten such investments may produce this yield.

Another way of evaluating this is based on the NPV of the future payoff less the initial investment. Each successive year that it takes to yield the return reduces the NPV, assuming that the cost of capital is 10%. Venture investors and stock market analysts often deal with uncertainty by fixing a discount attributable to the likelihood of failure; the longer that a company takes to reach an exit event, the greater the discount. If the venture investors putting in the first $1 million do not find a way to mitigate the impact of an unexpected delay on their return, typically anticipated to some degree by how the initial preferred stock terms are structured, or with more onerous terms for a follow-on investment, a company can definitely expect subsequent investors to dilute their ownership by insisting on a lower valuation (a "down" round of financing).

For the case under consideration, genetically modified crops offer a pertinent real-world example from another emerging technology of the cost impact of regulatory-mandated testing increases and delays in market launch on the market opportunity. Bayer et al. (2010) examined the comparative effects of increased regulatory compliance costs and delays in market launch on biotechnology-modified crops in the Philippines, including *Bacillus thuringiensis* (Bt) rice, which has been engineered to be resistant to pests with the Bt gene encoding for a toxin that affects insects eating the plant. Their closed market model showed that a quadrupling in the cost of regulatory safety testing decreased the NPV of the Bt rice market by only 1%, while a delay in product launch of 1 year decreased NPV by 12% and a 3-year delay decreased it by 34%.

Delays are not accepted well by the stock market, and publicly traded companies suffer when they must announce a delay. Hendricks and Singhal (1997) found that the impact of a delay in a product launch, whatever the reason, decreased the market value of a company by about 5% on average. There are many cases where the decrease can be much larger, and the stock price may or may not recover. The company might experience ongoing negative impacts from a product delay, including higher development and manufacturing costs, loss of market share to competitors, and negative perceptions regarding the management's competence

(Chen et al. 2007). Chen et al. also found that the negative impact was often not restricted to the company experiencing the delay, but extended to the stock price of its competitors. The case cited was that of Centocor and the unexpected delay in its septic shock drug after FDA declined to approve the product based on the available data. The product had been expected to be the first in a line of blockbuster products coming out of the young biotechnology industry. While the share price of Centocor lost 41% in 1 day, its competitors Amgen, Genzyme, and Xoma also saw declines in their stock prices (Cohen 1992). Possible reasons given for this market response were that FDA's stance on similar products might affect pending approvals from these other companies and that this might hinder market growth and acceleration across the industry. The response seems counterintuitive in the sense that Centocor's delay could also have been seen as providing market advantages to the others by delaying Centocor's competition. The overall finding from Chen et al.'s assessment of over 300 product delay announcements was that rival firms lose share price when a competitor stumbles, rather than gaining price due to a perception of improved competitive position.

Conclusions

Efforts like those of the project team and the results summarized in this Symposium can provide a sound and rational basis for identifying oversight needs and potential frameworks appropriate for an emerging technology like nanobiomedicine, where products related to human health already face a well-established regulatory structure. The promise of this technology is real, as is the potential for unanticipated effects on human health from the novel materials being created. Clearly, not all nanoscale materials pose unique risks associated with their size or composition. The argument for considering the risk that new or extended oversight frameworks may limit development due to delays and increased costs of capital bears careful consideration, particularly when the potential benefits of the emerging technology on human health are considerable, or even transformational. Clarity in the regulatory requirements and advance notice of potential changes are key to minimizing the effect on the pace and financing of innovation.

Acknowledgments Preparation of this article was supported by National Science Foundation (NSF) grant #0608791, "NIRT: Evaluating Oversight Models for Active Nanostructures and Nanosystems: Learning from Past Technologies in a Societal Context" (Principle Investigator: S.M. Wolf; Co-PIs: E. Kokkoli, J. Kuzma, J. Paradise, and G. Ramachandran). The views expressed are those of the author and do not necessarily reflect the views of NSF.

References

Adams CP, Brantner VV (2006) Estimating the cost of new drug development: is it really $802 million? Health Aff 25:420–428

Alesandri TM, Ford DN, Lander DM, Leggio KB, Taylor M (2004) Managing risk and uncertainty in complex capital projects. Q Rev Econ Finance 44:761–767

Baeyens K, Vanacker T, Manigart S (2006) Venture capitalists' selection process: the case of biotechnology proposals. Int J Technol Manag 34:28–46

Bayer JC, Norton GW, Falck-Zepeda JB (2010) Cost of compliance with biotechnology regulation in the Philippines: implications for developing countries. AgBioForum 13: 53–62

Chen S-S, Chung T-Y, Ho KW (2007) Intra-industry effects of delayed new product introductions. Rev Pac Basin Financ Mark Policies 10:415–443

Cohen LP (1992) Biotech Stocks are Caught in Centocor Downdraft. Wall Street J, April 16, C1

Food and Drug Administration (FDA) (2007a) Nanotechnology task force report. http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm. Accessed 31 August 2010

Food and Drug Administration (FDA) (2007b) Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays. http://www.fda.gov/cdrh/oivd/guidance/1610.pdf. Accessed 30 August 2010

Heesen MG (2010) Letter to Margaret Hamburg, FDA Commissioner, from National Venture Capital Association President Mark Heesen regarding novel therapies and technologies. http://www.nvca.org/index.php?option=com_docman&task=doc_download&gid=549&Itemid=93. Accessed 30 August 2010

Hendricks KB, Singhal VR (1997) Delays in new product introductions and the market value of the firm: the consequences of being late to the market. Manag Sci 43: 422–436

Hoerr RA, Gupta A, Matuszewski M (2009) Developing practices for safe handling of nanoparticles and nanomaterials in a development-stage enterprise: a practical guide for research and development organizations. In: Webster TJ (ed) Safety of nanoparticles: from manufacturing to medical applications. Springer, New York

National Science Foundation (NSF) (2008) National Patterns of R&D Resources: 2008 Data Update. Detailed Statistical Tables, NSF 10-314, March 2010. http://www.nsf.gov/statistics/nsf10314/pdf/nsf10314.pdf. Accessed 30 August 2010

Oberdörster G (2010) Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. J Int Med 267:89–105

Price W (2007) Introduction to venture capital. http://www.slideshare.net/pricew/introduction-to-venture-capital. Accessed 31 August 2010

Ramachandran G, Wolf SM, Paradise J, Kuzma J, Hall R, Kokkoli E, Fatehi L (2011) Recommendations for oversight of nanobiotechnology: dynamic oversight for complex and convergent technology. J Nanopart Res. doi: 10.1007/s11051-011-0233-2

Sjöö K (2008) The influence of uncertainty on venture capital investments in renewable energy technology: an exploratory study. Master thesis, University of Oslo, Norway. http://www.duo.uio.no/publ/tik/2008/85712/Uppsatsen.pdf. Accessed 31 August 2010