Medical Device Development: Design, Engineering, Testing, and Legal Issues Protection: Steps in the Process to Success

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Introduction

The Food, Drug, and Cosmetic Act of 1938 defined medical devices as "instruments, apparatus, and contrivances, including their components, parts, and accessories, intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or to affect the structure of any function of the body of man or other animals." Society as well as the medical profession has an unrelenting desire for innovation and the development of new technology to improve diagnosis, treatment, practice efficiency, and quality of life for both the patient and the practitioner. This creates an enormous appetite for discovery, and expects, requires, and relies on innovative new products. With the advent of newer endoscopic techniques and the potential development of Natural Orifice Transluminal Endoscopic Surgery (NOTES) there is a potential need for many new devices in the practice of gastroenterology and hepatology.

Entrepreneurism in the field of medical devices begins with the observation of a need, which often occurs in the midst of providing clinical care where the available tools may not be up to the task. This need often leads the practitioner to develop a solution, which evolves over time as the problem and potential solutions are parsed out. The idea may simply be an improvement on a currently used device, or it may be revolutionary. In either case, the goals are generally the same: enhanced performance, decreased cost, and/or improved safety. But how is the idea put into practice? The first step is usually to create a team to help with the various aspects of developing the new device. Very rare is the individual who can envision an idea for a medical device and then design, engineer, license and market the device and protect the intellectual property rights therein. The inventor acts as the quarterback and each team member is given a specialized role, much like the pass rusher, kicker, or wide receiver. In the course of this paper, we hope to outline several aspects of the process and suggest a teamwork approach to bringing your idea to fruition.

Design, Engineering, and Development

The Department of Health and Human Services and the Food and Drug Administration (FDA) have established requirements for the process and documentation required in developing and manufacturing medical devices.[22] It requires detailed planning for the development, design input, design output, design reviews, design verification/validation, design transfer and design changes, all of which are documented in a Design History File. As a product is developed, the record of its development must be maintained. It is rare that an individual physician or even physician group has these skills and involving other professionals in this process is a key success factor.

A quality system certification program called ISO 13485:2003 has been established for companies designing and manufacturing medical devices. It is a Quality Management System for medical devices, specifically for regulatory purposes and is available on the internet. The ISO 13485:2003 provides medical device manufacturers a stand alone standard for quality management systems that must demonstrate compliance with

regulatory requirements. By selecting development and manufacturing companies that are certified by a third party as meeting the ISO 13485:2003 requirements, you can have confidence that they are operating in a way that meets FDA regulations.

While ISO 13485:2003 provides a framework for development, a more practical approach is needed to determine if a concept is likely to succeed. There are many approaches, but Johnson & Johnson, Worldwide Franchise Development at Ethicon Endo-Surgery[23] uses a "gating process" in the form of a spiral to periodically evaluate the likelihood that a new device can achieve commercial success. As noted in the reference,[23] new product development requires a different process than sustaining product innovation. "Sometimes you don't know what you don't know." Each stage of the process considers all of critical success factors for a new idea and sequentially are:

1. Clinical Need & Understanding
2. Idea Generation with alternatives
3. Models & Prototype
4. Evaluation
5. Voice of Customer (VOC) Inputs
6. Commercial Understanding
7. External Variable (IP, Regulatory, Clinical)
8. Documentation (Patents, Disclosures)
9. Access Risk & Uncertainty
10. Decision of Go-No Go
11. Planning
12. Manufacturability
13. Sterilization

As the product development proceeds, each factor is investigated in greater depth with higher cost and longer timelines. The first spiral cycle can be relatively fast (1-2 months) and low cost ($10-20 thousand). The next steps become increasingly longer and more expensive with the final commercialization and release for sale, often costing several million dollars.

Generally the design and development can be split into three phases:

1. Concept Development and Design
2. Regulatory
3. Transfer to Production

The first and most critical step in concept development and design is preparing a written product specification. This should fit the clinical need and provide an understanding of how the device will work, what procedure it will accomplish and the critical physician – patient characteristics. This is a living document that is continuously updated as the project proceeds. It is also the first fundamental definition of what you are trying to accomplish.

Next, an engineering specification is prepared based on the product specification that defines the technical features of the product necessary to achieve the desired performance. This includes dimensional information, flexibility requirements, special design features, performance such as strength, materials compatibility, special testing, etc. It becomes the blueprint for designing and testing the product (Input – as required by the FDA). Frequently, there are design requirements established by the FDA that should be considered in developing the performance characteristics of the product. These can be found on the FDA website [24] by searching for "guidance document 'device description'."

After the initial idea is fleshed out, the design and development process begins with multiple design variations. Each option is weighed and considered until conclusive design paths are decided upon. This is a place where many individual developers fail, in that they do not have the expertise or experience to work their way through the process. During the design process, the device is created with careful consideration to size, fit, function, manufacturability, assembly, ease of use, effectiveness, patient acceptance and or comfort, and ability to be sterilized. Often, the next step is to create 3D models using computer aided design software. Accompanying review and revisions begin as well. Following such revisions and redefining of design scope and product specifications, a final set of 3D models are created.

The next step includes creation of a prototype. It may be a fully functional model or may simply be a "mock-up" that is useful for illustrative purposes only. It should address any fundamental design issues that must be solved to achieve successful performance of the product. In some cases, design options must be carefully reviewed to search for alternate approaches that could be more reliable, easier to make, or offer improved performance. Documentation of the alternatives considered can be valuable in preparing patent applications to assure that different alternatives are protected.

Procedures for testing the prototype need to be documented and used to evaluate performance of the device to demonstrate that it meets the Input requirements. The test results become the Output documentation. Additional prototypes are usually created for use in marketing, sales and review by the prospective end users of the device. Their feedback is critical to establishing and verifying the design requirements.

Sterilization

Sterilization of a medical device, although commonly outsourced, is a critical step in the design, creation, and production process. Materials, colors, and form of new devices must be selected with sterilization in mind. Sterilization can both drive and be driven by these factors. Four common sterilization techniques currently used for medical devices are ethylene oxide (EO), gamma radiation, steam autoclave, and electron beam sterilization. All have their benefits and limitations, which again may drive and/or limit design features. Lastly, post-sterilization validation and testing of parts is recommended to determine if this step in the process will affect product form, fit, or function. Many great medical device ideas fail, when it becomes clear that they cannot be sterilized in a cost-effective manner.

Ownership and Intellectual Property

Protecting Inventions and The Patent System

The purpose of patent protection is to exclude other parties from manufacturing, using, or selling your new invention. The patent system grants to the inventor(s), a limited time to exclude direct competitors, i.e., twenty years from the date of first filing the patent application. The inventor(s) receive his or her grant in exchange for public disclosure of the technology in the form of the issued patent, which, of course, is available for all to consider, modify or improve upon.

Documenting Ideas and Designs

Protecting an invention (which can be in a new discovery, process or even the shape of a device) begins with diligent efforts to identify *via* written documentation the new discovery or design. You will help secure any future patent rights by:
(i) documenting ideas for new or improved devices including their design and functionality, (ii) marking all such documents as confidential, (iii) maintaining their confidentiality for a certain period of time (i.e., until patent application is filed, published or issued into a patent), and finally (v) timely filing applications for patent.

Any one idea, at its inception, may or may not be the complete formation of what becomes the end invention, and often is the impetus for further modifications and improvements, research, and testing. You should document early ideas and design concepts and their evolution, sketch the design of the device and its components from varying angles, and make new sketches of any variations or modifications. Documentation establishing the evolution of a concept may become very important if someone else claims to have made the same invention. Records kept in the manner suggested below provide important evidence, which may be crucial in establishing inventorship and/or proving who was first to invent a medical device.

The courts have recognized certain practices as helpful in meeting the evidentiary tests. A common practice is the use of a bound notebook to contemporaneously document ideas, designs, testing methods and results in chronological sequence. Each entry and/or page should be numbered, dated and signed by the investigator and independently witnessed. Over time, as a design is tested, improved, re-tested, and/or proven, the notebook becomes a contemporaneous chronology of the development process and realization of an invention. Pagination of the notebook pages can also be helpful in showing chronology – especially where there are gaps of time between entries.

Notebooks should be kept in a secure location with limited access by only those directly concerned with the research and development of the device. Never tear out pages from a bound notebook. An incomplete or manipulated notebook may reduce its evidentiary value. If mistakes are made, never erase or black out text. Instead, cross out any errors and initial the crossed out text. If notes or data are created on one or more single pieces of paper, the paper can be added into the notebook by attaching it by glue or staple to the first blank space in the notebook to fit the insert, and signing across a portion of the inserted data and the page of the notebook. In the event that a particular idea is the result

of collaboration, then each collaborator's contribution should be identified with particularity and specificity. Electronic versions of such notebooks exist, but must certainly use a "tract changes" method that is locked and can be proven to have not been altered in future investigations.

Confidentiality Is Important

Once ideas and designs are documented, mark all notebooks and other documents and media describing the device, or containing supporting development and testing data, as confidential and proprietary. Marking documents and media is an opportunity to state a claim of ownership in the disclosed ideas and materials (e.g., "Confidential and Proprietary Information of *[insert your name or name of employer]*").

Inventions should be maintained in confidence until they a patent application is filed and ideally until the application is published by the Patent Office. Maintaining confidentiality may be critical to marketing and patentability. Premature publication of the idea, public use or sale of a product may result in the forfeiture of any ability to gain patent protection. In most countries, an invention is not patentable if it has been disclosed in a printed publication, used publicly, or sold before the filing date of a patent application on that invention and in most countries patentability is lost after any public disclosure of the invention.[26] "The general purpose behind [these bars to patentability] is to require inventors to assert with due diligence their right to a patent through the prompt filing of a patent application."[27] The United States, however, provides a one year grace period to file a U.S. patent application by or before the one year anniversary of any publication, or public use or sale of the invention in the United States. If one desires patent protection outside of the United States, however, acts of publication, use and sale before filing for patent protection must be avoided.

The confidentiality standard for patentable inventions is somewhat in contrast to the push to publish results in academic medicine. Fortunately, a balance can be struck between the need for confidentiality to protect potential patent rights and the need to publish for academic purposes. The two should be pursued in parallel. Often, a draft manuscript serves as the primary source of text and data for a patent application. Researchers should disclose their inventions along with any corresponding draft manuscript or funding application describing the invention or supporting data to their institution prior to submitting the draft manuscript or grant application for review. A patent application (e.g., provisional patent application) can be filed relatively quickly on the subject matter disclosed in the draft manuscript or funding application. As research progresses and results prove or disprove your ideas, be sure to keep your institution informed of any new potentially patentable discoveries or improvements. If clinical trials are needed to prove the use of the idea, these will have to be registered with the government and data will come into the public domain at some point in the life of those trials. Be diligent in pursing patent protection as early as possible to avoid premature publication that can jeopardize patent protection.

The Confidentiality Agreement

If disclosure of an invention to another party is required prior to its publication by the patent office, use a confidential disclosure agreement, or non-disclosure agreement, to

restrict use and obligate the receiving party to secrecy. A confidentiality agreement should be used as a secondary level of protection, second to filing for a patent. It is noteworthy that some circumstances, like the peer review process, or conference presentations, typically do not allow for the execution of confidential disclosure agreements. In these cases, getting a patent application on file as soon as possible is the only protection against misappropriation or the bar to patentability in the case of conference presentations.

Confidential disclosure agreements can be difficult to enforce, and the filing of a patent application that describes an invention provides the best line of defense in any dispute involving inventorship or ownership of a disclosed invention. Usually, the party who is disclosing confidential subject matter submits its template contract for signature, which naturally, should favor the disclosing party. There are basic elements that should be present in most confidential disclosure agreements.

Scope of Obligation

There is always a defined scope of what constitutes confidential information. It may include, for example, a brief non-confidential description of the precise subject matter being disclosed, such as the name and serial number of a named patent filing not yet published, or it may be broader and reference all discussions between one party to the another during a certain time period. Confidential information may be defined to include only that which is identified in writing and marked as confidential or it may include oral disclosures as well. A disclosing party will generally want to use a broad definition, while the receiving party will attempt to narrow the scope. Additionally, there is an array of about five "standard" provisions that exclude as confidential information that is: (i) in the public domain or becomes part of the public domain through no fault of the recipient, (ii) already in the possession of the recipient as evidenced by contemporaneous documentation, (iii) independently developed by the recipient as evidenced by contemporaneous documentation, (iv) lawfully received from a third party, or (v) required by law. A disclosing party will want to limit the exclusions of confidentiality and require written contemporaneous documentation of any existing exclusion within a certain time period, whereas, a receiving party will likely prefer broader exclusions. Finally, the obligations of confidentiality are limited to a particular term from about 3 to about 10 years.

Limitations on Use

There should always be a limited purpose for which a recipient of confidential information can use or share the disclosed information. It should be the responsibility of the recipient to ensure that there is no unauthorized use or disclosure. Unauthorized use and disclosure compromises the value of the confidential information. In such case, the owner of the confidential information should have the right to injunctive relief to prevent further unauthorized use or disclosure in addition to any damages available at law for loss of value or rights. To sustain control of the confidential information, the disclosing party should secure the right to request at any time, and certainly upon expiration or termination, the return of or destruction of any confidential information.

Filing for Patent Protection

The best way to protect an invention is of course to file an application for patent and obtain patent protection covering the invention, modifications and alternative forms of the invention. Here we discuss developing a patent filing strategy, the requirements of patentability and the patent examination process.

Developing a Patent Filing Strategy

Several factors influence when and where patent applications are filed, as well as whether to file a provisional application, utility application, design patent application or PCT application. Factors to consider are: the amount of competition in the field, the stage of development of the invention, potential commercial value of the invention, the possibility of licensing or assigning the invention, and the amount of money available to commit to the patent process.

A working prototype is not needed prior to filling a patent application. Indeed, most patent applications for medical devices are filed before a working model of the device is made. A patent application can be filed as soon as the inventor has the complete concept of the invention in mind and can describe the invention with enough particularity to enable others of ordinary skill in the field to make and use the invention.

Since 1995, the U.S. has offered applicants the option of filing a provisional application, which is not examined by the USPTO, but which provides a priority date for the subject matter disclosed in the application and allows the inventor to mark his product as "patent pending." A provisional patent is a low-cost alternative ($100 filing fee) or a preliminary step before filing a non-provisional patent that gives one additional year of protection - maybe enough time to test market the invention before investing in the cost of a regular patent.

The provisional application does not require claims, an oath or declaration or the filing of an Information Disclosure Statement and it is never published. It requires only a written description of the invention and any drawings necessary to understand the invention. Because the filing requirements are so minimal, a provisional application can be prepared and filed in a relatively short time, if necessary, to protect an invention that will be disclosed at an upcoming meeting or in a publication. However, a provisional patent application should always be as complete as possible since in all likelihood, it will be serve as the basis of a later filed non-provisional application. The purpose of the provisional application is to document the date of invention and establish a priority date. If, however, a formal patent application is not filed within 12 months, the provisional application is considered abandoned.

Even if the invention continues to evolve within the year after a provisional application has been filed, the modifications can be protected by filing one or more additional provisional applications. The disclosures of all provisional applications (or more) can then be combined in a conventional application, which must be filed no later than one year from the filing of the first provisional application. Alternatively, any new

information that was not included in the provisional application can be added to the non-provisional application at the time of filing the latter. The only downside is that the priority date of the added information is the time of filing the later application.

An applicant can elect to file a non-provisional utility application at the onset. Unlike provisional applications, a non-provisional application must conform to a specified format and must contain at least one claim, and an oath or declaration of the inventor(s) is required. Consequently, the preparation time and filling fees associated with a non-provisional application are significantly higher than for a provisional application. The patent application includes an abstract of the invention**,** a brief background discussion of the problem the device addresses, a summary of the invention, followed by a detailed description of the invention with any drawings necessary to understand the invention. The patent ends with at least one claim, which are the most important part of the patent application. The claims define what is protected under the patent, and must be supported by description in the body of the application (the specification).

When the filing requirements are complete, the application will be assigned to an examiner in the appropriate art unit. Currently, applications do not begin the examination process until about one to two years after filing and the examination process (prosecution) can take anywhere from one to several years.

The rights granted under a U.S. patent are limited to the U.S. and its territories and have no effect in other countries. Almost every country has its own patent law, and if an inventor desires patent protection in a particular country, then a patent application must be filed in that country, in accordance with that country's requirements. Fortunately, there are international treaties that simplify applying for international patent protection, including the Patent Cooperation Treaty, otherwise known as the PCT.

The PCT is an international agreement for filing patent applications in PCT member countries. As of July 2007 there were 137 PCT member countries, including most major countries, such as the U.S., Europe, Japan, China, and Canada. However, not all countries are members of the PCT. Therefore, if an inventor desires patent protection in a non-member country, a separate application must be filed in that particular country. The PCT system does not provide for the grant of an international patent, but it simplifies the process of filing patent applications and delays the expenses associated with applying for patent protection in other countries, while also providing the inventor more time to assess the commercial value of his or her invention. Under the PCT, an inventor can file a single international patent application in one language with one patent office in order to seek protection for an invention in up to 137 countries throughout the world. Filing a PCT application is relatively inexpensive, about $4000, most of which is government filling fees. PCT applications undergo a preliminary examination, and a positive examination report from the PCT system often makes prosecution of national stage applications go more smoothly. This can substantially reduce prosecution costs down the road. At the end of the PCT International Phase applications must be filed in each country in which the inventor wants a patent (“the National Phase”).

Filing a PCT application is also an attractive option for inventors who intend to license their inventions. The long pendency period of the PCT application allows an inventor to keep his or her options open at relatively low cost while searching for a licensee who can then pay the costs of prosecution in any countries in which the licensee is interested. The inventor(s) should consider the potential commercial value of the invention throughout the world and file patent applications in those countries in which the invention is most likely to be commercially successful and afforded appropriate patent protection. The life expectancy of the patented product and ease of designing around the invention should be considered. Patent prosecution from filing through the examination period to issue of a patent can be extremely expensive so selection of countries for filing should be carefully considered.

Prosecution of a U.S. patent cost upwards of $25,000-$40,000 and take some 2.5-5 years to prosecute. Foreign patent applications are even more expensive and often take longer to review. Inventors should also consider the cost of enforcing the patent. If someone violates your patent rights, it is up to you to find them and prosecute them, often at significant expense.

Patentable Subject Matter

Patent claims directed to machines, *e.g.*, medical devices, manufactures and compositions of matter are broadly referred to as "product" claims. Claims covering both machines and articles of manufacture are referred to as apparatus claims, and the elements of apparatus claims are generally the structural components of the apparatus. The elements of composition of matter claims, on the other hand, are typically chemical in nature, and may be a new compound, DNA, nucleic acid probes, vectors, antibodies, a transgenic animal, or genetically engineered bacteria, for example. Together these three classes of product claims cover anything made or altered by humans. The particular class in which an invention falls, however, does not have any substantive or legal significance in obtaining or litigating the patent.

Claims directed to processes are referred to as "process" claims. Included among patentable processes are new uses for a known process, product or apparatus. In general, patent applications directed to medical devices will include both product claims directed to the device itself, as well as claims directed to methods of using the device, *e.g.* , to treat a particular condition.

Requirements for Patentability in the U.S.

A patent applicant is entitled to a patent only if five requirements are met: the invention is useful,[28] new ("novel"),[29] and nonobvious;[30] the invention is disclosed and described in such a way as to enable others to make and use the invention;[31] and the invention fits one of the statutorily defined general categories of patentable subject matter.[32] The utility requirement ensures that in exchange for patent protection, the applicant discloses an invention that is useful and operative. In general, this is a *de minimis* hurdle to patentability, and a patent will be denied only if the invention has no practical utility, with one notable exception. In the case of some pharmaceutical or biotechnology-based

inventions, patent applicants may be required to show that the invention is actually useful in treating the claimed disease or condition.

The novelty requirement ensures that the invention is not already known in the prior art. The test for novelty determines whether the invention was made before, sold more than one year before the patent application was filed, or in public use or publicly known before the application was filed. However, even if an invention is novel, it may still be unpatentable if it is obvious to a person of ordinary skill in the art, *i.e.*, represents a trivial step forward in the art.

The nonobviousness requirement measures the technical accomplishment of the invention. It is often the most difficult test of patentability. Recently, the Supreme Court reviewed the obviousness requirement, and tightened the standard of obviousness, making this hurdle to patentability even steeper.[33]

The written description and enablement requirements of 35 U.S.C. § 112 ensure that the invention is sufficiently described so that one of ordinary skill in the art can improve the invention or design around it without infringing it, and utilize the invention once the patent term expires. This requirement is a part of the bargain made between patent applicants and the PTO; in exchange for the right to exclude others from making and using the invention for a period of time, patent applicants must disclose the invention to the public in a manner that will provide the public notice of the metes and bounds of the claimed invention and assure dissemination of information concerning the invention.

Best Mode

The best mode requirement is intended to prevent an inventor from concealing from the public a preferred or better way of making or using the claimed invention than that which is disclosed in the specification. This requirement is rooted in the deal the patentee has made with the public- limited exclusivity for up to twenty years in return for full disclosure of the invention. The best mode requirement is based on the inventor's knowledge at the time the application was filed, and is entirely subjective.[34]

"Burying" the best mode within the specification may constitute non-disclosure, but this does not mean that the best mode must be specifically pointed out in the specification. The duty to disclose best mode ends when the application is filed. However, although there is no duty to update the best mode after the patent application is filed, in the case where a continuation-in-part application is filed by the applicant (to include new subject matter in the application), there is a duty to update the best mode if applicable.

Procedures Before the U.S. Patent and Trademark Office

Examination and Prosecution of Applications

When a non-provisional patent application is received by an examining group it is assigned to the appropriate technology or "art" unit, and then assigned to an examiner in that art unit. The examiner first determines whether the application meets the requirements for obtaining a filing date, *i.e.*, contains a specification which ends in at

least one claim and includes any required drawings. The examiner then conducts a search of the prior art relevant to the claimed subject matter. The examiner's findings are reported to the applicant or the applicant's attorney, if one has been appointed, in a formal document referred to as an "Office Action. The Office Action lists all the prior art considered to be relevant by the examiner and a detailed explanation for any rejections of any of the claims. The Office Action also sets forth a time period for response, which usually can be extended up to a maximum statutory period of six months, upon payment of a fee. The patent applicant must respond to all of the rejections and objections within the statutory time period or the application will be held abandoned. A response can include arguments in traversal of the examiner's rejections or objections, and/or amendments to the claims or specification, as appropriate. Arguments can be supported by extrinsic evidence, such as publications or a signed declaration of a person familiar with the invention. Any amendments made to the application must be supported by the original disclosure and cannot include any new information ("new matter"). The applicant can also request a personal interview with the examiner to discuss the invention and Office Action. Interviews may be conducted at the examiner's office or over the telephone.

After the response is filed, the examiner reconsiders the application. If the examiner is persuaded by the response, a Notice of Allowance will be issued. However, if the examiner is not persuaded, a new Office Action is issued. The second Office Action is considered "final," unless the examiner cites new grounds for rejection and those new grounds were not necessitated by any amendments. Until a final Office Action issues, the patent applicant and the applicant's representative are entitled to an interview with the examiner to discuss the Office Action. After a final Office Action is issued, it is within the examiner's discretion to grant an interview, enter amendments or consider extrinsic information.

Once a final Office Action issues, the applicant has several choices. The applicant can file a response, with a Notice of Appeal of the final rejection to the Board of Patent Appeals and Interferences (the Board); file a continuation application; or, if any claims were indicated as allowable, cancel the rejected claims and allow the application to issue with the allowed claims. Alternatively, the applicant can elect to abandon the application, either expressly, or by failure to timely respond to the Office Action.

Inventorship and Ownership

Patent law distinguishes between inventorship and ownership and each is treated differently.[35] In *Beech Aircraft Corp. v. EDO Corp.*, 990 F.2d 1237, 1248 (Fed. Cir. 1993) "Inventorship was found to be a question of who actually invented the subject matter in a patent. Ownership, however, was found to be a question of who owns legal title to the subject matter claimed in a patent, patents having the attributes of personal property."

Inventors have proprietary rights in their inventions, but may transfer those rights. The proprietary rights in a patent can be conveyed to others by agreement even before the

invention is conceived. While ownership rests with whoever holds legal title to the invention, inventorship belongs solely to the person or persons who actually invented the claimed subject matter and cannot be transferred.

Inventorship

An inventor is the first person to have a complete conception of the invention and who does not abandon the invention. Conception occurs when the inventor has formulated the complete invention in his or her mind, and all that remains is to construct the invention without the requirement of undue experimentation.

When an invention is made by more than one person, the inventors are joint inventors (or co-inventors). It isn't necessary that the inventors worked together physically on the invention, or that each made an equal contribution to the invention to be joint inventors. Nor is it required that each inventor contributed to the subject matter of each claim in a patent.[36] It is only required that joint inventors collaborated with each other, and that each inventor contributed to the conception of the subject matter of at least one claim in the application.

Ownership of Inventions

In the absence of an agreement to the contrary, the inventor owns his/her invention or joint inventors jointly own their invention.[37] Most researchers employed by large corporations, hospitals or universities, however, have an obligation to assign their ownership rights in inventions to their employer under an employment agreement that expressly addresses the issue of ownership of inventions, or instead under a general policy regarding intellectual property.[18] Generally speaking, if an employee has not expressly agreed to be bound by an employer's policy by signing it, courts may find under contract law that the employee is not bound by the terms of the policy. An important consequence of joint ownership in the U.S. is that each inventor or more likely their employers (under an employment contract) has full rights under the patent. That is, each inventor (or owner of assigned rights) may make, use or sell, license or assign the invention without any obligations to the other inventors (or owners of assigned rights). This takes on particular importance if researchers employed by different employers collaborate on a project without first agreeing to ownership of any resulting inventions. Collaborative research agreements can be entered into by two or more parties who, separately or together, carry out research in a defined research project. The parties generally agree to share results and information arising from the research, and agree on a course of commercialization of any developed inventions and split of any proceeds.

Sponsored Research and Government Funded Research

Ownership of inventions and their associated work product in the biomedical field is further complicated by the fact that most biomedical research is funded by third parties, such as the federal government or private investors. Funding by third parties is usually governed by the terms of complex agreements (sponsored research agreements) between the parties which are made before any research begins. A sponsored research agreement is an agreement whereby industry utilizes the researchers of a university, nonprofit corporation or nonprofit research center to conduct research without the necessity of

hiring the researchers as employees. Basically, the industry sponsor gives money to the university or research center in exchange for the results of a particular scientist's defined research project. These agreements often, although not necessarily (especially in the context of clinical testing an industry sponsor's device), provide that ownership vests in the research institute, while the industry sponsor usually receives an exclusive license in any resulting patents, and use and possibly ownership of any work products. Sponsored research agreements between an industry partner and a university are often governed by university policies concerning publications, since the free exchange of ideas is a highly regarded value of academia, while other research partners are generally more willing to agree to terms that provide for protection of trade secrets as well as patentable inventions.

Government interest in federally funded research generally turns on relevant statutory law and administrative regulations concerning government contracts. The ownership of inventions and patents made by universities, non-profits and small business entities with federal government funds is governed by the Bayh-Dole Act.[38] The Recipients of government funding, as well as the U.S. government, maintain rights to inventions arising from government funded research.

The Bayh-Dole Act confers unto universities, non-profits and small businesses the right to take title to inventions created from research funded by the government. The contracting institutions and businesses retaining ownership are permitted to exclusively out-license the inventions to other parties for commercial development and research purposes. Certain contractual terms and conditions of a funding agreement are mandated by the act, including: (i) a requirement to disclose inventions to the funding agency; a requirement to elect to retain title of inventions within two years of disclosure to the federal agency; (ii) agreement to file patent applications prior to taking any action that may be a statutory bar to patentability; (iii) periodic reporting on utilization of the invention; (iv) notice on the face of any patent that the invention was made with government funds; (v) march-in rights of the government to the invention (the government right to require the contractor, assignee or exclusive licensee to grant a license to a third party); and (vi) a restriction on any transfer of the invention requiring that any products embodying the invention or made using the invention be manufactured substantially in the United States.

In consideration for ownership of inventions and patents to those who receive government funding, the U.S. government receives a nonexclusive, irrevocable license to the invention.[40] The government and entities acting on behalf of the government may use the invention for government purposes and includes the right to sublicenses. The government also has march-in-rights to require the patent holder to grant a license in any field upon reasonable terms under certain circumstances if the funding agency determines that such action is necessary.[41] Government rights to inventions and other requirements of the act flow down to any licensee or subsequent owner of the invention.

It is important to note that failure to timely disclose inventions and elect title can lead to a loss of title and right to practice the invention.[39] In *Campbell Plastics v. Brownlee*, 389 F.3d 1243 (Fed. Cir. 2004), Campbell Plastics used Army money to develop a gas mask

that allowed the wearer to drink water. During the course of the research and development Campbell disclosed certain drawings and descriptions in status reports. Campbell argued that the invention was sufficiently disclosed. But Campbell did not follow the contractually proscribed requirement of completing the DD Form 882 and the court found that Campbell did not expressly identify the invention and elect title in any of the status reports and other disclosures. As a result, the Army obtained title to the invention. In Campbell, the U.S. government gained little, if anything, by forfeiture of patent rights, since it already had a royalty-free right to use the patent, including the right to sublicense. Because of this case, institutions receiving federal funding now must assume that the U.S. government will elect patent ownership if given an opportunity.

Regulatory Phase of Design & Development

This stage of development involves creating a process for producing the product that statistically meets all of the design specification requirements. It should include verification that the design output meets the design input requirements. The testing results must be documented and retained in the design history file. The process must also be validated to show the product consistently meets the defined user needs.

Many aspects of the product must be addressed in this phase according to FDA guidance documents, biocompatibility, and sterilization requirements as discussed later in this paper. Specific issues to be considered are:

Quality Plan
Documented test procedures
Environmental stability
Failure Mode Effects and Critical Analysis (FMECA; Risk analysis)
Labeling documentation
Instructions for use
Packaging definition
Sterilization testing
Shelf life testing
Packaging and distribution
Traceability

All of these items must be addressed and used for submission for FDA approval for the product. Typically, a minimum of 150 units need to be manufactured for the required testing and evaluation and the phase typically takes 5 to 10 months for completion depending on the product and tests required.

Resources for Designing and Developing the Product

In order to take the product from concept through the design process, there are four avenues that can be taken. The first is to collaborate with the appropriate individuals (engineers, designer, material scientists, etc) in exchange for a portion of the intellectual property rights, whereby developmental costs would be divided among the group of

inventors. Another approach is to contract with a device developer for a fee to help develop your idea. This permits the inventor to exercise a greater degree of control over his invention and potentially test various designs (all of which may be potentially patentable), but choose which to develop into the prototype stage. One can also approach commercial device companies with their idea to determine if there is interest in developing the product, and finally, one can simply license the idea to a commercial entity. As a rule, the more developed the product is, the more likely it is to be of interest to a commercial device manufacturer. Companies constantly review many ideas but choose to develop very few. If your idea is not picked up by company A, it may mean they have their own device in development that they believe will solve the same problem, that the device would be too expensive to develop or they lack the appropriate resources, or that the device does not fit into the company's current or envisioned product line and/or they do not see a sufficient market for the device. The actual "reduction to practice," or development of a working prototype, can be a time-consuming and very expensive endeavor. The are also no guarantees it will be brought to market, with or without a patent(s).

Large medical device companies often continue to make small improvements on the existing devices, perhaps culminating in a new generation of devices. This practice generally results in a less-expensive, faster, and lower risk developmental program. However, new device categories are generally developed by small, venture-capital supported companies. Venture capital is another source for potential funding, but one from which ultimate control may be taken from the inventor. Typically, such funds would be used to fund a business entity, perhaps built around a device, rather than the device development itself. Some venture capitalist firms employ or consult with attorneys specialized in FDA and licensing issues, and regulatory, engineering, manufacturing, and marketing consultants.

The financing of the development of medical devices is beyond the scope of this manuscript, but the reader should know there are several possibilities. These include using their own funds, seeking venture capitalist money, or using federal grant money (such as through the SBIR process). The Bayh-Dole Act assigns all intellectual property rights from devices developed under a federal grant to the academic institution.[1] In general, academic facilities will tend to license a potential product earlier as they often lack the funds or the process to fully develop the device. In some instances, however, particularly when more than one device is likely to be developed, a "start-up" company can be formed around the initial device and device category.

Federal Funding

Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) grants are available to business entities to fund the proof of concept stage. The SBIR grant is meant for small business development while the STTR grant is intended to assist in the development of a partnership between various small businesses or between small businesses and an academic institution. The initial SBIR/STTRR grants typically last for 6 months. If the initial phase 1 study is successful, substantially larger grants are potentially available for phase 2 investigations. Phase 2 applications are expected to

include a commercialization plan. It is expected the inventor/sponsor would seek non-SBIR/STTR funds for phase 3 and the fulfillment of commercialization objectives. In order to be eligible for an SBIR grant, the principal investigator must be employed as their primary occupation, in an American-owned for-profit small business consisting of less than 500 employees. For an STTR grant, the primary investigator may be a full time employee of the academic institution, but must also have some type of formal employment with the small business concern. It is expected that a minimum of 40% of the grant-related work be performed by the small business concern and a minimum of 30% of the work performed by the academic partner.[2,3]

Medical Device Regulation

Although drugs have been regulated by the FDA (at least to some degree) since 1906 with the passage of the Food and Drugs Act (FDA),[4] devices were not regulated at all until 1938 with the passage of the Food, Drug, and Cosmetic Act.[5] regulation under this law was limited to restriction of "adulterated" or "misbranded" items; safety and efficacy were not required. This did not change until 1968 with the passage of the Radiation Control for Health and Safety Act, designed to regulate unsafe levels of radiation exposure from medical devices.[6] Demonstration of non-radiation safety concerns as well as validity of efficacy claims were not required until passage of the Medical Device Amendments of 1976.[7] This legislation divided devices into three categories depending on perceived risk. Class I devices are the lowest risk and in most cases, formal FDA review is not required prior to market introduction although labeling, adverse event reporting, and good manufacturing practices (GMP) are regulated by the agency. This class includes devices that are not of use in the protection of human health and impose no risk to humans (although surprisingly, lead gonadal shields were included in this class). Class II devices impose higher risks, but do not themselves affect the maintenance of life; safeguards such as post-marketing surveillance and specific performance standards may be required. Most Class II devices require FDA clearance for marketing through either the pre-market notification application (PMA) or 510[k] mechanisms. Examples include diagnostic angiogram supplies and CT scanners. The 510(k) mechanism represented a somewhat abbreviated version of the PMA and often requires only 60-90 days for review as compared to 12 months for a PMA. Demonstration of "substantial equivalence" to currently marketed devices may be sufficient for marketing approval, although clinical trials of the new device may either be required or included in the application. Demonstration of "substantial equivalence" to currently marketed devices may be sufficient for marketing approval, although clinical trials of the new device may either be required or included in the application. Class III devices pose the greatest potential risk and include life-supporting and many implanted devices. Most such devices require FDA of a PMA that includes clinical trial data showing the device's safety and efficacy prior to market clearance. For rare disease (eg < 4,000 patients in the USA, not to be confused with orphan designation of a medication), the Human Device Exemption (HDE) may be used, in which case safety and probable benefit over probable risks should be demonstrated. Prior to marketing approval, it is expected that device safety and efficacy for the selected indication(s) be demonstrated.

All devices introduced after 1976 require a pre-market notification by the FDA, now commonly known by its FDCA section number, 510(k). The original intent of this section was to require manufacturers to notify the FDA or their intention to market a new product. New products that lacked pre-1976 equivalent required clinical trials prior to marketing approval. In addition, the FDA may require post-marketing monitoring in certain circumstances. New products for which a "substantially equivalent" product on the basis of cited scientific literature and expert opinion, which existed on the market prior to 1976, could be marketed immediately without any additional evaluation, or at least until such data is requested by the FDA. The definition of "substantial equivalence" was left to the FDA and did not necessarily require clinical trials. Subsequently, the FDA permitted the evolution of devices with small incremental improvements without the need for additional clinical trials for each innovation (for example, the introduction of helical CT).[8-10] The FDA was more empowered to require clinical trials to validate "substantial equivalence" with the passage of the Safe Medical Devices Act in 1990.[11] In 1997, the FDA began focusing more on higher risk devices under the 510(k) notification and under section 210 of the Food and Drug Administration Modernization Act of 1997. The FDA was subsequently permitted to assign the review of class I and class II products to accredited non-governmental concerns. It is of note that section 201 of this act permit the FDA to accept efficacy data from a previous clinical trial to support the application of subsequent devices, and that section 217 permits device approval based on a single well-controlled clinical trial (as compared with two trials generally required for drug approvals). Section 201 also allows for an "Agreement Meeting"(see below), during which the FDA and the inventor/sponsor agree on a binding investigational plan. This may lead to a "Determination Meeting," provided for in section 205, during which the FDA and inventor/sponsor agree on particular acceptable efficacy and safety outcomes. Section 202 provides for the priority review of devices that represent breakthrough technologies, for which there are no current alternative solutions, or that offer truly substantial advantages over current practices. Section 522 permits the FDA to require post-marketing surveillance if the agency feels that is necessary.

The Food and Drug Administration (FDA) is charged with ensuring the efficacy of devices as well as the safety of these devices, and therefore has regulatory approval over sales, indications for use, labeling, and marketing. Close collaboration between physician, inventor/academic institution, industry, intellectual property counsel, and the FDA is essential to the process. The European Union (EU), while fundamentally similar in purpose to the FDA, approaches the approval process of medical devices in a slightly different manor: rather than a focus on efficacy, the focus is on safety (http://ec.europa.eu/enterprise/medical_devices/index_en.htm). Approved devices are granted a CE Mark. This mark is not an abbreviation for anything, although it is thought to have originally stood for Communaute Europeenne or Conformite Europeenne, French for European Conformity.[14]

In Canada, medical devices are regulated under the Medical Device Regulations section of the 1998 Canadian Food and Drug Act. This act was in part designed to bring Canadian regulations more in-line with the EU. All marketed devices require a Medical Device License issued by Health Canada. Devices are classified similar to the FDA

classification, except there are four classes versus just three for the FDA. The level of risk assigned to the device is dependent on that proposed indication for the device, type of patient contact, the device technology, and consequences of device failure. These include: Class I (example: tongue depressor (exempt from licensing); Class II- may be invasive, but in contact with the body for < 30 days and not in contact with the central vascular system (CVS) or central nervous system (CNS) - surgical scalpel or needles - must assert safety and efficacy have been tested, but not necessary to submit the actual data unless specifically requested; Class III- remain in contact with the body for $\geq$ 30 days, but not in contact with the CVS or CNS - artificial hip - must provide documentation of safety and efficacy prior to marketing approval; and Class IV - high risk devices, failure of which would result in death or serious health consequences - heart valve - this also requires a risk assessment and explanation of the risk reduction measures adopted for practice. Safety Standards are similar to those of the FDA and include evaluation of material strength and composition for specific applications, mechanical test methods, biocompatibility, sterilization processes, impact of degradation and leaching of materials, and specific safety issues for electrical devices and blood treatment devices.[15]

Marketing approval for devices by the FDA is essential for prospects of reimbursement, and therefore of sales. The Health Care Financing Administration (HCFA, eg Medicare) will only provide reimbursement for such devices approved by the FDA for their intended use.[12] Third-party payers generally follow suit. In certain circumstances, routine medical care associated with the use of study of an investigational device, but not the device itself, may be reimbursed by Medicare.[13]

Guidance Meetings Pre-Investigational Device Exemption (IDE) Meetings

Product development often begins with a pre-IND "meeting" with the FDA. This submission is optional, but such interaction with the agency will assist the inventor/sponsor informally in a developmental plan, including pre-clinical and clinical testing phases. There are two types of "meetings." "Informal Guidance" Meetings do not involve the exchange on written information. "Formal Guidance" Meetings include a formal written request for review by the inventor/sponsor. The agency is required to provide feedback to the inventor/sponsor within 30 days upon receipt of the request.

Pre-Investigational Device Exemption (IDE) Meetings
The inventor/sponsor submits preliminary information for comment to the Office of Device Evaluation (ODE) prior to submission of a formal IDE application. This submission is logged into the pre-IDE tracking submission upon receipt by the Document Mail Center (DMC), referred to the appropriate division(s) for review, and receipt acknowledgment is sent to the inventor/sponsor. Although there is no standard format, the inventor/sponsor should indicate the reason for the submission and supply sufficient background information such that the agency can make meaningful recommendations. The inventor/sponsor may ask the agency to comment on the most appropriate animal model, a proposed safety protocol, proposed control population, proposed endpoints, etc. ODE also reviews and approves a sample informed consent document. Comments may

be supplied by the agency in a teleconference, as a written response, or at a face-to-face meeting. Typically, the inventor/sponsor formulates either broad or specific questions for agency comment. Such a "meeting" is suggested in order to avoid assumption of agency requirements, and thereby the risk that the development plan as envisioned by the inventor/sponsor is not what the agency has in mind. Although there is no formal review time commitment, in general, the agency responds within 60 days. It is to be noted, however, that review by the agency of a pre-IDE submission is not "in depth," and furthermore, any designs or data reviewed under a pre-IDE will generally be re-reviewed at the time of a formal IDE submission. Furthermore, the device in question should have reasonable progress in its design stage and indication for use such that the agency's responses are meaningful. A Pre-IDE "meeting" may also be requested on just part of the formal IDE submission if necessary. If the inventor/sponsor disagrees with the agency's advice, this disagreement will need to be resolved via submission of a formal IDE. Studies deemed "Non-Significant Risk" as described in 21 CFR 812 do not require FDA approval to be conducted and ODE is therefore not typically involved in study design or protocol development. Nevertheless, a pre-IND meeting may still be useful to the inventor. Pre-IND meetings may also be useful to assist in the planning of in vitro or animal studies as well as to develop a clinical protocol based on animal investigations either completed or currently underway. If the inventor/sponsor truly believes they have designed the most appropriate pre-clinical and clinical protocols, then a pre-IDE meeting should not be requested. The inventor/sponsor may also submit a Pre-IDE application consisting of those sections of the application for which they would like to obtain FDA guidance.

Biological Testing

Biological evaluation of medical devices is required to ascertain any potential toxicities resulting from contact of the device with any portion of the body via local or systemic effects on skin, internal organs, blood, etc.(Figure 2) This also includes any potentially harmful effects on fertility and reproduction as well as carcinogenic potential. Although such toxicities by themselves will not necessarily limit device development, the importance of the device should outweigh any potential risks. Biocompatibility and cytotoxicity testing may suggest the need for replacement materials in the device design. In order to design appropriate testing, one must consider the use of the device - location in or on the body, and degree of exposure (for example: skin only, internal sterile, internal non-sterile), and frequency and duration of exposure. Typically, evaluation will include detection of acute, sub-acute, and chronic toxicity, skin and mucus membrane irritation, sensitization, hemocompatability, genotoxicity, carcinogenicity, and effects on fertility, reproduction and development. There may be additional requirements for some specific products such as evaluation for neurotoxicity or immunotoxicity. There may also be a requirement for tests to determine sterility, toxicology, stress and wear, and/or shelf life. For devices in which materials are used that have been tested previously, repeated biocompatibility testing may not be necessary in the absence of new coating or other material alterations. In circumstances where new materials are not used, substantial equivalence with current commercially available materials that have been previously tested may be shown. The current testing standards were developed by the International

Standards Organization (ISO) and have supplanted various country-specific standards (www.iso.ch).[18-20] ISO standard 10993-1:2003(E) is a good starting point in determining what testing will be necessary. This non-governmental organization maintains strong ties to 158 governments around the world, and its standards often become accepted practice via either laws or national standards.

It is to be noted that ISO 10993 is not "all inclusive," and additional testing may be required depending on the materials, construction, design, construction, and indication for the proposed device. Similarly, some tests will be required for most devices while others may be required only on a case-by-case basis. The inventor/sponsor is encouraged to discuss a proposed testing protocol with the FDA prior to embarking on a rigorous and expensive venture that may be either inadequate or over-robust. (Figure 1)

Testing Procedures

Cytotoxicity

Purpose: The purpose of cytotoxicity testing is to determine whether the proposed device is biocompatible with the human body and its constituents and whether device material(s) may contain significant quantities of material harmful to cell growth. This is especially important for devices that will be implanted within the body on a long-term basis. This test alone, if negative, however, does not ensure biocompatibility.

Methods: Isolated cells rather than organs, organ systems, or the whole-body are evaluated when exposed to the test device material. Incubated cell monolayers are exposed to test or control materials. This may require the disruption of a device with an extract formed from the resultant particulate matter. The fluid extract is then applied to the cell monolayer, replacing the normal cell nutrient media (elution method). Periodic microscopic examination for up to 3 days is undertaken to observe the monolayers for signs of toxicity such as a change in size, changes in cellular components, discoloration, or cellular disruption or lysis. Samples of the device materials can also be applied directly to the incubating cell monolayers (overlay method). Saline extracts of the test materials may also be created and added to cell suspensions where the inhibitory effects on cell growth can be measured. Another method involves exposure of a cell line to an extract of the test material. The cell line is incubated and cell counts between test material and control are compared.

Sensitization

Purpose: The purpose of sensitization of hypersensitivity testing is to determine the interaction between device materials and the body's immune system. Skin testing in laboratory animals is the preferred method as reactions to biomaterials are more commonly dermal-cell mediated rather than humoral or antigen-antibody reactions. Reactions may in some cases develop only following repeated exposure or following continuous, prolonged contact. This test may be especially important for devices with repeated dermal exposure.

Methods: This test evaluates whether there is a risk of chronic exposure to irritants in the test material. Typically, guinea pigs are used as test subjects because they are similarly sensitive to dermal irritants as humans. The test material is applied to the shaved backs of the animals for a minimum of 6 hours under an occlusive dressing (repeated patch, Buehler test). The process is repeated up to 3 times daily for 3 weeks and is followed by a 2-week recovery period. This is followed by re-challenge with the test material during which the animals are observed for a delayed cutaneous response consisting of erythema or edema when compared with vehicle-injected animals.

A second sensitization test, the maximization or Magnuson-Kligman test utilizes saline or vegetable oil-based extracts of the test material. The extracts are injected into guinea pigs as well as intradermally in order to simulate extraction by bodily fluids and intravenous solutions followed by a 2 week recovery as described above.

Systemic Toxicity

Purpose: The purpose of systemic toxicity is to identify potential systemic toxicities associated with the device depending on routes of administration, including topical application, inhalation, intraperitoneal, and oral.

Acute: occurs within 24 hours after either single or repeated doses
Subacute: occurs within 14-28 days of administration
Subchronic: occurs within 90 days of administration or after $\leq$ 10% of the animal's lifespan
Chronic: occurs > 90 days after administration or after > 10% of the animals lifespan

Methods: saline or oil-based extracts of the device are prepared and administered to test animals utilizing the proposed route of device use. Based on the length of proposed exposure, the inventor/sponsor can choose which testing method(s) are appropriate based on information contained in the International Organization for Standardization document ISO 10993-1. Animals are compared to controls that received vehicle injection at the appropriate time. Typically, for an acute toxicity study, this might involve five mice or rats per group. For longer-term studies, periodic examination with blood and urine tests and weight determination are generally carried out in a larger group of animals as well. Necropsy may also be performed.

Surgical implantation of the device may be undertaken because over time, implantable devices in humans may degrade and the resultant break-down products may be toxic. In order to evaluate this potential toxicity, additional material from the device is often implanted.

Devices that undergo exposure to blood should be pyrogen-free. In order to test for pyrogens, extracts of the materials are injected intravenously into rabbits. A significant rise in temperature within several hours indicates the presence of pyrogens.

Genotoxicity
The Ames test if often used to assess the presence of a mutation. This test uses a bacterium for which there is a simple, specific mutation. The bacterium is then exposed in culture to an environment with all the required nutrients except for the one the bacterium cannot synthesize because of the mutation. It is logically assumed that the bacteria that are able to survive do so because they have been able to correct the mutation. The greater the number of surviving bacteria, the greater the expected threat to humans.

Hemocompatability
This involves testing of materials or material extracts to determine if they can cause hemolysis (red blood cells to rupture). This testing should be performed on materials that come into contact with the blood stream or are used as a conduit to the blood stream.

Carcinogenicity
This requires long term testing for periods of up to 2 years to determine carcinogenic properties. This testing is to be done on devices with new chemistries that pose a high risk of carcinogenicity.

Reproductive/Developmental Testing
These tests include those to evaluate fertility, as well as the presence of congenital malformations and developmental delays (in utero and following birth) in offspring of animals in whom the device has been used.

Biodegradeability
Evaluation of the biodegradability properties of the device may be required. Such testing may include the natural ability, degree, and time period of the device to degrade.

Early Collaborative or Determination Meetings
The reader is referred to sections 520 (g)(7) and 513(a)(3)(D) of the Food and Drug Administration Modernization Act of 1997 (http://www.fda.gov/cdhr/modact/earlymtg.pdf).[11a,11b]

Determination Meeting

The FDA provides for two early collaboration meetings. These should take place early in device development in order to avoid unnecessary testing or worse, to have to repeat investigation because key pieces necessary in the approval process were not included. A Determination Meeting [described in 513(a)(3)(D)] is available for those that plan to submit a PMA [not for those planning to submit a 510(k)]. The purpose of the meeting is for the FDA to provide the inventor/sponsor information on the kind of scientific evidence that will be required to demonstrate effectiveness for the proposed indication; it focuses on the broader outline of the approval process. Following such a meeting, the FDA will determine whether clinical trials are required, and with the applicant, determine the "least burdensome" approach to device approval.[5] This will include the type of controls necessary if clinical trials are required. A "meeting" may take place in the form

of a face-to-face meeting, a videoconference, a teleconference, or in writing. The FDA's determination must be supplied to the inventor/sponsor within 30 days following the meeting.

Agreement Meeting

The Agreement Meeting [described in 520(g)(7)] is similar to a Determination Meeting, but is available to those planning to submit a 510(k) for eligible devices. It must be held within 30 days of submission. The applicant should submit a detailed description of the device and proposed condition it would be used for, a proposed plan to determine efficacy, information on expected device performance (if available), and a detailed clinical protocol.[5] Agreement may be reached on such things as sample size, inclusion/exclusion criteria, endpoints, study duration, number of study sites, a Data Safety Monitoring Board (DSMB), planned statistical analysis, or other issues. As long as new scientific evidence following the meeting indicates the device and endpoints as agreed to between the inventor/sponsor and the FDA do not constitute a danger to public health, the determinations and agreements made are considered binding. The inventor/sponsor is therefore unable to change the device design, proposed indication(s), and proposed protocol. It must be recognized that the FDA may be unable to reach "agreement" if prior communication with the agency was insufficient and rendered the staff unfamiliar with the device to be evaluated and the issues surrounding its indication. Once the inventor/sponsor has followed through with recommendations made in the pre-IDE meeting, a formal IDE application is submitted for review.

Clinical Trials

Clinical trials of investigational/unapproved significant-risk devices require FDA approval in the form of an Investigational Device Exemption (IDE, 21 CFR 812; www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812). Typically, drug approvals require two double-blinded, randomized, placebo-controlled trials showing safety and efficacy for each drug or each indication. However, unlike medications, devices often undergo continued evolution where problems are continually evaluated and the device re-engineered with, in many instances, with minimal change to the device. In addition, the proper use of the device is not limited to a particular indication or dosage as with a medication, but is often related to the use and skill of the practitioner. This may compromise a clinical trial as well as clinical practice where the device is used. Therefore, endpoints of clinical trials involving devices are often adjusted to allow for differences in practitioner skill.

The IDE application provides the FDA with sufficient information on the device design and materials, pre-clinical data, potential risks, study population, and expected outcome, as well as the particular study proposal(s) planned. The FDA is required to respond to the IDE application within 30 days. The Center for Devices and Radiological Health (CDRH) is charged with the review of medical devices. An IDE application is considered approved 30 days following receipt by the FDA unless the FDA otherwise informs the investigator/sponsor that it is not approved or approved with certain

condition; a formal "approval" to begin a study is not sent to the investigator/sponsor. In order to fulfill the requirements under an IDE, though the device must be labeled "CAUTION- Investigational Device restricted by Federal (or United States) law to investigational use," subjects must sign an institutional review board (IRB)-approved consent. The study must be appropriately monitored to protect the participating subjects, and reports on the progress of the study must be made to the participating investigators, IRBs, and the FDA. A non-significant risk study (for example, a new biopsy channel cap for an endoscope) requires only approval of the IRB prior to initiation.

IDE vs 510K

A 510(k) is a pre-market submission made to the FDA to demonstrate the device is "substantially equivalent" to a device marketed prior to May 28, 1976, and may be marketed as safe and effective for its indicated use. "Substantially equivalent" is generally interpreted by the FDA to mean it has the same intended use and either the same or potentially similar technological characteristics as the predicate device or if different, that there are no new concerns with regard to safety of efficacy.[21]

The Premarket Approval (PMA) is a substantially more rigorous (and expensive) device marketing application. The review process may take 6 months or longer and the device may be reviewed at an FDA Advisory Board meeting open to the public. Once approved and posted on the internet, there is a 30 day period during which petitions may be made by the public urging the approval decision to be overturned.[16] FDA approval of a PMA indicates that the agency has determined there is sufficient scientific evidence to assure the device is safe and effective for its intended use. This is essentially a license to market the device.

The inventor/sponsor must provide the FDA with the name and address of the clinical trial monitor, as well as written monitoring procedures (unless there is a single investigator who will also serve as the study monitor). The FDA guidelines (53 FR 4723, 1988) will be useful to review. Although the FDA does not have jurisdiction over foreign sites, data from such sites may be acceptable in support of a pre-market approval application (PMA) as long as the study was conducted in accordance with the principles of the "Declaration of Helsinki."

The standard fee for submission of a PMA is $281,600 although this fee is waived for the first PMA application from firms with gross receipts or sales < $30 million/year. The fee is also reduced for small business entities. For a 510(k) submission, the fee is $4,158 and is slightly less for a small business.[17] Devices used solely for pediatrics are fee-exempt. CDRH is now using "Recognized Third Parties" (non-governmental, for-profit entities) for certain devices to review 510(k) applicants in an attempt to streamline the review process.

Transfer Phase

The transfer phase is taking the processes, documentation, and results of the Regulatory phase and transitioning it to production volume. This typically involves a more in-depth documentation, training of production personnel, equipment and tooling acquisition, quality inspection documentation, lot history documentation (for traceability of materials and processes), and process validation.

The IDE Application
The inventor/sponsor must show that the potential benefits of the device (and clinical trial) outweigh the potential safety concerns. The application must include the name and address of the sponsor, a report of prior investigations with the device, including non-clinical studies with a biography of such studies and copies of published and unpublished adverse event information, the investigational plan with risk analysis and trial monitoring procedures, a description of the manufacturing, packaging, storage, and use of the device, a list of all investigators, institutions, and IRBs, copies of all informed consent forms, and device labeling. The report of prior investigations must be complete, the description of the device detailed (including design rationale, engineering drawings, specifications, and materials), and the proposed investigational plan complete and scientifically sound with defined objectives and rationale for the number of animals or human subjects planned.

Pre-PMA Meetings
These meetings are held to discuss the results of the clinical trial results and the format of the planned application. Once the PMA has been approved, you now have achieved success and have a device that is ready for introduction to the marketplace!

License Agreements

Technology licensing is a primary route taken by inventors and academic and research institutions to put innovative technology into public use. The strategy involves finding a development or commercial partner to develop and exploit technological developments ("licensing-out"), and provides certain advantages. The risk and cost of development and distribution are spread to the licensee, and the goodwill of a licensee may add to the product's perceived market value and acceptance by the public. Mainly, licensing-out technology provides earning potential in the form of initial license fees, milestone payments, and ongoing royalty income. The following elements should be considered in drafting or negotiating a license agreement. The duration of a license should not exceed the life of the licensed patents to avoid antitrust (patent misuse) problems. If however, other intellectual property, such as know-how, trade secrets, copyrights, or trademarks, are part of the same license, the term of the license may continue for a term beyond the life of the patents for a reduced royalty rate.

Description of Licensed Intellectual Property
Accurate description or identification of the subject matter being licensed is important to the bargain and often drives other deal terms. Lack of clarity of the subject matter being licensed is a common problem that may be avoided by the crafting custom-fit definitions

to describe the intellectual property being licensed. Often licensed technology is not fully captured by identification to a patent and/or copyright registration. Beyond the registered subject matter, there may be additional trade secret or know-how information desired or willing to be licensed for full range of permissions. For example, identification of the patent number to an endolaparoscope may not adequately identify the software element required to operate the device, and vice-versa. There may also be trade secrets or know-how that aid in the development, testing, manufacturing or use of the device, which should be separately identified and may merit increased royalty rates or a longer term of the license in connection with the know-how.

Description of Granted Rights

The license grant provision sets forth the scope of the licensee's right to use the licensed intellectual property. There are three levels of exclusivity: exclusive, co-exclusive and non-exclusive. An exclusive license grants the sole right to use and exploit the licensed intellectual property to one other party. Exclusive rights typically include the right to grant further sublicenses. Co-exclusive licenses include granting the same rights to a limited set of two or more parties, or retaining for licensor the same rights granted to licensee. In a non-exclusive license, multiple parties have rights to the same intellectual property and there are typically no-sublicensing rights granted to any of the non-exclusive licensees. Where government funding was used to develop intellectual property which is the subject of a license, the licensee's rights are subject to the U.S. government's non-exclusive, royalty-free and irrevocable license to use and have other use on its behalf for government purpose, and the government march-in rights.

The grant provision may also be limited by a field of use. That is, the licensee's right to practice the invention is not for any purpose, but rather, is limited to a defined field (e.g., a particular indication(s) like cancer, Alzheimer's disease, therapeutics, and/or diagnostics). The scope of a licensee's rights to practice an invention may also be defined by geography; worldwide or limited to a particular jurisdiction or country(ies).

Financial Consideration

In determining the financial consideration for a license, the value of the intellectual property and the terms of the license should be considered foremost, and there should be some give and take between consideration received upfront and that received downstream, along with the size and liquidity of the licensee. A licensee will likely prefer to limit its upfront exposure and defer costs, whereas, money in the pocket is preferable to the licensor. The customary categories of consideration, include: (i) an upfront license fee, which is a one-time, non-refundable, upfront payment that provides incentive to the licensee to carry out its obligations under the license, and compensates the inventor/owner for his or her inventive efforts, (ii) reimbursement for past and future patent prosecution costs, (iii) minimum royalties, which are a set fee paid periodically regardless of whether or not there are product sales or necessary market approvals, and which should motivate a license to fulfill its commercialization obligations, (iv) milestone payments, which are fees paid upon occurrence or achievement of a particular event, and (v) royalties, which are a percentage of the profits received for product sales.

Due Diligence
Due diligence provisions attempt to generate action by a licensee to commercialize the technology. As stated above, financial consideration in the form of upfront payments and minimum royalties can be a good motivating factor. A licensee that has to pay high upfront and/or minimum royalties may be more inclined to commercialize product to recoup the upfront costs downstream with product sales. A development timetable with identified milestones should be established to set the parties expectations and the licensee's development obligations. Reporting obligations keep the licensor informed as to the progress or lack thereof. With any due diligence provision, failure to meet the requirements may be tied with an opportunity for the licensor to terminate the license. In this regard it is beneficial to specifically identify the development goals and requirements to minimize disputes.

Representations and Warrants
Representations and warrants are statements made by one party that the other party relies on for entering into or continuing to perform under the license, and, if breached, may serve as a means to terminate a license. Representations typically asked of a licensor include statements as to the state of the licensed intellectual property, for example, that it is in good standing, unencumbered, valid and non-infringed. A licensor may also obtain representations and warrants from the licensee as to its good standing, authority and ability to contract without conflict, ability or qualifications to perform under the contract, and licensure as required to take a product to market.

Exit Strategy
The best licenses contemplate the worst case scenarios. Think ahead to those situations in which you would want to terminate the license and draft contract provisions accordingly. Customary termination clauses include termination (i) for material breach with opportunity to cure, (ii) for breach of representations and warranties with and opportunity to cure, and (iii) for bankruptcy. Failure to meet milestones or exercise due diligence requirements should also trigger the right by licensor to terminate the license. If a license covers more than one piece of intellectual property, or the development of more than one product or indication for the same product, consider partial terminations or non-exclusive licenses in place of exclusive terms if due diligence requirements are not met. The recent *MedImmune v. Genentech* case, shifted leverage to licensee to be able to challenge a licensed patent without breaching the license. A license should include disincentives against a licensee from challenging the validity of the licensed intellectual property during the term of the license.[42] Also contemplate and incorporate into the license your requirements to continue development or commercialization if the license terminated, by its own terms or by breach; such requirements may include for example, money, support or transition services, work product to date, permitted access to a device or drug master file, right to assume sublicenses, and intellectual property assets.

Selecting a Trademark

While a patent protects your invention, it does not protect a brand name. To establish and maintain ownership rights in a brand name for whatever products that embodies your

invention you must turn to trademark law. A trademark is any word, name, symbol, logo or device that is used to identify and distinguish products from one another. In developing a new trademark there are two pools. First, choose a trademark that is "strong" and that can be protected by registration with the Trademark Office. Second, choose a potential trademark that is not likely to be confused with another.
It is important to choose a "strong" trademark as they receive a wider range of protection and are more valuable to a buyer or potential licensee of your invention. The strongest marks are inherently distinctive marks, of which there are three types: fanciful, arbitrary, and suggestive. A fanciful mark is a coined word that is newly created and does not have any previously known meaning. Examples of fanciful marks are XEROX for copiers, KODAK for film, and EXXON for gasoline. Arbitrary marks are common words that have no apparent relationship to the goods and services for which the mark is used. Examples of arbitrary marks include SHELL for gasoline products, APPLE for computers, and CAMEL for cigarettes. Suggestive marks are marks that allude to a quality or characteristic of the goods or services, but require a leap of the imagination to reach a conclusion as to the actual nature of the goods. Some examples include CHICKEN OF THE SEA for tuna and L'EGGS for women's hosiery. Brand names like these should be your model when selecting a trademark.

As one can imagine, it is very difficult to conceive of strong and distinctive trademarks. As a result, most "first choices" are weak or not protectable at all. Such marks are called "descriptive marks." You should avoid selecting a mark that directly conveys a characteristic, quality or nature of your product. Such marks cannot be registered unless, usually through long-association, a mark has come to mean only one product. Examples of descriptive marks include SHAKE 'N BAKE for bread crumbs, RAISIN BRAN for cereal, and NU-ENAMEL for paint.

"Generic words" also cannot be trademarked. For example, CAMERA for cameras and COMPUTER for computers are not registerable. Generics are words that cannot be exclusively claimed by only one person. These words must remain available to the public.

Determining whether your chosen mark is "available" requires the skill and experience of a trademark attorney. The standard for trademark infringement is whether the marks under comparison are sufficiently similar, that they are likely to cause confusion among the relevant consumers about the origin, sponsorship or affiliation between the goods. Marks do not have to be identical to be confusingly similar. The nuance of what is, or is not, an infringement depends on a comparison of marks on the basis of their sight, sound and meaning. For example, TORNADO and CYCLONE cannot co-exist for the pools because they have the same meaning even though obviously, visually different. As further examples, these trademarks have been held to be confusingly similar based on their phonetic similarity: DRAMAMINE and BONAMINE, LISTERINE and LISTOGEN, SNAPPER and SNIPPY.

If a mark infringes someone else's trademark rights, a costly lawsuit may ensue and often a new mark must be adopted. Therefore, it is in your best interest to avoid selecting a

mark that is similar to another mark already in use. Obtaining a "clearance" opinion from an attorney is a type of insurance against such set-backs. After determining your chosen mark is not in use, you must begin using your mark in commerce in order to establish your rights in the mark. This requirement can be satisfied by a license between you and a licensed manufacturer.

Summary

The road from a new idea for a medical device to commercialization is long and involved. Often it can take 2 to 7 years depending on the complexity and uniqueness of the device. There are many pitfalls that can derail or prevent continuation of the development. One of the critical issues not discussed in this paper is the need for "reimbursement codes" to allow hospitals and physicians to charge insurance companies and Medicare when the device is used. This is critical for commercial success.

However, bringing a new medical device into commercial use can be a rewarding venture. First, it can it be very financially rewarding. But even more important, there is a special feeling of accomplishment in knowing you have helped reduce pain and suffering, cure a disease, save a life or made a procedure more effective and efficient.

References

1. www.autm.net/aboutTT/aboutTT_bayhDoleAct.cfm

2. Http://grants.nih.gov/grants/guide/pa-files/PA-07-280.html. Accessed June 11, 2007

3. Http://grants.nih.gov/grants/guide/pa-files/PA-07-281.html. Accessed June 11, 2007

4. Food and Drug Act of 1907, ch 3915, 34 Stat 768 (1907)

5. 1938 Food, Drug, and Cosmetic Act, Pub L No 75-717, 52 Stat 1040, 21 USC 301-394

6. Radiation Control for Health and Safety Act of 1968, Pub L No 90-602, 82 Stat 1171 (1968)

7. Medical Device Amendments of 1976, Pub L No 94-295, 90 Stat 539 (codified as amended in scattered sections of 21 USC)

8. Merrill RA. The architecture of government regulation of medical products. 82 Va L Rev Code 1753, 1996

9. Smith JJ. Regulation of medical devices in radiology: current standards and future opportunities. Radiology 218:329-335, 2001

10. Pritchard WF, Carey RF. Primer on medical device regulation: US Food and Drug Administration and regulation of medical devices in radiology. Radiology 205:27-36, 1997

11. Safe Medical Devices Act of 1990, Pub L No. 101-629, 104 Stat 4511, 21 USC 301-394

11a. Food and Drug Moderization Act of 1997, Pub L, No. 105-114, 111 Stat 2296 (1997), 21 USC 301-394

11b. U.S. Dept Health Human Services, Food and Drug Administration, Center for Devices and Radiological Health. Early Collaboration Meetings Under the FDA Moderinization Act (FDAMA); Final Guidance for Industry and for CDRH Staff. Www.fda.gov/cdhr/ode/guidance/310.html accessed 6/2/2007

12. Manual to Health Payors. Washington DC: Health Care Financing Administration, 1986.

13. Health Care Financing Administration. Medical coverage policy: clinical trials. Baltimore, Md: Health Care Financing Administration, September 19, 2000

14. http://en.wikipedia.org/wiki/CE_mark. Accessed June 12, 2007

15. McAllister P, Jeswiet J. Medical device regulation for manufacturers. Proc Instn Mech Engrs 217:459-467, 2003

16. http://www.fda.gov/cdrh/devadvice/pma

17. http://fda.gov/cdrh/devadvice/314a.thml

18. Guidance on IDE Policies and Procedures. US Dept Health Human Services. FDA. Center for Devices and Radiological Health. Rockville, MD. Document 882, 1998

19. Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices. US Dept Health Human Services. FDA. Center for Devises and Radiological Health. Rockville, MD. Document G95-1, May, 1995

20. Use of International Standard ISO-10993: Biological Evaluation of Medical Devices Part-1: Evaluation and Testing. US Dept Health Human Services. FDA. Center for Devises and Radiological Health. Rockville, MD.

21. http://www.fda.gov/cdhr/ode/dd510kse.pdf

22. Medical Devices: Current Good Manufacturing Practice, FDA, 21 CFR Part 820

23. Forum on NPD Best Practices, Michael F. Clem, DVM, MS, September 13, 2005, Warton School of Business, Philadelphia PA

24. http://www.fda.gov and searching for Guidance Documents for the particular device being developed.

25. Bonito Boats, Inc., v. Thunder Craft Boats, Inc., 489 U.S. 141, 151 (1989).

26. 35 U.S.C. §102(b). United States Code Title 35, Section 102(b) (2000 & Supp. IV 2005).

27. *LaBounty Manufacturing, Inc., v. U.S. Int'l Trade Comm'n*, 958 F.2d 1066 (Fed. Cir. 1992).

28. 35 U.S.C. § 101. United States Code Title 35, Section 101 (2000 & Supp. IV 2005).

29. 35 U.S.C. § 102. United States Code Title 35, Section 102 (2000 & Supp. IV 2005).

30. 35 U.S.C. § 103. United States Code Title 35, Section 103 (2000 & Supp. IV 2005).

31. 35 U.S.C. § 112. United States Code Title 35, Section 112 (2000 & Supp. IV 2005).

32. 35 U.S.C. § 101. United States Code Title 35, Section 101 (2000 & Supp. IV 2005).

33. *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (U.S. 2007).

34. *Glaxo, Inc. v Novopharm Ltd.*, 52 F.3d 1043, 1052 (Fed. Cir. 1995).

35. *Beech Aircraft Corp. v. EDO Corp.*, 990 F.2d 1237, 1248 Fed. Cir. 1993

36. 35 U.S.C. § 116. United States Code Title 35, Section 116 (2000 & Supp. IV 2005).

37. 35 U.S.C. § 262. United States Code Title 35, Section 262 (2000 & Supp. IV 2005).

38. The Bayh-Dole Act, 35 U.S.C. §200 – 212, as implemented by 37 C.F.R. §401.

39. *Campbell Plastics Eng'g & Mfg. v. Brownlee*, 389 F.3d 1243 (Fed. Cir. 2004).

40. 35 U.S.C. §202(c)(4). United States Code Title 35, Section 202(c)(4) (2000 & Supp. IV 2005).

41. 35 U.S.C. §203. United States Code Title 35, Section 203 (2000 & Supp. IV 2005).

42. *Medimmune, Inc. v. Genentech, Inc.* 127 S. Ct. 764 (U.S. 2007)

1. www.autm.net/aboutTT/aboutTT_bayhDoleAct.cfm

2. Http://grants.nih.gov/grants/guide/pa-files/PA-07-280.html. Accessed June 11, 2007

3. Http://grants.nih.gov/grants/guide/pa-files/PA-07-281.html. Accessed June 11, 2007

4. Food and Drug Act of 1907, ch 3915, 34 Stat 768 (1907)

5. 1938 Food, Drug, and Cosmetic Act, Pub L No 75-717, 52 Stat 1040, 21 USC 301-394

6. Radiation Control for Health and Safety Act of 1968, Pub L No 90-602, 82 Stat 1171 (1968)

7. Medical Device Amendments of 1976, Pub L No 94-295, 90 Stat 539 (codified as amended in scattered sections of 21 USC)

8. Merrill RA. The architecture of government regulation of medical products. 82 Va L Rev Code 1753, 1996

9. Smith JJ. Regulation of medical devices in radiology: current standards and future opportunities. Radiology 218:329-335, 2001

10. Pritchard WF, Carey RF. Primer on medical device regulation: US Food and Drug Administration and regulation of medical devices in radiology. Radiology 205:27-36, 1997

11. Safe Medical Devices Act of 1990, Pub L No. 101-629, 104 Stat 4511, 21 USC 301-394

11a. Food and Drug Moderization Act of 1997, Pub L, No. 105-114, 111 Stat 2296 (1997), 21 USC 301-394

11b. U.S. Dept Health Human Services, Food and Drug Administration, Center for Devices and Radiological Health. Early Collaboration Meetings Under the FDA Moderinization Act (FDAMA); Final Guidance for Industry and for CDRH Staff. Www.fda.gov/cdhr/ode/guidance/310.html accessed 6/2/2007

12. Manual to Health Payors. Washington DC: Health Care Financing Administration, 1986.

13. Health Care Financing Administration. Medical coverage policy: clinical trials. Baltimore, Md: Health Care Financing Administration, September 19, 2000

14. http://en.wikipedia.org/wiki/CE_mark. Accessed June 12, 2007

15. McAllister P, Jeswiet J. Medical device regulation for manufacturers. Proc Instn Mech Engrs 217:459-467, 2003

16. http://www.fda.gov/cdrh/devadvice/pma

17. http://fda.gov/cdrh/devadvice/314a.thml

18. Guidance on IDE Policies and Procedures. US Dept Health Human Services. FDA. Center for Devices and Radiological Health. Rockville, MD. Document 882, 1998

19. Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices. US Dept Health Human Services. FDA. Center for Devises and Radiological Health. Rockville, MD. Document G95-1, May, 1995

20. Use of International Standard ISO-10993: Biological Evaluation of Medical Devices Part-1: Evaluation and Testing. US Dept Health Human Services. FDA. Center for Devises and Radiological Health. Rockville, MD.

21. http://www.fda.gov/cdhr/ode/dd510kse.pdf

22. Medical Devices: Current Good Manufacturing Practice, FDA, 21 CFR Part 820

23. Forum on NPD Best Practices, Michael F. Clem, DVM, MS, September 13, 2005, Warton School of Business, Philadelphia PA

24. http://www.fda.gov and searching for Guidance Documents for the particular device being developed.

25. Bonito Boats, Inc., v. Thunder Craft Boats, Inc., 489 U.S. 141, 151 (1989).

26. 35 U.S.C. §102(b).

27. *LaBounty Manufacturing, Inc., v. U.S. Int'l Trade Comm'n*, 958 F.2d 1066 (Fed. Cir. 1992).

28. 35 U.S.C. § 101.

29. 35 U.S.C. § 102.

30. 35 U.S.C. § 103.

31. 35 U.S.C. § 112.

32. 35 U.S.C. § 101.

33. *KSR Int'l Co. v. Teleflex, Inc.*, No. 04-1350 (U.S. Apr. 30, 2007).

34. *Glaxo, Inc. v Novopharm Ltd.*, 52 F.3d at 1043, 1052.

35. *Beech Aircraft Corp v. EDO Corp.* 990 F, 2d 1237, 1248 Fed Cir 1993

36. 35 U.S.C. § 116.

37. 35 U.S.C. § 262.

38. The Bayh-Dole Act, 35 U.S.C. §200 – 212, as implemented by 37 C.F.R. §401.

39. *Campbell Plastics v. Brownless*, 389 F.ed 1243 Fed Cir 2004

40. 35 U.S.C. §202(c)(4).

41. 35 U.S.C. §203.

42. *Medimmune v. Genentech*, 127 S. Ct. 764 (2007)

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