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The rapidly changing legislative, reimbursement, regulatory, and technology landscapes, coupled with increasing civil and criminal liability, have posed significant challenges and offered tremendous opportunities for medical device manufacturers.

To help you address these developments, the Medical Device attorneys of Foley & Lardner LLP provide fully integrated experience in U.S. Food and Drug Administration (FDA) and health care regulatory issues, reimbursement, intellectual property law (IP), business law, litigation, and public affairs, enabling us to collaboratively craft effective strategies and implement them with clients.

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Early Trends for Venture Capital for Medical Device Companies in 2007

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In the last issue of *The Pulse*, I noted that 2006 was an excellent year for venture capital investing in the United States, and that one of the primary drivers of the robust activity was medical device companies. As noted in the last issue, medical device companies accounted for the most venture capital (VC) deals during the three months ended September 30, 2006 (pharmaceutical companies accounted for the greatest amount of funding). Data from the fourth quarter confirmed the record year for venture investing in medical device companies. According to data from Thomson Financial, the life sciences sector covering biotechnology and medical devices was the pacesetter in 2006, receiving $7.2 billion in investing in 731 transactions, both records for the sector.

In light of the robust market, what can be learned from 2006 to project venture capital medical device investing in 2007? Based on a review of certain transactions and continued discussions with local area venture capitalists who focus on the medical device sector, we continue to project that 2007 will be a strong year and see positive VC investing trends. As recently noted by PricewaterhouseCoopers and the National Venture Capital Association, increases in investment were focused on the right areas and produced a well-balanced mix of investing in early-stage companies, first-time financings, expansion, and later-stage investments. It is noted that one of the keys to the medical device area is the room for scale and growth that can be achieved. Another very important note is that quarterly investment levels appear to be steady and reasonably prudent and, as such, there is not a sense of overfunding in the marketplace. As a result, we expect funding levels to continue to increase at steady levels.

From a staging standpoint, the trends for early-stage, expansion, and later stage are all pointing in positive directions. In 2006, funding for startup and early-stage companies increased both in terms of number of deals and dollars, 16 percent and 11 percent respectively. Expansion stage companies saw a significant increase in deals and dollars, accounting for 44 percent of all the VC deals completed in 2006.

As noted in the previous issue, we project that medical device companies should expect to see several layers of VC investing. A typical investment for 2007 may include an initial A round of $3 million to $7 million, from which the company can achieve certain milestones. If the milestones are achieved, the investors are likely to build a syndicate and increase the funding in the B round, likely to be in the $10 million to $30 million range. Ultimately, medical device companies should anticipate or seek a five-year funding commitment. As for other specific terms, we currently anticipate that, depending on the nature of the company in which funds are being invested, that the initial round will "cost" the founder approximately 30 to 35 percent of the equity of the business, that the investors will receive a dividend preference and weighted-average anti-dilution rights, and will have a liquidation preference that will allow the investors to receive back their investment plus dividends, and then a right to "participate" in the remaining proceeds, which participation will be capped at some level. For example, an early-stage medical device company raising an initial $5 million round that gets a $8 million "pre-money" valuation, should expect that the investors preferred stock

will have the right upon liquidation to receive its $5 million investment back, any unpaid or undeclared dividends, and then to participate on an "as-converted" basis, pro-rata with all of the common stock; provided, however, that the participation may be capped (perhaps at three times the original investment amount) if the company has enough leverage to negotiate a cap.

Based on the foregoing and our experience the first two months of 2007, we continue to be extremely confident that the strong medical device investment trends will continue in 2007.

Patent Reform — The Real Solution?

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The United State Patent and Trademark Office (PTO) is promoting substantial rule changes as the way to reform and thereby help companies avoid long delays in obtaining patents and also prevent irregular and uneven patent examination; however, increased funding and staffing may provide needed relief without the risk of new problems that the proposed rules may bring.

The medical device industry is no stranger to the PTO. Medical device innovators file numerous patent applications every year, and medical device manufacturers must keep an eye on the ever-changing patent landscape to avoid freedom-to-operate issues. Current problems at the PTO affect medical device businesses on both sides of the patent fence. Medical device businesses seeking to protect their innovations must grapple with delays in the patent examination process and uneven examination quality. On the other hand, medical device businesses seeking patent clearance for a new product sometimes must contend with granted patents of dubious merit.

The PTO has promised reform, but more practical changes at the PTO may be more likely to benefit the entire medical device industry. For example, for the fiscal year 2008 budget, President Bush requested $1.916 billion for the PTO, which represents its full anticipated fee collections. The PTO also plans to hire an additional 1,200 patent examiners during the 2008 fiscal year. Adequate funding and staffing of the PTO examining corps should translate into a better examination process and higher patent quality — improvements that both medical device innovators and manufacturers will enjoy.

In contrast, there has been much debate over the proposed rule changes behind the promised PTO reform. While the PTO says that the rules are designed "to make its operations more efficient, to ensure that the patent application process promotes innovation, and to improve the quality of issued patents," it is not clear how they will solve the issues at hand. The four major rule changes relate to Claims Practice, Continuation Practice, Information Disclosure Practice, and Accelerated Examination. Although the proposed rules are directed to different aspects of the patent examination process, they are unified by a common principle of shifting burdens from the PTO to the patent applicant. Thus, the Claims Practice rules would require the applicant to identify "representative claims" for the patent examiner to focus on; the Continuation Practice rules would limit the number of continuing applications an applicant may file, and the Information Disclosure Practice rules would require the applicant to explain the relevance of submitted documents. The Accelerated Examination rules, which are the only proposed rules to have taken effect, require applicants seeking accelerated examination to conduct a pre-filing search and submit an analysis of the "most closely related" references. While it is easy to see how these rules will lighten the PTO's burden, it is not clear that the benefits will outweigh the significant costs they will impose on medical device innovators, both in terms of increased patent prosecution costs and increased risk of litigation.

Each of the proposed rules will markedly increase patent prosecution costs for which medical device innovators will have to budget. For example, the Information Disclosure Practice rules will dramatically increase patent attorney input required to prepare an Information Disclosure Statement, because the proposed rules will require an explanation of cited documents and their relevance to each patent claim. In some cases, this may require consultation with the inventors. Thus, medical device innovators also may experience increased costs in terms of the time their scientists may have to spend on patent matters.

The proposed rules also are likely to increase the risks of patent litigation, particularly with respect to charges that a patent is unenforceable due to inequitable conduct. For example, the designation of certain claims as "representative" under the Claims Practice rules, the explanations required by the Information Disclosure Practice rules, and the search and analysis required by the Accelerated Examination rules each could be the basis of an inequitable conduct charge. In this way, the proposed rules may undermine the value of new patents, at least until the courts reject frivolous challenges on these grounds.

While the costs these rules would impose are easy to identify, their benefits to the public are much less clear. It is difficult to see how any of the proposed rules would increase patent quality or reduce the number of questionable patents. Why should medical device manufacturers expect innovators to do a better job at uncovering and analyzing relevant prior art than the PTO has been able to do? Some say that shifting these burdens to the applicant will ease the burden on individual patent examiners, leaving them more time to conduct more thorough examinations. However, any saved examination time simply may be spent on examining more applications, particularly with political pressure to reduce the ballooning pending patent application backlog.

While the PTO may have other valid reasons for the proposed rules, it is more likely that the promised increased funding and staffing, and not the new demands on patent applicants, will bring changes to the examination process and patent quality that will benefit both medical device innovators and manufacturers.

Integrated Legal Strategies for Combination Biomedical Products

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As convergence of technologies enables the birth of avant-garde combination products or devices, the classical distinctions between what the U.S. Food and Drug Administration (FDA) considers a "drug," "device," or "biologic" begin to blend together. Envision, for example, a molecular machine programmed to "seek and destroy" cancer cells in the body. These machines would combine into one therapeutic product — a nanoscale device for delivering a payload of drugs, together with a biologic component that self-assembles into a protective capsule around the delivery site. The drugs would affect only the cancer site within this protective capsule, thereby improving efficacy and minimizing side effects.

Just as a nanotechnology combination product unites these three physical components — drug, device, biologic — so too are the regulatory, intellectual property (IP), and business law issues increasingly related with regard to the legal aspects of these products. To succeed in the marketplace, the innovators of combination products must be armed with an integrated legal strategy.

Regulatory Issues

All products submitted for FDA approval are first assigned to a particular center within the FDA that will have primary jurisdiction for regulating the product. Drugs, devices, and biologics each have their own center. Combination products (i.e., drug-device, drug-biologic, or device-biologic products) are assigned to a center based on the "primary mode of action" of the combination product. For example, if the primary mode of action of the above-described molecular machine is that of a biologic, then the product would be assigned to the Center for Biologics Evaluation and Research. The "primary mode of action" is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. Making this determination, however, is often difficult. Weighing the contributions of each component is imprecise. More practically, there are large variations between the three centers in terms of time and money required to obtain FDA approval. Therefore, a combination product's designation to a particular center could have a big impact on a company's ability to attract financing and to reach its scheduled milestones. This is an example of where regulatory law intersects with business issues.

The FDA has announced that it expects to classify many nanotechnology products as combination products. Companies in the nanotechnology space should be prepared to make a case for why their products ought to be assigned to a particular center, rather than relying on the FDA to decide by itself. This requires a clear explanation of the nanotechnology product's "primary mode of action" within the body. Early designation is possible, without the need for preliminary animal toxicity data. Applicants can compare their products with similar products that the FDA has recently approved. Requests can be made either informally or by formally submitting a Request for Designation. Because a favorable designation can greatly shorten a product's time to market, applicants are well advised to carefully consider the product's regulatory pathway at the outset of the development process.

IP Issues

A patent application should be filed in the United States Patent and Trademark Office (PTO) before applying for FDA approval. Applicants must be careful, however, when making statements to the PTO about the product's therapeutic effect, lest the FDA later use those statements when assigning the product to a particular center. This is an example of where regulatory law intersects with IP. The patent application only needs to describe the invention to the PTO in such detail as to enable others in the field to make and use the invention. The patent application does not need to speculate about the invention's primary mode of action, which should be examined later with more tests and then be described in a Request for Designation to the FDA. By knowing these differences at the PTO stage, an applicant can avoid arguing against himself later at the FDA stage.

Combination products also present the problem of obtaining patents needed to broadly exclude competitors. If a patent covers only a device combined with a specific biologic, then a competitor might avoid infringement by switching to a different biologic. Ideally, the applicant should have included the alternative biologic in the original patent. If the alternative biologic was not known at the time of the initial patent filing, the applicant should use multiple "continuation" patents to protect the new components as they are discovered. Currently, the PTO allows applicants to file an unlimited number of continuation patents. A proposed rule change, however, would place strict limits on these continuations. If this proposal ever becomes a PTO rule, it would greatly reduce a patentee's ability to fully protect all variations of its combination product. Nevertheless, the patents should be drafted with the goal of blocking the manufacturers who supply the separate components of the combination product — not just the doctors or patients who administer

the combined, final product. For example, if the patent covers only the final combination of a drug, a device, and a biologic, then a manufacturer can escape direct infringement by supplying only the drug and biologic components — thus, the doctor or patient will be the direct infringer when he or she incorporates the device component supplied by a third party. Patenting the separate components would avoid this dilemma.

In addition to excluding competitors, the innovators of combination products also must worry about infringing other parties' patents. The likelihood of infringement increases with each additional component of the combination product. In particular, a seller of combination products must have freedom-to-operate for each separate component (i.e., drug, device, biologic) before it can sell the combination. Thus, a manufacturer might need permission from multiple parties in vastly different fields. For instance, a manufacturer might need to negotiate a separate license agreement with a large pharmaceutical company for the drug component; a microelectromechanical system (MEMS) company for the device component; and a biotechnology startup for the biologic component. These three companies will inevitably differ in their business interests, sophistication, and the perceived importance of their patents. And because each additional license will decrease the manufacturer's incentive to market the combined product, the manufacturer should seek an "anti-stacking" provision that caps the net royalties paid to all patent holders. This is where the IP and business issues overlap.

Business Issues

Combination products require carefully structured business agreements between patent holders, financiers, suppliers, and distributors. Manufacturers must comply with the FDA's "Good Manufacturing Practice" requirements of sterility and quality control. The National Institute of Occupational Safety and Health (NIOSH) and the Occupational Health and Safety Administration (OSHA) also provide guidance for protecting the manufacturer's employees. If a licensee will be the party that manufactures and sells the combination product, then the owner of the technology should consider writing this compliance into the license agreement and require indemnification in case of breach or loss.

The success of a combination product will ultimately hinge on strategic choices regarding its distribution and reimbursement. Do you sell the drug-device-biologic product to a large pharmaceutical company that specializes in pharmaceutical drugs; to a medical device company; or to a company that makes both? Will doctors receive the completed product, or will they themselves insert the drug into the delivery device? Because nanotechnology is inherently cross-disciplinary, the physicians who administer nanotechnology combination products might need to be trained across several medical disciplines. For example, orthopedic surgeons might work with neurologists to administer a spinal cord-regenerative device laced with growth factors.

Companies must be proactive in addressing the public's perception of nanotechnology. The FDA has stated that it knows of no adverse health effects associated with nanotechnology products. Despite the lack of actual risks, nanotechnology products are subject to perceived risks, thanks in part to Michael Crichton's fictional nano- "grey goo." Perceived risks create market barriers that are just as problematic as actual risks. For this reason, companies through their research and public relations departments should continue to educate the government and the public through such initiatives as the Nanotechnology Environmental and Health Implications working group and the public forum Nanotechnology Workshops.

Conclusion

Nano-enabled combination products will inevitably change the way we diagnose and treat patients, ultimately allowing us to "seek and destroy" diseases within the body. To successfully reach the marketplace, the developers of combination products must consider the overlapping regulatory, IP, and business issues.

Clinical Trials: A Pathway Under Scrutiny and Expansion

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The critical path to market is paved through clinical trials. Navigating this pathway is becoming more challenging and expensive, and less finite and predictable. Due to a string of high-profile reevaluations and recalls of new medical therapies that have caused serious problems in patients, various government authorities are increasing the level of scrutiny used to evaluate the conduct of, and data generated from, clinical trials. The government also is demanding greater numbers of clinical trials be conducted to support the approval of new products. Companies in the medical device industry must therefore upgrade the capability of their clinical trial systems in order to adjust to and take advantage of these new challenges and ultimately remain successful.

Recent events, including the reevaluation of the TAXUS® and CYPHER® coronary drug-eluting stents (DES) and the recall of the prescription medication VIOXX®, have promoted the call for increased scrutiny of the way clinical trials are conducted and for an expansion in the number and duration of clinical trials. These calls have emanated from consumer groups, government agencies, including the United States Department of Health & Human Services, Office of the Inspector General (OIG), and members of Congress seeking to better ensure the safety and efficacy of drugs and medical devices being used in the United States.

Each of these voices has raised particular concerns with the quality and

volume of information being made available to the U.S. Food and Drug Administration (FDA) by the manufacturer of the medical device or drug (sponsor). These groups question whether the information presented is inadequate for the agency to conduct a meaningful deliberation about the safety and efficacy of the medical intervention. In a report issued in June 2006, the OIG noted that the FDA's approval process is based on data derived from clinical trials conducted on a relatively small number of human subjects, often ranging between 1,000 to 5,000 people. The OIG indicated that once a product is approved by the FDA the use of this product expands exponentially, which often results in an increase expression of adverse reactions associated with the product.

In the case of the DES, the FDA released a statement on January 4, 2007 indicating that new data suggest a small but significant increase in the risk of stent thrombosis (blood clotting) in patients who have been treated with the TAXUS® and CYPHER® devices. The FDA Circulatory System Device Advisory Panel noted that the limited size of the pre-market clinical studies were insufficient to detect or characterize significant adverse events that occur at low rates. According to Bloomberg.com, the DES market is a $6.6 billion per year industry, and estimates that nearly four million American patients have been treated with a DES. The FDA panel recommended that larger and longer pre-market clinical trials and longer follow-up for post-approval studies will be needed to better assess the benefit and risk profile of DES.

This occurrence was never more evident than in the case of VIOXX® where, according to FDA reports, the approval decision for VIOXX® was based on data derived from pre-market clinical trials conducted on 5,000 human subjects. However, when recalled, over one million patients were using the drug; and over one hundred thousand patients had suffered serious side effects.

In response to these concerns, the Center for Devices and Radiological Health (CDRH) has focused its attention on examining the level of effective monitoring by the sponsor of the conduct of the clinical trials and on developing a more systemic process to evaluate post-market data. The FDA has stepped up the level of scrutiny in overseeing the conduct of clinical trials. As part of the FDA's Bioresearch Monitoring Program (BIMO), the agency has issued over 18 warning letters related to the conduct of clinical trials. These letters identify significant deficiencies from compliance with applicable federal regulations associated with the way the clinical trial is being conducted, which raise concerns with the quality of data being collected and presented to the agency and/or the level of protection from unnecessary risks being afforded to the human subjects. This concern of effective monitor exists for both pre-market clinical trials and post-market clinical studies.

In addition to increased scrutiny of clinical trial performance, the FDA has indicated that effective safety analysis must involve an expansion of the number and duration of clinical trials, in particular in the area of post-market clinical studies. In 2005, CDRH issued a report entitled "Condition of Approved Studies as a Postmarket Tool for PMA Approved Cohort 1998-2000." In this report CDRH examined the agency's processes for continued evaluation for medical devices that were approved for marketing subject to the requirement for ongoing systematic collection and evaluation of data pursuant to Federal Regulation, Title 21, Part 814.82. The report findings were grim. The report states that CDRH imposed conditions for approval on 45 of 127 approved medical devices from 1998 to 2000, and at the time of the report the agency was unable to locate the sponsors' required annual reporting information from 26 (58 percent) of these devices.

Recently the FDA announced actions to strengthen its post-market program for medical devices. In a statement issued on November 9, 2006, the FDA announced a series of steps the agency will undertake to improve the way it monitors the safety of medical devices after they reach the marketplace. According to Dr. Daniel Schultz, Director of CDRH, the agency intends to enhance the post-market problem assessment process, which will involve the increase use and reliance on data generated from post-market clinical studies.

As a result of actions in the marketplace and concerns raised by various stakeholders, those sponsors and investigators who are conducting or planning to conduct a controlled clinical trial, pre-market, or post-market will be operating under a more watchful eye of the FDA. However, the FDA's increased vigilance in the area of compliance will be coupled with calls to the FDA for an increase in the number and duration of clinical trials in order to develop more comprehensive and evolving data on the safety and efficacy of medical devices. In light of these two seemingly contradictory messages, sponsors and investigators should be mindful of the adage, "the best defense is a good offense."

Thoughtful planning is the key. Immediately following the successful completion of pre-clinical testing, a sponsor should be engaged in developing and implementing a critical path strategy for the clinical trial phase, which addresses:

- Engagement with the FDA and the Centers for Medicare and Medicaid Services
- Development of the study design and protocol, focusing on the target endpoints
- Selection of support services, including contract research organization (CRO), central institutional review board (IRB), and central lab
- Selection of research sites and investigators
- Management of communications, including investor communications

A well-designed, tightly contracted, and soundly implemented clinical trials critical path will generate quality data and protect the rights of human subjects in a manner that ensures both efficiency of operations and compliance with federal regulations.

Biomedical-Related Technology Transfer Issues in Industry-Sponsored University Research Agreements

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This is a follow-up to the article in the last issue of *The Pulse*. In that article we introduced the topic of technology transfer, generally; and now in this article I will highlight some particular issues to consider in the structuring and negotiation of industry-university sponsored research collaborations.

A sponsored research agreement between an industrial company and a university describes and specifies the research to be performed at a university, for which an industrial sponsor provides consideration in the form of research funding. Although the terms and conditions of any particular research agreement are tailored to govern the interactions between the parties, there are several general "flavors," or types, of research arrangements. For example, industrial sponsors can provide unrestricted research grants under one type of agreement, whereby a university conducts research with little or no input from the sponsor. At the other end of the spectrum are more detailed sponsored research agreements, or laboratory funding agreements, focused on a specific scope or body of work, under which the funding sponsor's researchers may actually collaborate with university researchers, and the sponsor can have a greater say in the direction and scope of the research. In addition to governing the conduct of the research, sponsored research agreements also define the parties' respective rights in the results and any intellectual property (IP) that is created or developed during the course of the research. Although universities and industrial sponsors have differing fundamental perspectives regarding such collaborations, a better understanding of the other party's perspectives, the issues that frequently arise, and the related legal landscape, will help you plan and structure university-industry collaborations, streamline your negotiations, and facilitate the conduct of the research.

Since different types of IP are treated differently under the law, and utilized in different ways, an important issue to consider is the type of IP that is anticipated to result from the project, and the rights desired therein. For example, biomedical-related inventions, often subject to protection under the patent laws and related patent licensing, may require a different approach than, say, software inventions, which may be protected by copyright, and/or subject to "open source" license considerations. If patentable inventions are anticipated, it may prove beneficial to discuss and agree, in advance, on invention disclosure procedures and timing, identifying which party will direct and pay for the prosecution of patents, and, also, the parties' rights in "improvements" and their respective "background IP." In addition, defining a "field of use" for practicing (and licensing) an invention can "create value" for the parties by providing for rights that align with a party's respective competencies, and its research and business goals. This can go a long way toward resolving a difficult negotiation.

In addition, when determining the allocation of rights in IP arising out of sponsored research projects, it is important to consider the goals, direction, and mindset of the other party. The pursuit of theoretical scientific inquiry and the traditional mission and objective of a research university has been the development, building, and the dissemination of knowledge "for the public good" have long been hallmarks of the traditional research university. In contrast, industrial companies generally are focused on developing competitive advantages and delivering shareholder value. Accordingly, the parties may have differing perspectives on ownership, license rights, length of exclusivity, option periods, control and funding of patent prosecution and maintenance, and the like. Depending on the anticipated project output, it may be helpful for the parties to consider and address, during agreement negotiations, the treatment of IP developed by the university, the sponsor, and IP developed jointly.

Another issue that frequently arises in industry-sponsored university-based research relates to confidentiality and publication rights, again due to the differing perspectives of the participants. Universities often retain rights in their own research results and methods, and negotiate to reserve the first and unrestricted right to publish these. On the other hand, sponsors seeking a competitive advantage may be in no hurry to publicly disclose a new technology that provides a competitive advantage in its market, and may wish to preserve some portion of a discovery in confidence, at least until a patent application is filed. A balance potentially can be achieved by specifying a mutually-agreeable "pre-publication" review period, during which publications are screened for confidential information and "potentially patentable" inventions. In fact, such provisions can result in a mutual benefit, particularly to the extent that such "pre-publication" review would prevent an enabling public disclosure that may disqualify an invention from eligibility for patent protection.

In addition to publication rights, the issue of "export control" regarding research technology has become increasingly important in university-industry research agreements. Various U.S. government laws and regulations, including the International Traffic in Arms (ITAR),

Export Administration Regulations (EAR), and others, classify certain technologies as "export controlled," meaning that even the disclosure or discussion of such technologies with nationals of certain foreign countries is deemed an "illegal export." The fines and sanctions for noncompliance with export control laws can be particularly severe. Although a discussion of the various laws, classifications, and exceptions is beyond the scope of this article, issues can arise where information/technology provided by a sponsor, or developed during the course of a research project, meets the criteria for being "export controlled." Before providing information to a university researcher, an industrial sponsor would be well-served to consider whether the information may be controlled for export. If such information is to be shared or generated during the course of the research, both parties should consider whether and how the restrictions on its dissemination can be managed, of course, in compliance with applicable U.S. laws and regulations.

The issues discussed here represent a few of the points that can come up when negotiating university-industry collaborative research agreements. In addition to understanding the legal landscape, putting "standard" or "template" agreements in place with frequent research partners has the potential to streamline future negotiations. The key terms and "boilerplate" provisions, which are not anticipated to change from project to project, may be agreed-upon in an initial negotiation, with the understanding that such terms can be used with respect to future projects, with little or no negotiation. For example, each future project would have its own scope of work, and the parties could proceed to agreement more efficiently by focusing any required negotiations on the project-specific terms. This process has the potential to become smoother as the parties and the key individuals on each side develop a good working relationship over time.

University-industry research has the potential to yield positive results and be a good experience for both parties. Success stories abound regarding technologies that have emerged from industry-sponsored research at universities, and which have found life as commercial products. In addition, such collaborations provide company representatives with an early look at nascent technologies in need of funding and further development to reach the commercial market. On the other hand, university students can gain exposure to potential employers and industry contacts through these types of collaborations. By attracting research investment in the form of research sponsorship dollars and other industry contributions to local economies (i.e., facilities, jobs, engagement of local businesses and service providers, and so forth), universities can fulfill their research mission and provide an economic benefit to their local communities.

Client Focus: Nanotope Corporation's Regenerative Medicine Technology

Below is an abstract from the article, "Biotechnology Brings Hope to Tissue Regeneration" by Lay Leng Tan in *Innovation* magazine (http://www.innovationmagazine.com/).

People stricken by paralysis because of spinal-cord injury suffer a personal tragedy and researchers worldwide are investigating various means to treat this terrible debilitating condition.

Nanotope Corporation was founded by a group of US scientists at Northwestern University believe their synthetic molecules could lead to regeneration of bodily tissue, including neurons. They have succeeded in fabricating molecules that promote differentiation of mouse embryonic cells into neurons and the suppression of cells known as astrocytes, a development that holds promise of reversing paralysis due to spinal-cord injury.

Samuel Stupp, the leader and Board of Trustees Professor of Materials Science and Engineering, Chemistry, and Medicine at the university, says that his team has created exciting new materials for regenerative medicine. By virtue of their chemical structure, the synthesised materials can interact with cells of the central nervous system in ways that may help prevent the formation of the scar tissue often linked to paralysis after spinal-cord injury.

Professor Stupp, who also directs the university's Institute for BioNanotechnology in Medicine, reveals that his team has created bioactive extracellular matrices by which they can manipulate cell behaviour, starting with a key issue in regenerative medicine — controlling the differentiation of a cell.

Team members have discovered the material using self-assembly of a type of peptide amphiphile that forms nanofibres in biological environments. They achieved this combination, dubbed matrix nanotechnology, via molecular design using a family of smart molecules that self-assemble into a matrix as well as have the capacity to signal cells. The researchers programme the solution such that when they introduce the molecules in liquid into a biological environment, the molecules group themselves to form a functional structure — for instance, they cause cells to differentiate, migrate, or proliferate.

Relying on certain parameters of the platform strategy, the investigators have searched for relevant biological knowledge about proteins, functions, structures, and have incorporated such knowledge into their matrix technology. They have customised the information for specific organs and tissues, and have achieved encouraging results in bone and neurons.

In neurons they have designed a three-dimensional network of nanofibres as a scaffold and coaxed molecules to self-assemble into a specific sequence of amino acids known to promote neuron growth. The findings were published early 2004 in an online edition of *Science*.

Professor Stupp enthuses about the implications of the nanoscale discovery. "We have uncovered a little gold mine in the sense that we have a strategy to create complex structures and therefore can manage many aspects of cell behaviour. These structures can trigger regeneration of tissues in ways not considered before."

Many venture capitalists and companies keen to tap the patented matrix technology have approached Northwestern University, which is cautiously evaluating the suitors to ensure that the courtship culminates in a marriage that bears fruit.

Professor Stupp elaborates on the strict screening process: "We want to make sure we put the technology into the hands of someone who will really develop it and make a difference to humanity. It has enormous potential for a profound impact on people and on the economy since the platform could cover almost any field. You could develop strategies to regenerate heart tissue, repair bone, make cartilage, and cure diabetes or spinal-cord injuries. With such complex targets, companies need to be focused as they approach the end.

"This type of technology, straddling biology and nanotechnology, will be interesting to develop well. It may require participation of different countries. Most likely a group, perhaps of investors, will create a startup that will license the technology, and I shall have an active role in this company to ensure the translation. This startup company can develop relationships with all kinds of individuals. Parties in Japan and Korea have expressed interest."

He expects that the company that can exploit this technology will be a 21st century pharmaceutical company — not a classic pharmaceutical, biotechnological, materials, or nanotechnology setup, but rather, a hybrid of these.

Professor Stupp intends to translate the technology and move the product to clinical trial within five years or less. All the strategic targets currently have no specific application, such as spinal-cord injury, and thus conducting a clinical trial might be easier. Relying on successful preclinical work on animals, he feels confident of getting approval for human tests.

Some general targets identified include the spinal cord, heart, bone, and cartilage, and another is diabetes. He envisions possible collaboration with hospitals and others outside the US. Besides regenerative medicine, the technology can apply to other diseases, like cancer.

"Our technology is comparable to stem cell technology; both can be combined to produce regenerative strategies. However, our technology can be effective even without stem cell technology as it is modular and versatile, applicable in cellular or acellular therapy. The work is about materials with biological activities because of their structures and their way of interacting with proteins in specific ways. We are thinking of using matrix and cell, or matrix, biotechnology, and cells."

Foley represents Nanotope Corporation in corporate matters and also assists in helping to prepare for regulatory review by the U.S. Food and Drug Administration (FDA). Foley attorneys served as lead counsel for the client in its Series A round of funding.

Foreign Corrupt Practices Act for Medical Device Companies: Ramifications of Non-Compliance

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Johnson & Johnson (J & J) issued a statement on February 12, 2007 advising that the company voluntarily disclosed to the United States Department of Justice (DOJ) and the U.S. Securities and Exchange Commission (SEC) that subsidiaries outside of the United States may have made improper payments in connection with the sale of medical devices in two small-market countries. J & J advised that the improper payments violated company policies, and may be covered by the U.S. Foreign Corrupt Practices Act (FCPA). The DOJ and SEC are reviewing the matter, and J & J is cooperating with the review. The press statement also advised that as a result of the above payments, the Worldwide Chairman of J & J Medical Devises & Diagnostics retired because those subsidiaries were his "ultimate responsibility by virtue of [his] position."

With the above public statement and voluntary disclosure, J & J has reminded all medical device and equipment companies that they, too, are at risk of an FCPA criminal and civil violation if any company, its employees, officers, subsidiaries, or agents offer, promise, make, or give bribes or anything of value, directly or indirectly, to foreign officials (including foreign government agency employees, foreign medical professional staff, health ministry personnel, or foreign procurement agencies or their staff, among others), corruptly, in order to obtain or retain business, or to gain some improper advantage. Medical device companies should ensure that they have effective FCPA and international antibribery compliance procedures and training, and also ensure that they and their subsidiaries maintain accurate books, records, and accounts, as well as an adequate system of financial internal controls. Medical equipment and other companies also must evaluate their programs to ensure that product incentive programs that may be

lawful in one country or circumstance do not violate the broad FCPA prohibitions against promises, offers, or payments of anything of value to foreign officials for an improper business purpose.

Medical equipment companies that fail to comply in these areas risk criminal and civil fines and penalties, multi-year U.S. enforcement agency compliance monitoring and reporting, reputational damage, prosecution of individual offenders, business disruption, and multi-million dollar investigative and attorneys' fees. J & J's voluntary disclosure of improper payments to the DOJ and SEC is just the beginning of an arduous, costly, and serious FCPA enforcement agency process. Medical device companies engaged in overseas sales and projects with foreign governments, their agencies, and personnel are particularly vulnerable and are required to have compliance programs that address their level of risk. Importantly, the companies must establish the system to minor and track the implementation of the programs.

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