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# Tissue Engineered Constructs: Perspectives on Clinical Translation

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**Abstract**—In this article, a "bedside to bench and back" approach for developing tissue engineered medical products (TEMPs) for clinical applications is reviewed. The driving force behind this approach is unmet clinical needs. Preclinical research, both *in vitro* and *in vivo* using small and large animal models, will help find solutions to key research questions. In clinical research, ethical issues regarding the use of cells and tissues, their sources, donor consent, as well as clinical trials are important considerations. Regulatory issues, at both institutional and government levels, must be addressed prior to the translation of TEMPs to clinical practice. TEMPs are regulated as drugs, biologics, devices, or combination products by the U.S. Food and Drug Administration (FDA). Depending on the mode of regulation, applications for TEMP introduction must be filed with the FDA to demonstrate safety and effectiveness in premarket clinical studies, followed by 510(k) premarket clearance or premarket approval (for medical devices), biologics license application approval (for biologics), or new drug application approval (for drugs). A case study on nerve cuffs is presented to illustrate the regulatory process. Finally, perspectives on commercialization such as finding a company partner and funding issues, as well as physician culture change, are presented.

**Keywords**—Tissue engineered medical products (TEMPs), Bioethics, Regulatory issues, Food and Drug Administration (FDA), Medical devices, Commercialization.

## INTRODUCTION: BEDSIDE TO BENCH AND BACK APPROACH

The field of tissue engineering and regenerative medicine is rapidly expanding, both in laboratory research and in clinical translation.[5] The development of tissue engineering scaffolds for clinical use has traditionally been a one-way, bench-to-bedside approach. Over the course of several decades, researchers have reached the consensus that an interactive, back and forth, "bedside to bench and back again" approach should be adopted to ensure successful translation of tissue engineered scaffolds into clinical practice.

With this approach, the motivation to develop any new tissue engineering scaffolds is to address unmet clinical needs. This requires a precise understanding of current clinical practice in order to identify those specific clinical situations that are yet to be successfully addressed or require improvement. For example, in bone tissue engineering, the repair of small segmental bone defects is routinely done in the clinic with excellent results. However, the repair of large segmental bone defects remains a challenge. Another example is the poly(methyl methacrylate) (PMMA) bone cement; it can be quite successful for certain applications yet not ideal as a repair material for vertebroplasty in older, osteoporotic patients due to modulus mismatch between the PMMA and the bone.

Once the unmet clinical needs are identified, the next step is to articulate a series of well-defined questions to help guide the scaffold's initial development and characterization, *in vitro* testing in cell culture models, and *in vivo* testing in small and/or large animal models. The intended clinical application should dictate the design requirements of the scaffold that include physical, chemical, mechanical, and degradation properties, as well as its biocompatibility and interactions with cells and tissues. Considerations for the technical demands of a scaffold (form, function, fixation, and formation) as well as testing of scaffold-based constructs have been reviewed.[7,8] As required by law, any

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research protocol involving animals needs to be approved by the Institutional Animal Care and Use Committee (IACUC) which regulates the animal care and use at each local institution.

Good Laboratory Practice (GLP) [Code of Federal Regulations Title 21 Part 58 (21 CFR 58)] and Good Manufacturing Practice (GMP) (21 CFR 820 for medical devices; 21 CFR 211 for drugs) regulatory policies are important considerations pertaining to laboratory testing and implant manufacturing. GLP and GMP serve different purposes. The GLP is a quality system designed to protect scientific data integrity by providing a clear and auditable record of the planning, performance, monitoring, recording, archiving, and reporting of open-ended non-clinical research studies, often needed for submission to the U.S. Food and Drug Administration (FDA) or the U.S. Environmental Protection Agency (EPA) for premarket approval. In contrast, GMP is intended to demonstrate whether or not individual batches of a regulated product are manufactured according to predefined manufacturing criteria and therefore concerns both production and quality control. Moving a cell-based therapy into the GMP environment and further into clinical trials has recently been discussed.[1]

In this review article, we will address several major challenges to the translation of tissue engineered medical products (TEMPs) to clinical practice. These include ethical issues, regulatory issues on both the institutional and the governmental levels, funding issues for product development, and issues related to physician acceptance of a new treatment method.

## CLINICAL RESEARCH

### *Ethical Issues and Conflict of Interest*

As emerging TEMPs are now entering into clinical testing in the United States and other countries, open discussions are needed regarding ethical issues in clinical trials. Several treaties and conventions have identified specific issues and suggested methods to safeguard human rights and fundamental ethical principles in tissue engineering research. These ethical and conflict of interest issues have been widely investigated and communicated in the peer-reviewed literature.[12,16] Two broad issues that have been studied in TEMPs are: (1) the use of cells and materials in preclinical studies, and (2) considerations for clinical trials using TEMPs.

#### *Considerations for Cells and Tissues*

Ethical issues regarding the use of cells for tissue engineering have been debated in both scientific and popular publications and mainly focus on the source of the cells used in TEMPs and the donation of cells.[4,12] Several of the ethical discussions have highlighted the controversies regarding the use of human embryonic stem cells. Some bioethical arguments claim that use of these cells might lead to elective abortions and encourage medical institutions to increase the number of abortion procedures. Another issue with the use of human cells or tissues is the ownership. There have been questions raised as to whether human cells/tissues can be subjected to laws regarding property rights. Some reports argue against granting property rights, as it would violate human dignity and also could lead to the exploitation of disadvantaged or marginalized populations.[15] In addition, objections to the therapeutic cloning of cells, reservations regarding the genetic engineering of cells for TEMPs, and the mixing of human and animal cells have been raised when ethical issues regarding the use of human cells are considered.[9]

The issues associated with the use of xenogenic cells or tissues for TEMPs include the risk of introducing bacterial, viral and other pathogenic agents into humans. In addition, several reports point out the fact that the donor animals will be subjected to pain and distress, and suggest that animals should only be used as the source of tissue/cells with proper justification. The objections to the use of animal cells also stem from religious issues and possible immunological issues associated with those cells.

Guidance for the clinical use of cells and tissues has been outlined by the FDA (various FDA guidance documents can be found at http://www.fda.gov/). Novel cellular and tissue-based products that provide increasingly useful therapies for a wide range of medical conditions are referred to as "human cells, tissues, and cellular or tissue-based products" (HCT/Ps) by the FDA.[14] A product meeting certain specific criteria may be eligible for regulation as a 361 HCT/P solely under 21 CFR 1271 and is not subject to premarket clearance or approval. The four criteria that must be met are: (1) It is minimally manipulated, (2) It is intended for homologous use as determined by labeling and advertising, (3) Its manufacture does not involve combination with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent (not raising new clinical safety concerns for the HCT/P), and (4) It does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function, or if it has such an effect, it is intended for autologous use or allogeneic use in close relatives or for reproductive use.

Minimal manipulation is defined in 21 CFR 1271.3(f) and should be considered on a case-by-case basis for TEMPs involving cells and tissues. For structural tissue, minimal manipulation means processing that does not

alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement. FDA's "Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue Jurisdictional Update" (http://www.fda.gov/RegulatoryInformation/Guidances/ucm126197.htm) explains that a tissue characteristic is "original" if it is present in the donor's tissue. A tissue characteristic is "relevant" if it could have a meaningful bearing on how the tissue performs when utilized for reconstruction, repair, or replacement. If processing has altered an original characteristic of a structural tissue and that the characteristic would have a potential effect on the tissue's utility, the tissue is deemed more than minimally manipulated. FDA has stated that cutting, grinding, shaping, soaking in antibiotic solution, sterilization by gamma irradiation, lyophilization, freezing, and demineralization of bone are all examples of minimal manipulation.

For cells or nonstructural tissue, minimal manipulation means processing that does not alter the relevant biological characteristics of cells or tissues. FDA has stated that density-gradient separation, cell selection, centrifugation, and cryopreservation constitute minimal manipulation. On the other hand, cell expansion in culture and human skin processed into human collagen are examples of more than minimal manipulation.[14]

An assorted variety of human cells, tissues, and organs are currently donated for tissue engineering research and clinical applications including blood, oocytes, solid organs, bone marrow, corneas, skin, umbilical cord cells and embryonic tissues. The protection of the privacy of the donors has been stressed in several reports. Unpaid donations have been suggested as an ideal method for obtaining these materials. Reports have also emphasized a need for proper policies through proposed government regulations.

The issue of obtaining informed consent from the donors has been highlighted by many investigators. Several guidelines have been indicated for informed consent, which include the following: (1) To ensure that prospective participants make a fully informed and independent decision on their participation in the study, (2) The aims and procedures of the trials need to be well-documented, (3) Risks and benefits involved need to be explained, and (4) The roles of the principal investigators need to be clearly defined. Several surveys indicate that potential donors tend to prefer tissue and cell donations for therapy over research use. Areas such as cancer research and improving treatment for infertility elicit more interest among tissue donors. Overall, it has been observed that the willingness to donate increases when the potential donor has knowledge about a particular condition or disease.

### *Considerations for Clinical Trials*

The ethical considerations for clinical trials are several in number, which include but are not limited to: (1) when the TEMP has undergone sufficient testing *in vitro* and in animals such that it is likely to be safe in humans, and (2) when the tissue engineering approach has generated sufficient data in the clinical trials to be introduced into population-wide clinical practice.

A number of factors make therapeutic and ethical use of TEMPs more complex than that of drugs. The approval pathway for clinical use is not clearly defined. For example, in the United States, new surgical procedures are not regulated by the FDA and can be introduced at the discretion of the treating surgeon. Allograft organ implants are regulated by the Department of Health and Human Services, not by the FDA. However, surgically implanted tissues fall under FDA regulations. Furthermore, TEMPs do show a certain degree of unpredictability due to the combination of the metabolic nature of the cells and an immunologically different recipient's body. Since potentially harmful changes may be introduced into the recipient, the clinical application of human stem cells should be closely and carefully monitored.

Several requirements for performing clinical studies have been well-defined. Initiation of these studies must be justified by an appropriate benefit-risk analysis and adequate human subject protection measures. All clinical trials should comply with the Good Clinical Practice (GCP) standards for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Another issue is sponsorship of clinical trials.[16] A recent study indicates that physicians overall have less confidence in industry-funded clinical trials and believe that government-sponsored clinical trials remain the best option to avoid any bias.[4]

The right to benefit from medical treatment is an important ethical aspect of clinical trials. Among the questions to be addressed in the organization of a clinical trial is to consider whether all individuals with a financial interest in a TEMP should be excluded from the testing process or leadership roles in the studies. Hence, it is important to ensure full transparency and make available on request all information regarding investigator financial interests in the development and testing of TEMPs. Overall, in addition to a community of experts that include researchers, clinicians, regulatory agencies and industry partners, oversight by an independent data safety monitoring board is required for a clinical trial and the development of a successful TEMP.

## Regulatory Issues

### Institutional Regulatory Issues

Similar to the role of the IACUC in animal research, the Institutional Review Board (IRB; 21 CFR 56) is charged with protecting the rights, privacy and welfare of all human participants in research programs conducted at each institution. The responsibilities of an IRB include review of the qualifications of clinical investigators, review of the adequacy of the research site, verification of Investigational Device Exemption (IDE) approval, assessment of the sponsor's determination of significant risk/non-significant risk or exemption, and approval of the Standard Operating Procedures (SOPs) for conduct of the clinical trial. The IRB has the authority to approve, require modifications in, or disapprove the clinical trial.

### Government Regulatory Issues

In the United States, the agency that oversees the development and commercialization of tissue engineering and regenerative medicine products within the federal government is the FDA. Similar regulatory bodies exist in other parts of the world. Examples include the European Medicines Agency (EMA) in Europe, the State Food and Drug Administration (SFDA) in China, the Ministry of Health, Labour and Welfare (MHLW) in Japan, and the Therapeutic Goods Administration (TGA) in Australia. Globalization and regulatory harmonization are still significant challenges for these regulatory authorities.[3]

#### FDA

The FDA is a science-based regulatory agency of the U.S. Public Health Service (PHS), with a mission to promote and protect the public health, through regulation of a broad range of products by assuring their safety and effectiveness. The FDA has six centers and several offices (www.fda.gov). The Center for Drug Evaluation and Research (CDER) regulates drugs. The Center for Biologics Evaluation and Research (CBER) regulates biological products. The Center for Devices and Radiological Health (CDRH) regulates medical devices and radiation-emitting electronic products. The other centers are the Center for Tobacco Products, the Center for Veterinary Medicine, and the Center for Food Safety and Applied Nutrition. FDA Offices that may be involved in the evaluation of TEMPs include the Office of Combination Products (OCP), the Office of Regulatory Affairs (ORA) and the Office of Orphan Products (OOP).

Many tissue engineering and regenerative medicine products are combination products as they may contain scaffolds, cells, and drugs. In this case, the OCP will determine the primary mode of action by which the product achieves its intended therapeutic effect, either drug, biologic, or device, and assign it to the proper center to lead the review of that product, with the other two centers providing input.

#### Investigational Studies: IDE/IND

Following pre-clinical studies, premarket clinical studies must be performed under exemptions from the laws (FD&C Act for new drugs and devices and PHS Act for biologics) that require demonstration of safety and effectiveness before introduction into interstate commerce. Consequently, an Investigational Device Exemption (IDE; 21 CFR 812) for device introduction or an Investigational New Drug (IND; 21 CFR 312) application for drugs or biologics must be filed with the FDA. The applications will include a description of the product and manufacturing processes sufficient for an evaluation of product safety, preclinical studies that have been designed to assess the product's risks and potential benefits, and a proposal for a clinical protocol, which describes the indication being treated, proposed patient population, patient inclusion and exclusion criteria, treatment regimen, study end points, patient follow-up methods, and clinical trial stopping rules. Both IND and IDE investigations require IRB approval before they may commence.

Before a medical device clinical research study may begin, a risk assessment must be made. Initially this assessment is conducted by the study sponsor. If the study is initiated by a medical device company, the regulatory sponsor is the company. If the study is initiated by the investigator, the regulatory sponsor is the investigator (sponsor-investigator). A significant risk (SR) designation requires the submission of an IDE to the FDA, approval by the FDA, and approval by an IRB prior to starting the investigational study. The full IDE regulations (21 CFR 812) apply. If the device is considered non-significant risk (NSR), an IDE application is not required to be submitted to FDA. In this case an IDE is considered to be in effect and the IRB serves as the surrogate overseer. In addition, the abbreviated IDE regulations must be followed [21 CFR 812.2(b)].

The first clinical studies conducted under IDE applications are often early feasibility studies. These studies allow for early clinical evaluation of devices to provide proof of principle and initial clinical safety data. An "early feasibility study" is a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication (e.g., innovative device for a new or established intended use, marketed device for a novel clinical application). It may be used to evaluate

the device design concept with respect to initial clinical safety and device functionality in a small number of subjects (generally fewer than 10 initial subjects) when this information cannot practically be provided through additional nonclinical assessments. Information obtained from an early feasibility study may guide device modifications, however, second or third generation designs do not always require a new clinical trial. Medical device development employs feasibility, pilot and pivotal study models. Pilot and feasibility studies are considered "first in human" (FIH) studies in which a device for a specific indication is evaluated for the first time in human subjects.

Unlike medical devices where a single confirmatory study is often sufficient for FDA approval, drug development involves Phases I through IV clinical trials, with each phase designed to answer a separate research question. The first study conducted under IND applications is often a Phase I clinical trial to test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. If these early studies indicate reasonable safety, Phase 2 studies may be developed to investigate proper and safe dosing and potential efficacy in a larger number of patients. Phase 3 studies utilize well-controlled clinical trial designs that support a determination of safety and effectiveness and lead to an application to the FDA for marketing approval of the product. Phase IV studies are performed after the product has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.

*Pre-Submission*

In 1995 the FDA established a pre-IDE program as a mechanism to provide feedback to medical device applicants prior to pre-market device submissions. Over time this program evolved to include feedback on other types of medical device submissions and to answer questions related to whether a clinical study requires submission of an IDE application. In 2014 this program was broadened and renamed the Pre-Submission (Pre-Sub) program to include biologics and drugs as well as medical devices. All of these feedback requests are now collectively referred to as "Q-Submissions" or "Q-Subs." Pre-Subs are generally useful for early feedback on specific questions during submission preparation. FDA encourages sponsors to review all relevant device-specific guidances prior to preparing a Pre-Sub, which streamlines their review and determination regarding substantial equivalence. The feedback provided assists in preventing repeat studies, identifying studies that are not well designed, and promoting studies of importance that have been overlooked. In order to avoid unforeseen complications during the product development and FDA approval processes, it is advisable to take advantage of these meeting opportunities that are encouraged by the FDA.

*Premarket Submissions: 510 k/PMA/BLA/NDA*

The Food, Drug, and Cosmetic Act established three classes for medical devices:

> Class I: General controls. Examples include occlusive wound dressings, surgeon's gloves, manual stethoscopes, and certain hand-held surgical instruments.
> Class II: General controls plus special controls. Examples include powered wheelchairs, infusion pumps, electronic stethoscopes, sonic surgical instruments, and surgical drapes. The application for marketing approval for Class II medical devices is the 510(k) premarket notification process.
> Class III: General controls, special controls, plus pre-market approval. These devices must be evaluated and approved by FDA *via* the premarket approval (PMA) process to ensure their safety and effectiveness. These are life-sustaining, life-supporting, and implantable devices, or new devices that have not been found to be substantially equivalent to devices that were lawfully marketed prior to May 28, 1976. Examples include heart valves, silicone gel-filled breast implants, automated external defibrillators, and intervertebral body fusion devices that contain any therapeutic biologic.

Device classification depends on the intended use of the device and also upon indications for use. For example, a scalpel's intended use is to cut tissue. A subset of intended use arises when a more specialized indication is added in the device's labeling such as, "for making incisions in the cornea". If the device is classified as Class I or II, and if it is not exempt, a 510(k) (premarket notification) application must be submitted and receive FDA clearance prior to marketing the device. All devices classified as exempt are subject to the limitations on exemptions. If the device is classified as Class III, then a PMA application will be required, and must receive approval, prior to marketing the device. In order to obtain 510(k) premarket clearance, the sponsor must demonstrate substantial equivalence of the device to a predicate device that was legally marketed prior to May 28, 1976, or a device that has been previously cleared through the 510(k) process.

The device classification process begins by identifying the classification level of the device. This can be accomplished by searching the FDA's device classification database, or by communicating with the appropriate FDA device advisory panel to identify the

device classification and its corresponding regulation. Using an embolectomy catheter as an example, it is a cardiovascular therapeutic device, and the regulation is 21 CFR 870.5150. The regulation states that this is a class II device to which performance standards apply. It is not exempt from premarket notification, therefore a 510(k) application is required.

Since the basis of a 510(k) is to demonstrate substantial equivalence to a lawfully marketed device (predicate device), such a device must be identified. This can be done by searching the FDA's 510(k) Premarket Notification database using the device name (embolectomy catheter) and the FDA advisory panel (cardiovascular) that assesses such devices. In this example, the results show that there are 27 cleared 510(k)s for this device classification. Opening one of the results in the listing shows that the Classification Product Code is DXE. In each of the results listed, there is a link to the 510(k) summary. The summary is a description of the tests that were conducted to demonstrate substantial equivalence to the predicate device. The summary also contains the 510(k) clearance letter from the FDA. The regulatory pathways for several commercial biomaterial product types have recently been reviewed.[13]

If the tissue engineering and regenerative medicine product is regulated as a biologic, then a biologics license application (BLA) that demonstrates the safety and effectiveness of the product must be reviewed and approved by the FDA Center for Biologics Evaluation and Research (CBER) before it may be marketed commercially. Similarly, if the TEMP is determined to be a drug, then the IND approval for first in human use must be followed by a New Drug Application (NDA) *via* the Center for Drug Evaluation and Research (CDER).

*Case Study: Nerve Cuffs*

In this section, we will give an example of how a tissue engineered nerve cuff may proceed through the regulatory process. It would begin with a search of the FDA's website for nerve cuffs. A nerve cuff is a neurological therapeutic device defined in 21 CFR 882.5275 as a tubular sheath used to encase a nerve for aid in repairing the nerve and/or to prevent ingrowth of scar tissue and for capping the end of the nerve to prevent the formation of neuroma. The product code is JXI and it is a class II medical device in which performance standards apply. A spreadsheet will then be developed from the information available in the published 510(k) summaries. This includes device material, pre-clinical studies, clinical studies, biocompatibility testing, bench testing, and the predicate devices. There are 16 cleared 510(k) nerve cuff applications of which seven are made of collagen, seven are synthesized polymers, and two are made of porcine small intestinal submucosa.

The FDA guidance for industry and FDA staff titled "The 510(k) Program: Substantial Equivalence in Premarket Notifications [510(k)]" shows a flowchart of the decision making process. This process highlights the importance of choosing a legally marketed predicate device that not only has the same intended use (e.g., for the reconstruction of a peripheral nerve discontinuity up to 20 mm in patients who have sustained a complete division of a nerve) but also has the same technological characteristics (e.g., device made of the same polymer) and does not raise questions of safety and effectiveness. This is important for showing substantial equivalence of the two products without having to conduct additional studies beyond those which the predicate device manufacturer conducted.

The first nerve cuff 510(k) was made of collagen and cleared by the FDA in 1985. There was no 510(k) summary available, therefore no information existed regarding a predicate device or studies conducted. The second nerve cuff 510(k) cleared by the FDA was in 1999. Since it was made of poly(glycolic acid), and the predicate device identified was a silicone nerve cuff, clinical studies were required to demonstrate that this change in material did not raise questions of safety and effectiveness.

A collagen nerve cuff was cleared by the FDA for marketing in 2003 for the indication "to be used for the management of peripheral nerve injuries in discontinuities where gap closure can be achieved by flexion of the extremity (e.g., to prevent ingrowth of scar tissue)". In 2014 the same company submitted a 510(k) for the same nerve cuff except with an additional intended use. Further animal and clinical studies were necessary in order to demonstrate that the additional intended use, "management of peripheral nerve injuries at the end of the nerve in the foot to reduce the formation of symptomatic or painful neuroma" did not raise questions of safety and effectiveness.

It should be determined early in the development of the regulatory strategy if this tissue engineered nerve cuff will be the only device or if it will be the first of a family of nerve cuffs. This is important in planning the animal or clinical studies and bench testing to be done. It is best to keep in mind issues and questions that may arise during subsequent iterations/further development of a product, that may be addressed during studies and tests for the first iteration or initial production of the product.

## COMMERCIALIZATION

The time to consider commercialization of TEMPs is much earlier than most investigators realize. The

earlier the investigators account for commercialization criteria (e.g., market size, competition, reimbursement, adoption by users, *etc*.) and develop the product in accordance with these criteria (e.g., preclinical testing against competing products), the more valuable their studies become in supporting a marketing application, and the higher chance they withstand in raising necessary funding or partnering with an existing company. For this reason, the development team for TEMPs should include individuals with non-scientific expertise such as finance, marketing, management, and patent and contract law. Many academic institutions have resources to assist investigators in attracting the right financial and business partners.

### *Company Partner*

There are four key points to keep in mind while searching for a company partner: (1) start-up company or established company, (2) consultation agreement or know-how agreement with an established company, (3) equity and royalty issues, and (4) inventor's level and nature of involvement.

Determining whether to start your own company or reach out to one that is already established is not an easy task. The fact is, there are challenges on both sides of the fence. For instance, starting your own company requires a great deal of hard work and effort to get the buy-in from potential 'angel investors' or finding other 'venture capital (VC)' funding.[2] You will need to be able to sell your concept/idea first and then you will need to convince potential investors why your product is the best available for current clinical needs. If you decide to partner with an established company that already markets TEMPs, that company likely already has expertise in your product's market sector and an existing clientele base, both of which can further enhance the buy-in power of your TEMP.[6]

The second key point worth discussing is the value of a 'consultation agreement' or a 'know-how agreement' with an existing company. In today's arena, the hire of consultants is a very common practice by industrial partners for several reasons. Firstly, it typically brings with it many years of expertise in a variety of different professions. This can help to significantly increase a company's potential for successfully marketing their product/device. Another reason is that a consultant is hired on a temporary, not permanent basis, therefore, benefit packages are not typically offered. One thing, however, to keep in mind during the drafting of this agreement, is that it be extremely detailed in regards to what the expectations, inclusions and exclusions are. The key difference between consulting agreements and know-how agreements centers on the development of new intellectual property. A know-how agreement includes provisions as to how new intellectual property that is generated as a result of the consultant's work with the company will be handled. The consulting agreement is fee for service with no expectation of the consultant sharing in the benefits of novel intellectual property. If the interaction between the consultant and the company is such that the generation of novel intellectual property is anticipated, then a know-how agreement is generally the preferred method to accomplish that interaction. The importance of paying close attention to the type of agreement between consultant and company is critical to protect the legal rights of all parties concerned.

Equity and royalty issues can also result in very serious consequences if not clarified up front and entered into the contract with an existing company. Your institutional Technology Transfer Office (TTO), which may operate under a number of different titles, can be extremely useful to help get a product/device into the marketing arena. It is advisable to use all available institutional resources to help ensure that you do not run into any deal breakers that may have been prevented if the appropriate expert services were used early on in the commercialization process. Prior to December 12, 1980, ownership of intellectual property that was funded through federal dollars was dictated by the research sponsor. Because of this, the development of TEMPs made possible through federal grants was seldom brought to commercialization.[10] The passing of the Bayh-Dole Act opened a new set of doors for federally funded projects and provided increased incentive for universities and institutions to develop a more robust support system for their personnel that allowed them to more aggressively pursue new discoveries in the medical field.

A few additional points to consider in the development and commercialization of TEMPs are what role the inventor will play in the company, especially if it is a new start-up company. An inventor is the person whose intellectual contributions led to the development of the TEMP under consideration. At what level will the inventor be involved in the company? It is certainly necessary for the inventor to be involved but the level of engagement will vary depending on whether or not this is a start-up company or one that is already established. For instance, if the company is a start-up, it is not uncommon for the inventor to be the Chief Executive Officer (CEO). However, this will involve a great deal of time and energy managing the financial and marketing aspects of the company to help ensure its profitability. Also, the inventor may choose to take on the role as Chief Scientific Officer (CSO), which makes perfect sense, as the inventor has the knowledge and skills necessary to address the scientific and technical aspects of the company.

### *Funding Issues*

The success of a TEMP will be directly related to its value, as well as its ability to attract the necessary funding for commercialization and marketing. Three important sources of funding worth considering are industry, investors and venture capital firms. There are also several federal funding programs available for research and development. Two such NIH programs worth noting are the Small Business Innovation Research (SBIR) program and the Small Business Technology Transfer (STTR) program (http://www.sbir.gov). The SBIR program is a highly competitive program that is geared toward funding domestic small businesses to engage in Federal Research/Research and Development (R/R&D) that has a high potential for commercialization. This is a three-phase program and currently includes participation from eleven Federal agencies. The STTR program is an expansion of the public/private sector partnership and includes joint ventures for small business and not-for-profit research institutions. In the STTR program, it is required that the small business formally collaborate with a research institution in Phase I and Phase II of the program. STTR's most important role is to bridge the gap between the performance of basic science and the subsequent commercialization of any resulting innovations.

### *Physician Culture Change*

Although other considerations and issues have been discussed previously, another worth mentioning is physician culture change. This is certainly nothing new to the field of medicine, but at the same time it needs to be addressed during the commercialization phase of a TEMP. The responsibilities of physicians are enormous, and whenever they are asked to consider the use of a newly developed product, device or therapy for the care of one of their patients, many of them will be hesitant. There can be varying reasons for this, the most important of which is the physician's assessment of potential risk for harm to her/his patient. The National Patient Safety Foundation (NPSF) has developed an educational program that discusses several key points as to what some of the issues are regarding physicians' culture change, and suggests methods to help improve the processes for acceptance by physicians of changes to the practice of medicine.[11]

### *Summary*

This is an exciting time with respect to advancements in patient care which span many areas, from population-wide care programs down to the care of individual patients. Several TEMPs have already reached the care of the individual patient, and it is likely that additional TEMPs will reach patient care in the near future. It behooves everyone involved in the development of TEMPs to learn and apply the steps involved from the identification of an unmet clinical need to commercialization and physician acceptance of a new TEMP in order to maximize the probability that the new TEMP will lead to improved care for all of us as patients.

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