

SESSION 7

INTRODUCTION TO LEGAL AND REGULATORY ISSUES

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INTRODUCTION

Emerging biomedical products utilizing living tissues present a new order of magnitude of complexity in their interactions with human patients. As such, they challenge established processes for protecting patients and the public health from deleterious adventitious agents, while testing the capacity of those processes to ensure timely access to beneficial therapies. At the same time, access to human tissues for purposes of medical product development—or, less benignly, for cloning or optimization of selected functional capabilities—present potentially very troubling legal and ethical issues.

In its consideration of legal and regulatory issues affecting the introduction of engineered tissue products, the WTEC Tissue Engineering Study seeks to compare the present approaches of the relevant regulatory authorities in the United States, Europe and Japan, together with certain national rules which may limit access to or the use of human tissue for medical applications.

This analysis has been inaugurated with an examination of the legal and regulatory status of engineered tissue products in the United States. Presentations given at this Workshop addressed patenting of tissue engineering, application of the evolving approach taken by the U.S. Food and Drug Administration (FDA) to the classification and pre-market review of engineered tissue products, and emerging concerns over the use of human tissues and protection of human subjects.

INTELLECTUAL PROPERTY¹

The U. S. Patent and Trademark Office (PTO) has not established any particular criteria for patent applications claiming new methods of manipulating human tissues to produce medical therapies. However, the PTO's latest guideline outlining the inventor's obligation to demonstrate a present ability to perform the invention to achieve a useful purpose (i.e., the requirement of "enablement") may threaten the present patentability of tissue engineering methods which may be integral to new tissue therapies but which are not developed to the point of delivering those therapies.

FDA REGULATION²

Human tissues used for medical purposes have been classified by the FDA as "human tissues intended for transplantation" or as medical products, either as devices (as in the case of dura mater, human lenticules and allograft heart valves) or as biologics (as in the case of blood, blood components, and blood products). Consequently, engineered human tissue products can be expected to be regulated by the FDA either as medical devices—through the Agency's Center for Devices and Radiological Health (CDRH); or biologics—

through its Center for Biologics Evaluation and Research (CBER). However, the criteria and process for such classification and subsequent marketing review will be substantially influenced by new regulations presently in development.

Much of the regulatory framework for engineered tissue products has yet to be promulgated by the FDA through formal, binding rule-making procedures. Nevertheless, the FDA has issued a number of documents over the past few years which, although not binding on the Agency, do provide the public with a formal expression of current thinking regarding the future regulation of engineered tissue products (see Table 1).³ Of these, by far the most important has been the Proposed Approach to Regulation of Cellular and Tissue-Based Products (the "Proposed Approach"), which was issued by the FDA on February 28, 1997.

Table 1

Key Documents Re: FDA Regulation of Human Cellular and Tissue-Based Products

1. Kessler, David A., et. al., Regulation of Somatic-Cell Therapy and Gene Therapy by the Food and Drug Administration, 329 N.E. J. of Med. 1169 (Oct. 14, 1993)
2. Notice: Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products (58 FR 53248; Oct. 14, 1993)
3. Notice of Interim Rule: Human Tissue Intended for Transplantation (58 FR 65514; Dec. 14, 1993)
4. Notice of Public Hearing: Products Comprised of Living Autologous Cells Manipulated *ex vivo* and Intended for Implantation for Structural Repair or Reconstruction (60 FR 36808; July 18, 1995)
5. Final Rule: Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products (61 FR 24227; May 14, 1996)
6. Notice: Availability of Guidance on Applications for Products Comprised of Living Autologous Cells. . (etc.) (61 FR 26523; May 28, 1996)
7. Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated *ex vivo* and Intended for Structural Repair or Reconstruction (May, 1996)
8. "Proposed Approach to Regulation of Cellular and Tissue-Based Products" (February 28, 1997)
9. Notification of proposed regulatory approach regarding cellular and tissue-based products (62 FR 9721; March 4, 1997)
10. Final Rule: Human Tissue Intended for Transplantation (62 FR 40429; July 29, 1997)
11. Notice: Availability of Guidance on Screening and Testing of Donors of Human Tissue Intended for Transplantation (62 FR 40536; July 29, 1997)
12. Guidance to Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation (July 29, 1997)
13. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (March, 1998)
14. Proposed Rule: Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products (63 FR 26744; May 14, 1998)
15. Proposed Rule: Suitability Determination for Donors of Human Cellular and Tissue-Based Products (64 FR 52696; September 30, 1999)

Building upon the concepts and strategies set out in the Agency's 1993 pronouncements regarding somatic cell therapies and transplanted tissues, the Proposed Approach outlines a plan of regulatory oversight, which can include a pre-market approval requirement, for such tissue products based on a matrix ranking the products, classified by certain characteristics, within identified areas of regulatory concern. Engineered tissue products would be classified according to: 1) the relationship between the donor and the recipient of the biological material used to produce the tissue product; 2) the degree of *ex vivo* manipulation of the cells comprising the tissue product; and 3) whether the tissue product is intended for a homologous use, for metabolic or structural purposes, or to be combined with a device, drug or biologic.

The Proposed Approach also announced the establishment of an inter-Center Tissue Reference Group to act as an ombudsman to resolve product classification disputes and ensure agency-wide consistency in the application of relevant regulatory authority over transplantable or engineered tissues used as medical therapies.

Presentations describing FDA's classification and pre-market review of Apligraf (Organogenesis) as a medical device and Carticel (Genzyme Tissue Repair) as a biologic demonstrated the agency is actively engaged in developing rational product approval pathways for engineered tissue products according to their classification for purposes of regulatory oversight. This approach was contrasted with the present uncertain status of such products within the European Union. The speakers did note, though, that potential inconsistencies or a lack of transparency in the application of regulatory authority over engineered tissue products would increase the complexity of introducing new medical technologies incorporating human tissues without materially advancing public health or safety.

ACCESS TO HUMAN TISSUES FOR RESEARCH

While critical to the general advance of medical research, access to human tissues for research or product development is highly sensitive to public disclosure of tissues taken or used without consent or under circumstances suggesting a commercial market in body parts. The absence of comprehensive federal or state legislation governing "research" tissues deprives the biomedical community of clear, consistent guidelines to follow in acquiring and using tissues, while simultaneously representing a legislative vacuum that may be filled with substantial adverse unintended consequences if done suddenly in response to some public outcry. Absent effective coordination, the initiatives of individual federal agencies to establish policies for research involving human tissues or subjects may impose conflicting requirements or expectations.

ESTABLISHING STANDARDS FOR ENGINEERED TISSUE PRODUCTS⁴

In December, 1997, with considerable FDA participation and support, the American Society for Testing and Materials (ASTM) launched a comprehensive strategy to develop standards for the production of tissue engineered medical products. Through a series of semi-annual meetings since then, the ASTM tissue engineering standards effort has provided an ongoing forum for identifying and, through a careful consensus-building process, addressing the critical details essential to a thorough characterization of engineered tissue products for regulatory review. These meetings draw together FDA reviewers, industry representatives, researchers and other interested persons. Many draft standards are in various stages of development.

CONCLUSIONS FROM THE PRESENTATIONS

Taken as a whole, the presentations on legal and regulatory issues revealed that

- the pace and direction of the development and clinical introduction of engineered tissue products can be affected by many federal agencies;
- a general disengagement of the biomedical community from the policy making processes of these agencies can deprive them of an important perspective on proposed actions;

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- as the FDA evolves its strategy for managing engineered tissue products, it should emphasize cross-Center consistency in product classification and product approval paradigms which respond to the particular attributes and challenges of products incorporating living human tissues; and
- the FDA's effort to develop a rational approach to the regulation of engineered tissue products is well-begun; it should be continued and expanded globally through international harmonization programs.

¹ General information regarding U. S. Patent & Trademark Office policies and procedures (including the recently issued enablement and utility guidelines) as well as all patents issued since 1976 can be found at the PTO website (www.uspto.gov).

² General information regarding FDA policies and procedures can be found at the FDA website (www.fda.gov). Specific information regarding the activities of the lead regulatory Centers, CDRH and CBER, can be found at www.fda.gov/cdrh and www.fda.gov/cber, respectively.

³ The Key FDA Documents listed at Table 1 (with the exception of Document #1) can be obtained through the FDA website (www.fda.gov/cdrh or www.fda.gov/cber) or, in the case of documents appearing in the Federal Register, through the Government Printing Office website (www.gpo.gov)

⁴ General information regarding the ASTM tissue engineered medical products standards development effort can be obtained at the ASTM website at www.astm.org (go to the page for Committee F04, Division IV).

ACCESS TO HUMAN BIOLOGICAL MATERIALS

Michael J. Malinowski, JD

ABSTRACT

In its August 1999 report, *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*, the National Bioethics Advisory Commission (“NBAC”) estimated there are more than 282 million human specimens in the nation’s laboratories, tissue repositories, and health care institutions. Given the extraordinary potential to improve human health associated with recent advances in genetic research, the biomedical research community must maintain continued access to human biological materials. In fact, in the field of tissue engineering, strong arguments can be (and are being) made for *increasing* access to human biological materials—most notably, arguments to permit federally funded researchers to work with embryonic stem cells.

However, access to human tissues for biomedical research is about to become much more complicated, if not directly narrowed, due to several sets of concerns. First, the accomplishments and ongoing advancement of genetic research are largely attributable to biomedical researchers’ enhanced capabilities to study and draw information from human biological materials. Consequentially, research that holds the potential to revolutionize health care is exacerbating concerns about the privacy and autonomy rights of individuals and reinvigorating long-standing arguments that individuals should have the right to control access to biological materials. Second, following intense media coverage of researcher conflicts of interests and other violations associated with patient deaths, there now is widespread acknowledgement of fundamental weaknesses in the United State’s framework for protecting human subjects. With maps of the human genome near completion, an unprecedented amount of biomedical research underway, and advances in disciplines as varied as spectroscopy, robotics, and computing introducing new sets of tools for discovering, mapping, and modifying genetic information, this awareness is belated at best. Systematic shortcomings reported in the midst of tremendous ongoing research has given credence to reservations, including the public’s fears of discrimination based upon information derived from genetic tests, at a time when, from a human health perspective, the opportunity costs of impeding biomedical research has never been higher.

This presentation will provide an overview of the pressing issues surrounding access to human biological materials, with particular attention paid to implications for the field of tissue engineering. The Common Rule, the primary codification of human subject protection in the United States, will be interpreted in this context. The discussion will include a primer on human subject protection considerations, including the identification of samples and specimens, with a summary of the positions taken by NBAC and others. Emphasis will be placed on the fact that the pace of progress in tissue engineering research is contingent upon resolution or avoidance of emotional controversies such as federal funding of embryonic stem cell research *in addition to* the multitude of personal autonomy and privacy concerns that generally surround the use of human samples in biomedical research.

PRESENTATION TALKING POINTS: ACCESS TO HUMAN BIOLOGICAL MATERIALS

Michael J. Malinowski

I. INTRODUCTION:

- A. This is an extraordinary time for the field of tissue engineering:
 - ❑ Science presentations at the workshop;
 - ❑ Advances in stem cell research over the past year or so;
 - ❑ NIH support for federal funding of some embryonic research; and
 - ❑ Fact that this WTEC initiative is underway.
- B. However, from a law-policy-regulatory perspective, this also is a precarious time:
 - ❑ Access to human tissues for biomedical research is about to become much more complicated, if not directly narrowed, due to several sets of concerns.
 - ❑ In addition to controversies that will impact biomedical research generally, tissue engineering research also has triggered some unique and highly emotional controversies.
 - ❑ Pending question: To what extent will public and political passion for biomedical research that holds the promise of medical breakthroughs be tempered by these concerns and controversies, many of which are attributable to long-standing, systemic issues not conducive to timely resolutions?
- C. I am going to use this opportunity to provide an overview of the pressing issues that are complicating access to human biological materials, with particular attention paid to implications for the field of tissue engineering.
- D. Primary observations:
 - ❑ There are systemic problems with the U.S. human subject protection framework that must be addressed, and should have been addressed years earlier. These issues are not conducive to timely resolutions, and the opportunity costs now could not be greater—especially for fields such as tissue engineering which are advancing rapidly towards the clinic with the promise of breakthrough treatments.
 - ❑ The escalation of reported shortcomings in the human subjects framework have forced awareness and given credibility to an entanglement of long-standing and emotional issues centered on the autonomy of individuals who participate in research and control over their biological materials in light of potential risks, such as discrimination based upon genetic information.

- ❑ Given the extraordinary potential to improve human health introduced by recent advances in genetic research, the biomedical research community must maintain access to human biological materials.
- ❑ In fact, in the field of tissue engineering, strong arguments can be (and are being) made for *increasing* access to human biological materials—most notably, arguments to permit federally-funded researchers to work with embryonic stem cells.

II. AVAILABILITY, ACCESS, AND USE

A. The resources at issue:

- ❑ In its August 1999 report, *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*, the National Bioethics Advisory Commission (“NBAC”) estimated there are more than 282 million human specimens (from more than 176 million individual cases) in the nation’s laboratories; repositories; blood, organ, sperm, ovum, and embryo banks; forensic DNA banks; and health care institutions.
- ❑ Collections are growing at a rate of 20 million cases per year.
- ❑ Two of the largest tissue repositories in the world are housed within the Armed Forces Institute of Pathology (“AFIP”), the National Pathology Repository and the DNA Specimen Repository for Remains Identification.
- ❑ Most repositories contain identified specimens because the majority of human biological materials already in storage were collected for diagnostic or therapeutic purposes (e.g., pathology laboratories and newborn screening).
- ❑ Current federal regulations, based upon long-standing interpretation, have allowed investigators to access stored specimens, remove identifiers (often via codification/encryption by the repositories), and use them in research without seeking the consent of or even notifying the source.

B. Present value:

- ❑ The accomplishments and ongoing advancement of genetic research are largely attributable to biomedical researchers’ enhanced capabilities to study and draw information from human biological materials.
- ❑ With maps of the human genome near completion, an unprecedented amount of biomedical research underway, and advances in disciplines as varied as spectroscopy, robotics, and computing introducing new sets of tools for discovering, mapping, and modifying genetic information, awareness and/or resolution of issues such as weaknesses in the human subjects protection framework and the absence of medical privacy protections are belated at best.
- ❑ Implication: Human biological materials have never been more valuable and the opportunity costs associated with impeding researcher access—namely delayed or even lost opportunities to dramatically improve human health—have never been higher.

C. Extent of change at issue:

- ❑ Human biological materials have been available, accessible, and used in biomedical research for decades, and many of these resources may become inaccessible/non-usable for biomedical research.
- ❑ Biomedical research, the culture surrounding biomedical research, and practices and procedures presume continued availability, access and use.

III. INDIVIDUAL AUTONOMY AND PRIVACY CONCERNS

- A. Shortcomings in human subject protection regulation and the absence of comprehensive, national medical privacy legislation are systemic problems fueling calls for conditions on access to human tissues for biomedical research:
- Researcher conflicts of interests and other violations associated with patient deaths have given rise to widespread acknowledgement of fundamental weaknesses in the United State's framework for protecting human subjects.
 - Attention placed on these systemic shortcomings in the context of reported incidents and in the midst of tremendous ongoing biomedical research has given credence to reservations, including the public's fears of discrimination based upon information derived from genetic analysis.
 - The augmented abilities to draw information from individual samples that holds the potential to revolutionize health care is exacerbating concerns about the privacy and autonomy rights of individuals and reinvigorating long-standing arguments that individuals should have the right to control access to biological materials.
 - This is a difficult time to problem solve because the research is ongoing and the opportunity costs in terms of potential benefits to human health are unprecedented.
- B. Reasons given for increasing control by sources and raising safeguards for confidentiality and privacy:
- Avoiding insurance and employment discrimination;
 - Avoiding stigmatization;
 - Avoiding negative stereotyping (group-based harms);
 - Avoiding familial conflicts;
 - Avoiding use of biological samples contrary to the source's wishes;
 - Per se control by individuals over use of their biological materials.
- C. Common Rule (45 CFR Part 46) considerations:
- Anticipate much higher standards for research going forward: greater control by sources and more rigorous safeguards for privacy and confidentiality.
 - Expect much more demanding justification to be required for any use of identifiers and access to patient information for research.
 - Interpretation by the National Bioethics Advisory Commission ("NBAC") in this context: *Report and Recommendations, Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (August 1999). The net effect of this interpretation is that any existence of identifiers, even with coding/encryption, triggers human subject protection regulation requirements (also as interpreted by NBAC in this context).
 - NBAC classification system, Common Rule ("CR") interpretation, and recommendations for CR implementation:

Classification	Related Terms	CR Applicability	Informed Consent Requirement
Unidentified	Anonymous	Not human subjects research.	
Unlinked	No identifiers or codes; anonymized.	HS research but, under CR, eligible for exemption from IRB review. Standard for exemption: minimal risk to subject.	If study is of minimal risk under CR (adequately protect confidentiality; no release to third party; plan to reveal findings to sources/their physicians when appropriate), informed consent not needed.
<u>Coded</u>	Linked; <u>identifiable</u> .	No CR exemption unless publicly available. <u>IRB review</u> .	If IRB determines minimal risk, waiver of informed consent requirement.
Identified.			

- ❑ IRB review when samples are coded—i.e., coded becomes synonymous with identifiable because identifiers exist, even if the key is not in the researcher’s control.
- ❑ Much higher level of specificity in informed consent documents:
 - (1) Spell out all options for potential subjects.
 - (2) Once informed consent documents exist, anticipate strict interpretation. The level of acceptable ambiguity/flexibility is likely to be directly regulated, and any ambiguity will be interpreted in favor of the subject.
 - (3) Quid pro quo: NBAC suggests an exemption from the consent requirement for coded samples upon a showing that consent is not practicable, BUT NBAC also calls for much more specificity in the informed consent process overall and more information relayed to the subject.
- ❑ Researcher use of codified samples from previously collected specimens usually is not justified without sufficient consent from the source.

D. Medical privacy:

- ❑ Health Insurance Portability and Accountability Act (“HIPAA”) mandate. Proposed regulations for electronic medical records.
- ❑ Medical records privacy statutes: Realistic possibility that subjects will be given explicit rights to limit access to their biological materials.
- ❑ Concept of group privacy in the context of genetics

E. Some support for expanding CR applicability to cover: (1) all research, rather than just federally-funded research, and (2) delivery of experimental treatments where resulting data may be used as part of a research study.

F. Some support for increasing information flow to subjects going forward and for making re-contact and subsequent consent necessary by making general consents to future use unacceptable.

G. Conflicts of interest:

- ❑ Human subject and system for research integrity predates the present era of extensive academic-industry research alliances.
- ❑ The resulting distrust is fueling demands for individual autonomy, privacy, and control as prerequisite for research participation.
- ❑ The public believes in biomedical research more than ever before, but faith in the biomedical community is on the decline (bench research counterpart to managed care).

IV. ADDITIONAL CONTROVERSY FOR STEM CELL RESEARCH

A. “Privatized” research in areas such as cloning, xenotransplantation, and embryonic stem cell research.

B. Each of these carries extraordinary political controversy into the field of tissue engineering in the face of human subject complications for biomedical research.

V. IMPLICATIONS FOR THOSE ENGAGED IN RESEARCH

A. Given the approx. 8-12 year bench-to-market development time frame for new pharmaceutical products, the prudent approach in light of emerging human subjects and privacy trends is to attempt to adopt the highest recommended standards:

- (1) Avoid identifiers;
- (2) Anticipate a shrinking definition of “minimal risk”
- (3) Maximize use of informed consent and expand the process (comprehensiveness/coverage of all options as well as quantity);
- (4) Maximize use of IRBs;
- (5) As standards are raised, do not assume grand-fathering/exemption of ongoing research.

B. Anticipate dependency on hired intermediaries to collect and unlink desired samples (control over identifiers held entirely by a professional service provider)—i.e., biological material supplier counterparts to contract research organizations (“CROs”) used in clinical research. We already have seen some companies founded—e.g., Collaborative Genomics in Boston area. These intermediaries will introduce considerable costs, but not in comparison to self-collection. Increasingly, bench researchers will need to be part of industry alliances in order to access compliant human biological materials—i.e., the equivalent of DNA libraries, sequencing and informatics capabilities, and other proprietary tools.

C. Established repositories containing materials already in storage, sometimes for decades, will hold declining utility for researchers. Moving forward, these cannot be heavily relied upon by the research community. Some will be used as the means to build “clean” biological material banks.

D. Federal funding:

- ❑ The pace of progress in tissue engineering research is contingent upon resolution or avoidance of emotional controversies such as federal funding of embryonic stem cell research *in addition*

to the multitude of personal autonomy and privacy concerns that generally surround the use of human samples in biomedical research.

- ❑ Congress, unable to even meet its own mandate on medical privacy, is unlikely to make federal funding available in an election year, and a year is a long time in a field like tissue engineering. Even disease-specific exceptions (e.g., diabetes, Parkinson's, and spinal cord injuries) are unlikely.
- ❑ DHHS has adopted a supportive, but cautious approach. DHHS will not fund research using human pluripotent stem cells derived from either human embryos or fetal tissue until final guidelines and an oversight process are in place.

VI. CONCLUDING THOUGHTS

- A. Especially in recent years, the public and politicians have been supportive of biomedical research, especially when breakthrough technologies for presently untreatable, life-debilitating/threatening conditions.
- B. Unfortunately, Congress, the Administration, and the law academics, bioethicists, and industry representatives that have driven much of the law-policy debate surrounding biomedical research over the past decade simply have not accomplished a policy counterpart to what the biomedical research community has accomplished in the laboratory:
 - ❑ Systemic issues such as medical privacy and human subject protection regulation are not conducive to timely solutions by the actors we have been relying upon.
 - (1) Despite the HIPAA mandate, Congress and the Administration have been unable to resolve the medical privacy issue, which increasingly is impacting basic research.
 - (2) Similarly, as illustrated by ongoing government efforts to introduce a regulatory framework for predictive genetic testing services (responsive to commercialization of BRCA testing in 1996-1997 and related concerns raised in the 1980s), such systemic issues are not conducive to timely solutions.
 - (3) Although ELSI has been addressing the controversies surrounding genetic information for nearly a decade, we do not appear close to a pragmatic solution. More fundamental issues, such as weaknesses in our human subjects protection framework, have only recently reached to top of the issues agenda.
 - (4) There has been a complete failure by those engaged in the law-policy debate to identify and pragmatically resolve issues such as weaknesses in human subjects protection infrastructure in a proactive manner.
 - ❑ Consequentially, these law-policy issues are now affecting the entire research community and threaten to impede basic research that will significantly improve human health.
- C. The research community must take a more active role in the law-policy debate surrounding biomedical research. Through your accomplishments in the laboratory, you have widened the gap between law and science. To prevent your research from being unduly impeded, you now must take an active role in lessening that gap.

CURRENT ISSUES IN U.S. PATENT LAW

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The Constitution of the United States gives Congress the power to enact laws relating to patents, in Article I, section 8, which reads “Congress shall have power . . . to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries.” A patent for an invention is the grant of a property right to the inventor, issued by the Patent and Trademark Office. Currently the term of a new patent is 20 years from the date on which the application for the patent was filed in the United States or, in special cases, from the date an earlier related application was filed, subject to the payment of maintenance fees. Effective May 29, 2000, the patent term will be extended to compensate for delays in prosecution due to the Patent Office. U.S. patent grants are effective only within the U.S., U.S. territories, and U.S. possessions. The right conferred by the patent grant is, in the language of the statute and of the grant itself, “the right to exclude others from making, using, offering for sale, or selling” the invention in the United States or “importing” the invention into the United States. What is granted is not the right to make, use, offer for sale, sell or import, but the right to exclude others from making, using, offering for sale, selling or importing the invention.

In the language of the statute, any person who “invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent,” subject to the conditions and requirements of the law. The word “process” is defined by law as a process, act or method, and primarily includes industrial or technical processes. The term “machine” used in the statute needs no explanation. The term “manufacture” refers to articles which are made, and includes all manufactured articles. The term “composition of matter” relates to chemical compositions and may include mixtures of ingredients as well as new chemical compounds. These classes of subject matter taken together include practically everything which is made by man and the processes for making the products. The patent law specifies that the subject matter must be “useful.” The term “useful” in this connection refers to the condition that the subject matter has a useful purpose and also includes operativeness, that is, a machine which will not operate to perform the intended purpose would not be called useful, and therefore would not be granted a patent.

Interpretations of the statute by the courts have defined the limits of the field of subject matter which can be patented. Examples of materials that cannot be patented include the laws of nature, physical phenomena and abstract ideas. Naturally occurring materials cannot be patented *unless altered “by the hand of man”*. Thus, an isolated element or cells are patentable; the ore or harvested tissue are not. A patent cannot be obtained upon a mere idea or suggestion. A complete description of the actual machine or other subject matter for which a patent is sought is required.

In order for an invention to be patentable, it must be new, that is, it cannot be patented if: “(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent,” or “(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country more than one year prior to the application for patent in the United States...” If the invention has been described in a printed publication anywhere in the world, or if it has been in public use or on sale in this country before the date that the applicant made his/her invention or more than one year before the date on which an application for patent is filed in this country, a patent cannot be obtained. In this connection, it is immaterial when the invention was made, or whether the printed publication or public use was by the inventor himself/herself or by someone else. If the inventor describes the invention in a printed publication

or uses the invention publicly, or places it on sale, he/she must apply for a patent before one year has gone by, otherwise any right to a patent will be lost.

Even if the subject matter sought to be patented is not exactly shown by the prior art, and involves one or more differences over the most nearly similar thing already known, a patent may still be refused if the differences would be obvious. The subject matter sought to be patented must be sufficiently different from what has been used or described before that it may be said to be nonobvious to a person having ordinary skill in the area of technology related to the invention.

Tissue engineering, as a field, is generally subject to the same rules as are other compositions and methods of use and manufacture thereof. As long as the “thing itself” is new, non-obvious, and subject to written description, it is patentable. The most significant problems we observe in patenting in tissue engineering are with the issue of written description and enablement. The Patent and Trademark Office (PTO) has posted on its web site interim written description and utility guidelines which can be found at <http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf> and <http://www.uspto.gov/web/offices/pac/writtendesc.pdf>. The PTO materials focus on a three-pronged test for determining whether an invention is “useful” within the meaning of the law: Does the invention have a utility that is specific, substantial, and credible? The first of these materials include definitions of the elements that make up this test. A specific utility is one that is particular to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. A substantial utility is one that defines a “real world” use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a “real world” context of use are not substantial utilities. A utility is credible unless the logic underlying the assertion is seriously flawed, or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

For example, for product claims that do not recite any utilities, disclosure or assertion of one specific, substantial and credible utility meets the criteria of 35 U.S.C. § 101. If no credible, specific, and substantial utility is asserted in the specification and none is well established, then the claims would be rejected under 35 U.S.C. § 101. Utilities that constitute curing or preventing a condition are sometimes not credible to one of skill in the art and thus may raise a question under 35 U.S.C. § 101. However, any rejection based on lack of credible utility must be supported by documentary evidence or sound technical reasoning by the examiner. Since most diseases or conditions can be treated, rejections under 35 U.S.C. § 101 for treatment claims rarely should be made. Each case is decided based on the specific facts. For example, since vaccines are regularly prepared to combat various viruses and organisms, vaccines would have a credible utility to one of skill in the art. Thus, vaccines should not raise a question under 35 U.S.C. § 101. Materials to be used for research, or methods of using those materials for research, raise issues of whether the utilities require or constitute carrying out further research to identify or reasonably confirm a “real world” context of use. *See, e.g., Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. 689 (S. Ct. 1966) wherein a research utility was not considered a “substantial utility.”

It is assumed at this point in the analysis that the specification has been reviewed and an appropriate search of the claimed subject matter has been conducted. It is also assumed that the examiner has identified which features of the claimed invention are conventional taking into account the body of existing prior art. The second of the materials on the web site address the issues of enablement and written description. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. If the examiner determines that the application does not comply with the written description requirement, the examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. The applicant then can present evidence in support, demonstrating that one skilled in the art could make and use that which is claimed without undue experimentation. It should also be noted that the test for an adequate written description is separate and distinct from the test under the enablement criteria of 35 U.S.C. § 112, first paragraph. The absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. 112, first paragraph, for lack of adequate written description. However, even in this case, it is possible to submit evidence that these details are known and readily understood by those skilled in the art.

Although legally there is no requirement for “actual reduction to practice” as of the date the application is filed, in practice we are finding that applications are being routinely rejected as “non-enabled” if there is no actual data in the application. We also see rejections based on data obtained *in vitro* on the grounds that it is allegedly not predictive of results obtained *in vivo*. Accordingly, particularly in a field where there is a lot of “constructive reduction to practice” (i.e., where many patent applications describe what could be done, rather than what has actually been done), we recommend including any data possible, or literature support, in the application, in anticipation of these rejections.

In addition to the significant change in patent term, a change we believe is essential in general due to enormous delays in processing which are occurring at the U.S. Patent Office through no fault of the applicants, another major change is the soon-to-be-effective publication of patent applications eighteen months after the first filing to which priority is claimed. On a practical basis, we do not see this as having much impact in the field of tissue engineering since scientific publications frequently follow quickly after most patent filings, and in most cases there are corresponding foreign filings that are already being published eighteen months after filing.

As we continue to move into 2000, my impression is that we are in a mode of “self-correction” of the excesses seen in the early 1990’s, when the Patent Office declared almost every application in biotechnology, including tissue engineering, non-enabled, then relaxed these standards in view of the shortened patent term resulting from implementation of the General Agreement on Trade and Tariff (GATT) on June 8, 1995. We are now seeing an increased stringency in review of applications based on enablement issues while at the same time being provided with an opportunity to recover *some* of the patent term lost due to the delays in prosecution at the Patent Office. I expect that it will take some time before we know to what degree these efforts will be successful in balancing the needs of applicants to obtain meaningful patent protection with the needs of companies not to be unfairly excluded from their ability to compete in the marketplace.

AN INDUSTRY PERSPECTIVE ON REGULATORY OVERSIGHT OF CELL AND TISSUE BASED PRODUCTS

Alison Lawton

INTRODUCTION

Genzyme Corporation is a leader in the development of cellular and tissue based products. Genzyme Tissue Repair currently markets two tissue based products, Carticel[®] (autologous cultured chondrocytes) and Epicel[®] (cultured autologous keratinocytes). In addition, Genzyme General is developing several other cellular based therapies, including additional autologous cell therapies, gene therapy and xenotransplantation products.

We believe as technology evolves, the biotechnology industry will produce many more tissue based products. The availability of these future products and their potential to provide advantages over currently available therapies, rest not only with researchers and industry, but also with the regulatory framework that is currently being established worldwide.

Cellular and tissue based medical products are currently subject to varied regulatory oversight depending on many factors. Those factors include considerations such as whether the product source is autologous or allogeneic, whether it is processed, stored, or used for a homologous function, and whether the cells or tissues have a metabolic or reproductive function. In addition to these factors, the regulatory pathway for cell and tissue products that are subject to clearance by FDA is shaped by the center that has the responsibility for review of the application. This factor plays a part in these products because the new technologies blur the boundaries of the FDA center's jurisdiction.

CURRENT US REGULATORY FRAMEWORK

The U.S. FDA have been proactive in their efforts to ensure that the standards of review for a product are the same, regardless of the center responsible for review of the dossier. In February 1997 FDA published the Proposed Approach to the Regulation of Cellular and Tissue-Based Products (Proposed Approach). The document laid the groundwork for a flexible approach to the regulation of products based on the level of concern they posed to public health.

While FDA has provided thorough review of products brought to its attention, the lack of overall regulatory framework has presented problems. FDA acknowledges that the existing approach to regulating cell and tissue based products is highly fragmented. Cellular therapies have been subjected to review by different centers within FDA (CDRH & CBER) based on historical inter-center agreements and other factors such as the mode of action of the product. The perception is that for some products the only difference between CDRH and CBER review has been based on the matrix in which the cells are delivered to a recipient. Each FDA center also brings their own perspective and expertise to bear in their reviews. This may not be an inappropriate way to provide regulatory oversight; however, as currently administered, it lacks a consistent and effective framework. It has been three years since the publication of the Proposed Approach and regulations have not yet been promulgated. Good Tissue Practices guidelines and the final rule on Establishment Registration and Listing likewise have not been published. This lack of a formal regulatory framework has the potential for creating differences in the marketplace for products where there is no scientific basis, which may inappropriately lead to potential competitive disadvantages for some products.

Product safety and quality

A unique aspect of cell and tissue therapies is that, unlike traditional pharmaceutical products, they can, and often are, produced by non-commercial sources such as hospital laboratories. For instance, many burn centers culture autologous keratinocytes to prepare skin grafts. These groups have not been subject to regulatory oversight by FDA and often do not employ the same level of controls as their commercial counterparts. They are usually unfamiliar with raw material testing, in-process controls, final product testing, validation of test methods, or process validation procedures. In the interest of protecting the public health, it would be reasonable to hold all manufacturers to the same standards to ensure that cell and tissue products are safe for their intended use.

Manufacturers of drug and biologic products that are subject to marketing clearance by FDA are required to demonstrate that the product is safe and has the identity and strength, and meets the quality and purity characteristics that it is represented to possess. Many test methods that are used to address these aspects of a product are not easily adapted to cell and tissue products.

Rather than chemical assays, manufacturers rely on biological assays to predict the functionality of the final product. Also, final product testing that is considered routine in the pharmaceutical industry, such as the sterility test method adopted from the United States Pharmacopoeia and codified in 21 CFR 610.12, is not easily applied to these products. The CFR method requires a 14-day incubation period that extends beyond the shelf life of many cellular based products. Similarly, the mycoplasma assay identified in 21 CFR 610.30 requires 28 days to conduct. Industry is investigating alternative test methods that will permit rapid detection of contaminating organisms. The goal is to develop test methods that are more suitable to these products. FDA has also recognized that cellular products are unique and on April 20, 1998 exempted them from the General Safety Test that is required for most other biological products.

The FDA issued a Guidance for CMC Information and Establishment Description for Somatic Cell Therapy Products in January 1997 during their review of the Carticel BLA and subsequent facility inspections. It is helpful that the FDA used this experience to issue a guidance document that can now be used by manufacturers of cell products. However, it would also be useful if further guidance documents could be developed in advance of the next generation product so that the hurdles and the learning experience for the first company is not so high as to discourage companies from being the pioneering one.

Other types of tests that have been useful for cellular products are molecular markers and cell morphology to establish product identity. Often, these methods are not readily available and, therefore, they need to be developed and validated prior to use.

Some of the newer cell and tissue engineered products have presented unique potential safety issues such as the example of porcine retrovirus in xenografts. In this example FDA, NIH and industry worked closely together to develop appropriate assay methods and a patient surveillance algorithm that could be employed for all porcine derived xenotransplant products. This is an approach that we encourage for future scientific issues relating to a particular class of cell or tissue engineered products.

Efficacy

The Proposed Approach specifies that clinical efficacy should be demonstrated for cell and tissue products that are more than minimally manipulated, used for a non-homologous function, combined with non-cell/non-tissue components, or used for metabolic purposes. The phrase more than minimally manipulated has been interpreted broadly by FDA so that virtually any processing of cells includes the product in this category. Even a simple expansion of the cell population is considered more-than-minimal manipulation. Therefore, most products would likely require evidence of clinical efficacy. Of course, investigations on products under the jurisdiction of CBER/CDER would be required to be conducted under an IND, while those under the jurisdiction of CDRH would be conducted under an IDE.

There are differences between the centers in their requirements to demonstrate product efficacy. At least one, randomized, placebo-controlled study is expected by CDER and CBER, while CDRH has traditionally

needed to be somewhat more flexible and routinely accepts other study designs. For cell and tissue products, these differences can greatly influence the time and resources necessary to gain market clearance. Efficacy requirements should be standardized for similar products regardless of which center has jurisdiction for the review.

Preclinical animal models can also be very challenging for these products. Many animals have sufficiently different anatomic and physiologic characteristics from humans that make extrapolation to the human condition difficult.

CURRENT EUROPEAN UNION REGULATORY FRAMEWORK

There are currently no pan-European regulations for control of quality, safety and efficacy of human tissue based products—whether they be autologous or allogenic in nature. Discussions to achieve that end have floundered on topics such as terminology and ethics, which are clouded by politics and religious beliefs in individual European Member States.

There are a number of member state initiatives, however, which are worth mentioning.

Sweden has become the ONLY member state to make a firm classification of the product as a pharmaceutical, according to the regulations 65/65/EEC et al. This determination has led to numerous discussions with the regulatory authority as to applicability of associated guidelines for pharmaceuticals.

At the other end of the spectrum, other member states such as the UK, Ireland and Denmark, have indicated that tissue based products are outside the scope of either pharmaceutical and medical device legislation, and hence ‘un-regulatable’. In these instances, companies can commercialise product at will, with no approvals necessary apart from import licenses, prior to supply to the customer.

In between these two extremes, member states employ a myriad of national regulations, with no apparent base for harmonisation. Spain request that product is “brokered” by third party Tissue Services Foundations, who effectively act as Quality Control for import of products. The TSF’s do not physically test material, but are informed of every single implantation or application of product, and are furnished with “Certificates of Conformity” for these batches. In Germany, tissue products are classified as “unfinished drugs”, and therefore not subject to submissions to the central regulatory authority, BfArM. Instead, a company must “apply the spirit” of the German drug law (including Good Manufacturing Products and import permissions), whilst individual Länder within Germany exert local restrictions which can be as disparate as the overall European situation. Further individual regulations are in development within France and Italy.

These are only a few examples of how differing regulations has made the pan-European regulation of human tissue products a difficult task. The lack of pan-European regulation is making the commercialization of tissue products very difficult, as no centralized marketing strategy can be developed. This sales side of tissue based products is made additionally complicated by the emergence in recent months of reimbursement groups requesting evidence of cost-effectiveness. These groups are reviewing a plethora of products ranging from pharmaceuticals to drugs to ‘services’, and making recommendations to health authorities as to whether they should be part of overall hospital budgeting. This represents in some instances an opportunity for a company, acting as a ‘pseudo-regulatory authority’, but in others it represents a hurdle in addition to the approval and application of product licenses. At present, these initiatives are country specific, but could well become the regulations in future years.

As discussed the centralization of European regulation covering human tissue products is some way from completion. More recently, the CPMP has issued a ‘Points to Consider’ document, which has suggested that ALL member states should regulate human tissue products as a pharmaceutical. Although fine in principle, this statement is contrary to efforts made historically by the medical device regulators, who have been working on a parallel track.

GLOBAL (HARMONIZED) REGULATIONS

It is clear from the US experience that a transparent and consistent approach to the regulatory oversight sets the stage for development and helps create the environment where research thrives. Recently, Japan has been developing and implementing regulatory framework for cell therapies and has encouraged research in this field.

We would welcome an ICH initiative to harmonize the approach to regulation of tissue and cellular based therapies worldwide. ICH5 conference in the fall of 2000 would be the appropriate forum to ratify such a proposed topic. Harmonization in this field is particular important where potential safety issues such as the transmission of infectious agents have no national or international borders when the recipients of these products either travel to or come into contact with travelers from around the world. In addition, in today's environment companies need to operate on a global basis. With no consistent approach to the regulation of these products across the world this is a barrier to the development and commercialization of such products and this ultimately means that patients will miss out on these potential new therapies.

Harmonized regulations for tissue engineered products would also provide the basis for future regulations of the next generation cell and tissue products such as xenotransplants and stem cell therapies.

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1. Proposed Approach to Regulation of Cellular and Tissue-Based Products. FDA, February 28, 1997.
2. Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated ex-vivo and intended for structural repair or reconstruction (MAS cell guidance). FDA, May 1996.
3. Guidance for CMC Information and Establishment Description for Autologous Somatic Cell Therapy Products (January 1997)
4. CPMP Points to Consider on Human Somatic Cell Therapy, draft Dec. 1999

COMMERCIALIZATION OF A TISSUE ENGINEERED PRODUCT

Challenges and the Role of Government

Patrick Bilbo
Director, Commercial Development

 **Organogenesis Inc.**

Primary Challenges of Commercialization of a Tissue Engineered Product

- Product Development
- Manufacturing & Quality Assurance
- Demonstration of Safety and Efficacy
- Regulatory Approval
- Reimbursement

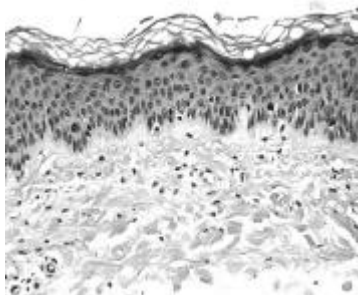
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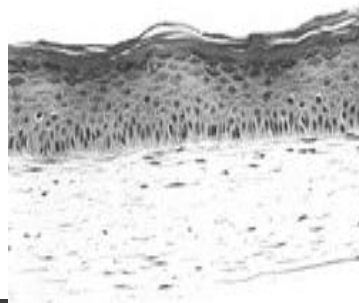
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*Living skin
replacement*

i Organogenesis Inc.

**Living skin cells,
organized**



Human Skin



Apligraf

i Organogenesis Inc.



Challenges of Product Development

- Determining appropriate clinical indication for use of technology
- Development of packaged product from a research project, with no established development path
- Development of internal expertise beyond research
- Predicting function of living product more difficult in vitro, and appropriate animal models are lacking
- Determining product attributes relevant to in vivo function
- Design freeze prior to IDE application

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Role of Government in Product Development

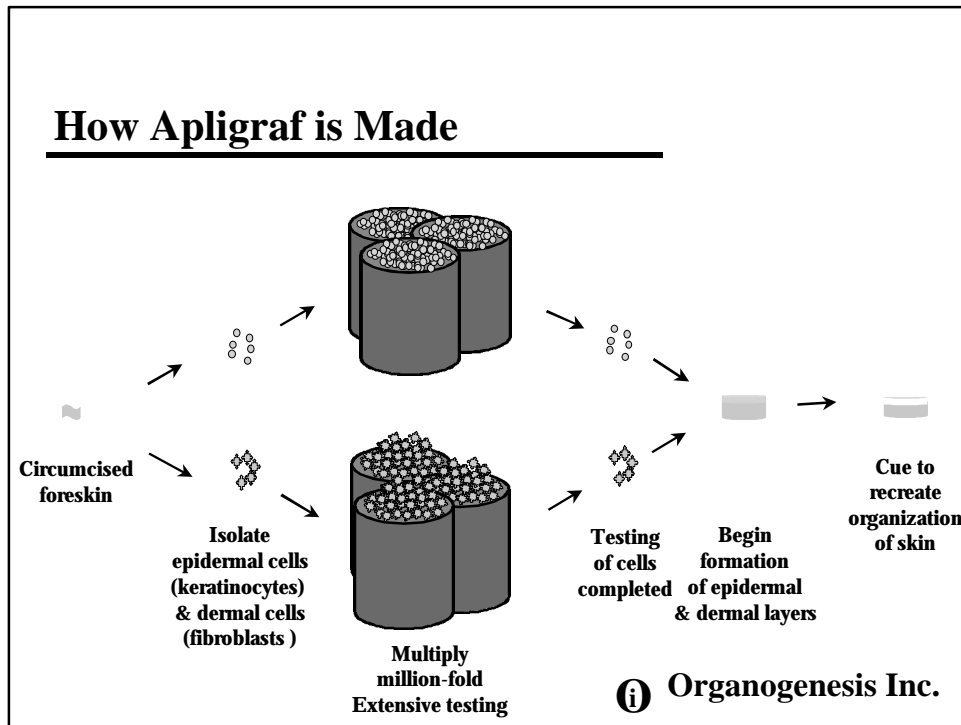
- Early in development there was little or no guidance from FDA
- Guidance document for interactive wound products developed in mid-90's, focus on requirements to start clinical trials
- Design Controls implemented in late 90's
- Design Controls oriented to traditional medical devices
- Tripartite/ISO 10993 Biocompatibility testing requirements
- ASTM Tissue Engineered Medical Products standards in development

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Challenges of Manufacturing and QA

- Reproducibility of living product
- Aseptic manufacturing - no terminal sterilization
- No inventory - little margin for error
- Short shelf-life - logistics and customer issues
- Must be able to select and measure appropriate product attributes for QC testing that are critical to product performance
- Microbiological testing requirements for components and final product - costs, time and complexity

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Apligraf Safety Testing

- 42 tests for adventitious agents and adverse cell changes
- Medical history and blood screening of the mother of tissue donor
- Microbiologic testing of cell banks and purchased biologic source components
- Tumorigenicity testing of cell lines
- FDA compliant process validation and quality control
- In-process and final QC testing for sterility and function

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Role of Government in Manufacturing & QA

- Good Manufacturing Practices
- Quality System Regulations implemented late '90s - expanded requirements including management review
- Guidance documents on characterization & testing of cell lines
- Pre- and Post-approval inspections to ensure compliance
- Harmonization with foreign agencies
- State regulation of tissue products

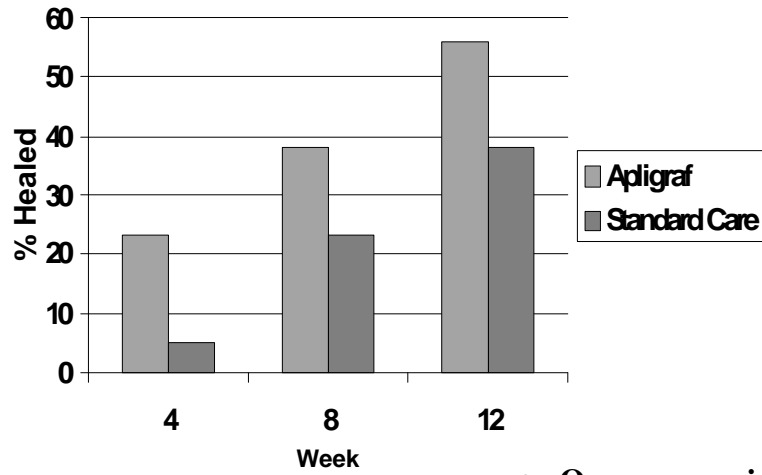
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Challenges of Demonstrating Clinical Efficacy & Safety

- Selection of an appropriate condition to be treated
- Development of clinical protocols that will allow approval
- No precedents early on in development
- Agreement on clinical endpoints for determination of safety and efficacy
- Minimization of bias
- Patient enrollment and follow-up

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Efficacy of Apligraf in Diabetic Ulcers

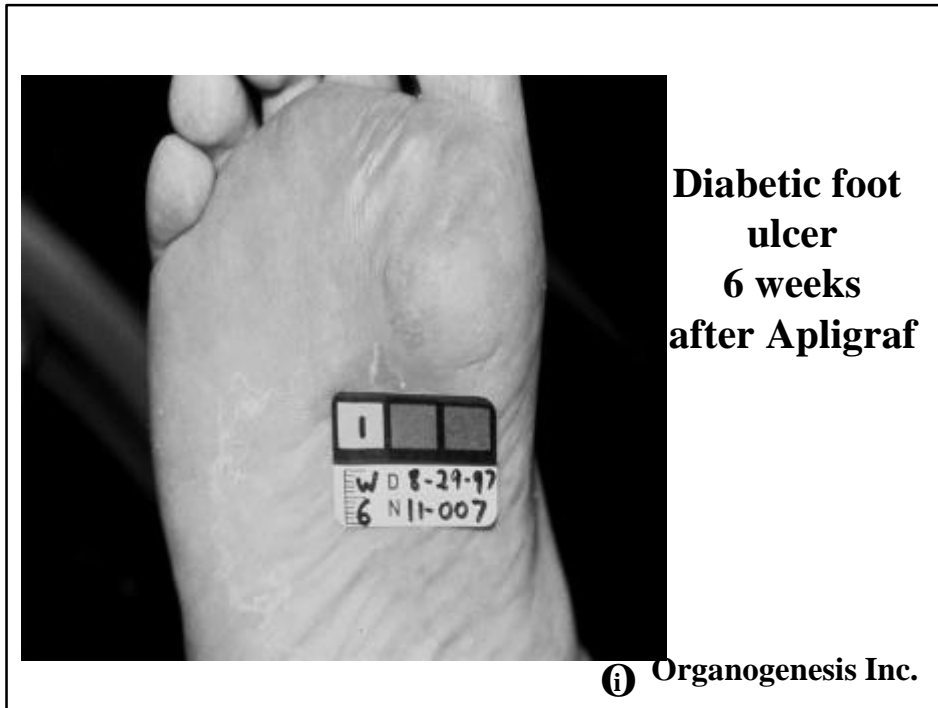


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Diabetic foot ulcer before Apligraf



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Role of Government in Clinical Research

- Temple report in early 90's
- Subsequent increased rigor required for device trials
- Good Clinical Practices (GCPs) - regulatory & industry standards
- Guidance document developed for interactive wound products - very general
- Statistical Guidance Document for Clinical Trials
- FDAMA creation of pre-IDE Determination and Agreement meetings for clinical study requirements

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Challenges of Regulatory Approval

- Determining product regulatory status - regulation of tissue engineered products somewhat arbitrary
- Biologic device - Co-review by two FDA divisions
- No specific guidance early in process - blazed a new trail
- Relationship with and confidence of FDA built over time
- Length of time of PMA review
- Potential for changes in FDA requirements and philosophy over course of development

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Apligraf Regulatory Timeline

- 1987 - IDE application submitted
- 1992 - Pivotal clinical trial started for first indication
- 1995 - Pivotal clinical trial completed for first indication
- 1995 - PMA application submitted
- 1996 - Pivotal clinical trial started for second indication
- 1998 - Final product approval

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Role of Government in Product Approval

- Development of tissue engineering expertise at FDA
- Reengineering of CDRH - increased efficiency
- Customer and performance oriented focus
- More informal communication
- FDAMA changes -
 - Opportunity for review meetings
 - Least burdensome path to approval
 - Alternative and faster review tracks (e.g., real-time review)
- Tissue Engineering division or branch at FDA?

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Challenges of Product Reimbursement

- Coverage and reimbursement as important as FDA approval
- Major impact on physician adoption of novel products
- Formal process cannot begin until FDA approval
- Different requirements for FDA and HCFA review
- Educating HCFA on technology and of relevance/completeness of clinical and cost-effectiveness data
- National coverage decision a difficult, lengthy and not clearly defined process

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Apligraf Reimbursement

- National coverage decision on procedure, not yet on product
- Coverage decisions without MCAC review
- Reimbursement through utilization at regional level - though inconsistent between regions
- Positive tide in coverage from private insurers and regional Medicare
- Two years of cost-effectiveness data generated for venous ulcers
- Diabetic ulcers: more serious consequences, higher costs, younger patients, influential advocacy groups

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Role of Government in Reimbursement

- Medicare coverage advisory committee - all or nothing decision
- Reimbursement of investigational devices
- New procedures for obtaining national coverage decisions proposed in 1999
- Do not establish coverage review and decision criteria
- Establishes some time frames for coverage decisions
 - Coverage decision or referral to MCAC within 90 days
 - MCAS and external assessments can take up to 1 year
 - No commitment to overall time limit

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