

434



Advanced Tissues Sciences, Inc.

**Presentation at FDA Public Hearing:
Combination Products Containing Live Cellular Components**

June 24, 2002

I. Introduction

Good morning. My name is Ron Warren, and I am Executive Director of Regulatory Affairs at Advanced Tissue Sciences, a La Jolla, California based company. At ATS, we employ some 200 people committed to redefining, developing, and marketing tissue repair and transplantation products. On behalf of ATS, and Smith & Nephew, our marketing partner, we are here to explain why our Company has strong opposition to any jurisdictional transfer of our tissue engineered wound products, which historically have been reviewed and regulated by the Center for Devices.

For the last decade, our Company has invested many millions of dollars into premarket development and commercialization of tissue engineered products as medical devices.

- Our first generation of efforts has been devoted to wound healing applications and, from these long and hard efforts, ATS now has approval to market Dermagraft[®], a dermal substitute for the treatment of diabetic foot ulcers, and TransCyte[®], a human-based temporary skin substitute for the treatment of burns.
- ATS also has progressed into clinical investigations of Dermagraft in periodontal wounds requiring root coverage; venous ulcer wounds; and pressure ulcer wounds -- and, most recently, we have sought and obtained a Humanitarian Use Device designation for use of Dermagraft in treating epidermolysis bullosa, a rare genetic disease that results in the development of recurrent wounds.
- As a final aspect of our first generation wound healing platform, we are also developing tissue-based products for the repair of damage to articular cartilage.

So, as you can appreciate from this extensive tissue engineered wound repair platform, the issues before this hearing today are of critical interest to my Company.

In developing our platform of wound healing products over the years, we have pursued product development strategies based on device requirements; we have spent significant resources on the creation and implementation of quality systems based on device regulations; we have implemented device premarket and postmarket compliance plans; we have put in place a device-oriented marketing apparatus; we have recruited and hired personnel with device regulatory expertise; and we have trained personnel in device requirements. In short, all of our wound healing tissue engineering efforts have been

undertaken as a device company, and it is the device paradigm around which we have built our expectations for the last decade.

We will be providing two perspectives today on why transfer of our devices to CBER is neither justified nor warranted. Dr. Gary Gentzkow, our Executive Director of Worldwide Medical Affairs, will first provide a premarket review and public health perspective on CDRH's historical authority over these products. I will then close out the discussion by offering regulatory, policy and equitable reasons, for why ATS considers it critical that its existing device status, obligations -- and rights -- be preserved.

As you will hear from us this morning, without assurances that device status will be preserved, we believe there is a risk -- not only for this company, but for the entire industry -- that much of this important technology will simply be left on the research bench, and will not be developed to the point of patient access.

I will now ask Dr. Gentzkow to discuss these concerns in the context of the first series of questions identified by the Federal Register.

II. Premarket Data Issues

What are the public health concerns related to these combination products as a whole and with respect to their individual components? What information should the agency require in the premarket submission to demonstrate the safety and efficacy of combination products that contain live cells used in combination with a device matrix for wound healing (e.g., wound repair, or skin regeneration, replacement or reconstruction)? What regulatory requirements are necessary to ensure that adequate manufacturing controls are in place for both the device and live cell components? What other issues are important (e.g., clinical trial design, informed consent, infectious disease concerns)?

Thank you, Ron and -- to the Panel and hearing attendees -- I appreciate the opportunity to convey ATS' comments and concerns on these important issues.

The Agency's "Question 1" inquires about public health concerns, premarket submission requirements, and manufacture/control and related issues that should be addressed with respect to this category of products. Before addressing the specific questions, there are several general themes that we ask the Agency to consider.

A. Public Health Considerations

First, to the public health message. The Federal Register inquires about the "public health concerns related to these combination products as a whole and with respect to their components." This is the first in a long series of questions and, thus, has been given some prominence. We are concerned that leading off with this question might leave the erroneous impression that there actually are public health problems with this category of products. If that was the intended impression, ATS respectfully disagrees.

As with all devices, there are safety issues which must be addressed in the premarket review process, and those safety issues must be balanced against benefits. However, for purposes of today's hearing, and the public health questions you have raised, I offer four observations on the general safety profile of these products:

1. First, all safety-related issues with ATS' products have been adequately addressed through the device premarket review and labeling processes. Dermagraft and TransCyte -- the two ATS products approved so far -- were first put into clinical studies in 1991. Yes, at that time, when such products represented an entirely new technology, theoretical concerns about safety were raised. Eleven years later, the Agency has had more than a decade to consider these products and any theoretical safety concerns have long since been addressed. Dermagraft alone, at its various stages of premarket development, involved 2,721 implants in patients. During those clinical studies, adverse experiences and laboratory abnormalities were those expected in patients with the diseases treated, and occurred at rates no higher than with control. Other questions, such as humoral and cellular immunity were addressed by specialized testing. Tests for sterility were designed and carried out according to existing Agency "Points to Consider" documents, and were updated as new testing became available.
2. Since approval, several thousand patients have been implanted with either Dermagraft or TransCyte. A total of 43,000 pieces of tissue have been distributed worldwide. During this time, the products have demonstrated a remarkable safety record. As with the premarket clinical experience, there have been no safety problems that could be regarded as caused by either product.
3. As a third observation, ATS is unaware of any public health concern related to other tissue engineering wound products that have been reviewed and approved by CDRH.
4. And, fourth, not only do these products represent no public health concern, to the contrary, they have been recognized as having extremely important public health benefits by the medical community, by the patients who benefit from them, and by the Agency itself.

The World Journal of Surgery reported in 2001 that, with aging populations and a chronic shortage of tissue for transplantation, the need for tissue engineering is "enormous and the potential benefits immeasurable."^{1/}

^{1/} S. Lalan, I. Pomerantseva, J.P. Vacanti, 2001. Tissue Engineering and Its Potential Impact On Surgery. World Journal of Surgery 25:1458-1466.

In last year's annual report, CDRH cited Dermagraft as one of thirteen designated "advances in patient care" and, elsewhere in one of the Agency's publications, Dermagraft is cited as "decreas[ing] the risk of infection, . . . and speed[ing] the healing process of . . . chronic wounds."^{2/}

Dermagraft also represents an important tool in the battle to control hospitalization, health care costs, and to improve the quality of life and care of diabetic patients. Foot ulceration is the most common complication of diabetes that requires hospitalization and, in addition to causing significant morbidity, it can lead to amputations and other forms of disability. In the U.S. alone, management of this problem is estimated to cost \$150 million a year.^{3/}

TransCyte has an equally compelling public health benefit. Just as one example, I know the Agency has given priority this year to the development and commercialization of products aimed at fighting terrorism. In the days following 9/11, FEMA assisted ATS to provide an urgent special shipment of TransCyte to care for the burn victims of the Pentagon attack. On a more "routine" basis, TransCyte is being used daily to help children and adults heal after the tragedy of burn injury.

With products that provide such important, often life-saving benefits, the pathway to market should not be impaired.

B. Mechanisms to Clarify Premarket Review Requirements

As a second introductory theme, the Federal Register notes that "successful development and marketing of these products may be slowed by uncertainty about jurisdiction, particularly as it relates to the nature and scope of regulatory requirements that must be met in order to bring these products to market."^{4/}

We applaud the Agency's desire to avoid premarket regulatory problems that might slow the path to market. However, if there are any uncertainties as to premarket requirements, the law already provides a mechanism to address and resolve these issues. Congress has instructed FDA to issue guidance pursuant to good guidance practices when there is a perceived need to provide a premarket data framework for companies and Agency reviewers to follow.

^{2/} FDA Consumer, Helping Wounds Heal, May-June 2002 (table of contents) available at: <http://www.fda.gov/fdac/302_toc.html>.

^{3/} K.G. Harding *et al.*, 2002, Healing Chronic Wounds. *British Medical Journal* 324:160-163.

^{4/} 67 *Fed. Reg.* 34722 (May 15, 2002) (emphasis added).

We know that establishment of premarket review requirements through Good Guidance Practices can and does work. Over the last several years, all three FDA Centers have come together and prepared a draft guidance document on chronic cutaneous ulcer and burn wounds, which, by the terms of the draft guidance, each Center will implement. While companies or FDA might object to certain elements of the premarket review criteria set forth in this document, the draft guidance now provides us all with a general framework to follow. Thus, it is unclear why Question 1 asks about information that the Agency should require in premarket submissions. It seems that FDA multicenter guidance on that question already exists.

If, from today's hearing, there is an identified need to modify or refine certain premarket requirements, we request that the Agency tailor its solutions to these limited needs, through the guidance process. Shifting jurisdiction will not solve the narrow data uncertainty issue, and instead will create many new uncertainties with respect to regulatory burdens and related costs, which in turn will slow the path to market -- something the Agency expressly is seeking to avoid.

C. Safety/Efficacy Data Issues

1. Premarket Review Requirements (Dermagraft® as an Example)

On the more specific data questions raised in the Federal Register about premarket submission data requirements to demonstrate the safety and efficacy of this category of products, we believe Dermagraft® for chronic diabetic foot ulcers provides a good example of how CDRH already has applied data requirements, which are reasonable, have been tested by time, and which we support. As I mentioned earlier, a draft consensus Guidance was developed by all three Centers for chronic cutaneous ulcers and burn wounds, and, while it was a work in progress during the pendency of the Dermagraft® PMA review, CDRH essentially followed this draft Guidance with respect to preclinical, toxicological, and clinical data requirements (see attachment). The Center for Devices' review, thus, was thorough and rigorous, but also properly tailored to the safety and efficacy issues presented by this category of product.

There is no evidence that CDRH is any less qualified to review the safety and effectiveness of these particular products than any other Center within the FDA. In fact, since these tissues are primarily device-like in character (i.e., structural), and because they act locally rather than systemically, the review perspectives utilized by CDRH are more appropriate. I would note as well that the Center for Devices has a long history and experience in the wound healing arena. Over the years, there have been literally hundreds of wound healing products under device jurisdiction, at various levels of active regulation.

For our cartilage orthopedic wound repair and dental wound repair products, we also are pleased that CDRH has clinician reviewers specific to these therapeutic areas -- clinician expertise that CBER historically has not employed. We have found that often it is the clinical knowledge of individual reviewers, more than regulations per se, that most impacts the regulatory review process.

Our experience says that premarket requirements, submissions, and expertise have evolved very nicely within CDRH. Yes, there were problems in early years as the knowledge base had to be acquired, but CDRH has developed expertise over more than a decade. We, therefore, urge the Agency not to fix that which is not broken, or worse, not to break that which is working fine.

2. Issues That Are Inappropriate for Premarket Review of These Products

Just as it is instructive to consider those issues that should be reviewed at the premarket stage, it is also useful to discuss what premarket issues are inappropriate or excessive for products of this type. Drugs and biologics, because they usually act systemically, often require a different kind of surveillance for safety, requiring much larger populations to be studied premarket in order to uncover potential adverse consequences that can arise in any body, organ, or system. A good example is CBER's review of OMJ Pharmaceuticals' BLA for Regranex[®], a recombinant protein product that -- like Dermagraft[®] -- is intended for diabetic foot ulcers. Because of the nature of recombinant protein products and their systemic issues, according to the public summaries of approval, there were 81 pharmacology tests; a battery of pharmacokinetic tests that included studies in primates; and a clinical pivotal testing program that included 925 subjects for efficacy evaluation, and 1,776 subjects for safety review. I think it is fair to say that, had Dermagraft[®] been forced to follow either the Regranex[®] preclinical or pivotal clinical pathway, a pathway ill-designed for a human tissue product, it still would be at the premarket stage -- or indeed may not have even been pursued, given the size and resource limitations of our Company.

Also, biologics' concepts, such as identity, purity, potency, and the like, simply are not applicable to tissues. Nor should one expect that they would be, since the biologics statutory framework was built around blood and blood products, viruses, therapeutic serum, toxins, antitoxins, and allergenic products -- all of which are quite different by their very nature.

We note that our support for CDRH is not intended in any way to criticize CBER, and its extremely able scientists. Nor are our comments intended to suggest that the CDRH pathway to market is without regulatory hurdles or difficulties. ATS's products were in development for a decade and the premarket data requirements were extensive.

Rather, the point we are seeking to emphasize is that CDRH's law and premarket approach are fundamentally more amenable to flexible premarket review and to fostering innovation, than are the law and premarket approaches followed by CBER. There are a number of examples in this regard:

- As one example, the evidentiary standard for approval of devices -- that of "reasonable assurance" -- is a different and more flexible standard than the BLA standard of "safety, purity, and potency." And so, CDRH -- by law -- is better able to tailor premarket review processes to those concerns that truly need to be addressed. CDRH's evidentiary standard for approval thus better accommodates

tissue engineered products, which are local, structural, and therefore, more device-like in nature.

- The many device premarket initiatives, embodied in both device law and policies -- and all aimed at speeding pathways to market -- are yet another series of premarket advantages that CDRH provides over CBER. Our clinical programs and PMA activities have been assisted by at least five device initiatives -- least burdensome review, the early collaboration mechanism, PMA modular review, 100-day meetings, and real-time labeling review -- all intended to facilitate the pathway to market. These mechanisms are either not available, or as broadly available, under CBER authorities.
- CDRH's significant issuance of good guidances -- needed because of the wide diversity of technology it addresses -- is another example of CDRH culture accommodating technology and clarifying the pathway to market.
- And, finally, in another important clinical context, the treatment of a rare and devastating genetic disorder, Epidermolysis Bullosa or EB, ATS has been granted a Humanitarian Use Device designation, which will greatly speed the pathway to patient benefit. As with the other clinical program and PMA review mechanisms previously mentioned, this authority is unique to device law.

For all of these reasons, we believe CDRH continues to be the appropriate Center of premarket authority. Combination products containing live cellular components, have been regulated by CDRH for more than a decade now, without any safety or efficacy concerns, and we feel strongly that there are no public health or other premarket or manufacturing concerns that warrant a change in jurisdiction. There is simply no "problem," which the Agency must fix.

Moreover, as you will hear in a moment from Ron Warren, our Executive Director for Regulatory Affairs, we anticipate a number of significant new regulatory, practical and commercial problems if FDA were to attempt a jurisdictional shift. Thank you for your time.

FDA's Questions 2 and 3

Given that primary mode of action determines jurisdiction for combination products, what information should the agency consider in identifying the level of contribution of each component to the therapeutic effect of the product? What information should the agency consider in determining which action is primary?

In instances where both components of a combination product containing live cells appear to make a significant contribution to the therapeutic effect of the product and it is not possible to determine which mode of action is primary, what other factors should the agency consider in the assignment of primary jurisdiction? Is there a clear hierarchy among these additional factors that should be observed in order to ensure an adequate review? Should these same factors be used to determine the appropriate type of premarket application?

III. Regulatory/Policy Considerations

In responding to the next series of questions identified in the Federal Register, my comments will focus on three topics in particular embodied in those questions: (1) the concept of primary mode of action; (2) other factors and considerations that should determine jurisdiction; and (3) more generally, ATS' views on the consequences and concerns of shifting jurisdiction from Devices to Biologics for this category of products.

A. Primary Mode of Action

1. Overview

Beginning first with the Agency's questions concerning the "primary mode of action" standard for combination products, we strongly support the Agency's historical interpretation of this concept, and believe that any informal use of a new interpretation -- such as "level of contribution of each component" -- is inappropriate from both a regulatory and science perspective.

From a regulatory perspective, FDA's historical approach has been to assess the primary mode of action based on the intended purpose of the combined product, and not the contributions of each component. Although the regulations do not define "primary mode of action," except to direct the analysis to the composite product and not its components, we now have ten years of Agency experience with this term. From this decade of interpretation, two important understandings have emerged.

First, we know by guidance, that the term "mode of action" has been interpreted differently than -- more loosely than -- the term "mechanism of action." Specifically, through both intercenter agreements and CBER cellular and tissue pronouncements, industry has been instructed to look to the primary intended function of the combined product. For example, in the intercenter agreement for drugs and devices, the Agency has stated that an "implant, including an injectable material, placed in the body for primarily a structural purpose, even though such an implant may be absorbed or metabolized by the body after it has achieved its primary purpose, will be regulated as a device by CDRH."^{5/} In the CBER-CDRH Intercenter Agreement, it is acknowledged that "cultured skin will be regulated by CDRH under the Medical Device Authorities."^{6/} Thus, when products have primarily a "structural," "physical," or repair/replacement/reconstruction" function, they historically have been afforded device status.

We also know that CDRH consistently has employed this functional approach to interpreting "primary mode of action" over the years -- granting jurisdiction to a wide variety of products, as diverse as spinal fusion products, porcine-derived protein matrices

^{5/} FDA, Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (Oct. 1991).

^{6/} FDA, Intercenter Agreement between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health (Oct. 1991).

for periodontal repair, surgical patches comprised of bovine-derived pericardium, and, most recently, demineralized bone. Wound repair products, in other words, are not the only beneficiary of this historical interpretation.

Given the long and consistent reliance by many companies on the Agency's historical interpretation of primary mode of action, any new interpretation -- particularly one that serves to shift jurisdiction -- would represent a substantial departure that would significantly affect this industry. Consequently, as AdvaMed has conveyed, there will be administrative law issues that must be considered before the Agency attempts to assign any new interpretation to this regulation.

There are also scientific and technology reasons why the Agency's proposed new interpretation would not be appropriate for this category of products. First and foremost, the desire of the Agency to parse out the relative contributions of constituent components is at odds with what is known about these types of products. It is recognized in the literature that the exact mechanism of action for this category of products is unknown. The Agency itself has recognized the limitations of current understanding in this area. For example, in the Dermagraft review, when in vitro data was submitted in the PMA to attempt to provide some level of information concerning mechanism of action, we were told that our efforts were only preliminary and inconclusive, and could not be reflected in labeling.

As a second scientific reason for why the Agency's proposal is infeasible, expensive tests to explore the precise contribution of constituent components -- the value of synthetic and extracellular components on the one hand versus cellular components on the other -- would be extremely difficult, if not impossible, for sponsoring companies to undertake. Bear in mind here, that all aspects of the product -- the synthetic, the extracellular, and the cellular constituents -- are not clearly divisible, and all work together to facilitate the same wound healing function. Any tests to parse their relative contributions, in our view, would serve no clear public health purpose, and would impede -- and could very well stop -- innovation, because of their costs.

Consequently, we believe the Agency's historical reasons for granting device jurisdiction for this class of products, are appropriate and should not be changed.

2. Dermagraft's Primary Mode of Action

In the case of Dermagraft, there are two reasons why the product's "primary mode of action" has been, and should continue to be, considered a device.

First, when you view the product as a whole -- which regulation, policy, and historical precedents tell us to do -- the product serves as a frank human dermal replacement for damaged skin in the wound bed. The fibroblasts, which co-exist with the structural mesh and extracellular matrix, are mature, and do not undergo further alteration or organization post-implantation. The product, once implanted, persists for some time in the wound bed. The product, thus, has all the attributes of a human dermal substitute replacement -- and substitutes or frank replacements have been reviewed consistently as devices over the

years.

Secondly, this product is, at its essence, a wound dressing, not unlike the hundreds of wound dressings currently under CDRH jurisdiction. It provides an environment that facilitates wound repair processes. The three dimensional scaffold and extracellular matrix are analogous to a large number of the non-interactive wound dressings currently under 510(k) review, and the mature fibroblasts simply augment the functioning of the essential wound dressing function.

I would note in this respect, that all wound dressings -- interactive or otherwise -- have effects on the body's wound healing process at some level. By way of example, Cook's Oasis non-interactive wound dressing product, which contains collagen and other macromolecules -- but not live cells -- has been described in press releases as providing "a natural scaffold like a cellular matrix with a three dimensional structure and biochemical composition that attracts whole cells and supports tissue remodeling."^{7/} This example highlights the seemingly arbitrary delineation, that the Agency is attempting to make between live cell and other wound products.

Rather than drawing arbitrary distinctions between those wound products that have live cells, and those that do not -- a distinction that we do not believe can be sustained because of the principle that like products must be treated comparably -- we urge the Agency to maintain its historical interpretation.

B. Other Factors Affecting Jurisdiction

The Agency's next series of questions ask what factors should be considered in the assignment of jurisdiction, and what the hierarchy of those factors should be.

1. Legal Considerations

Our legal advisors will tell us that foremost among factors, would be those of law. There are several significant legal impediments to simply announcing a jurisdictional change:

- For one, statutory changes may be needed, if the Agency is seeking to call this category of product a "biological." That statutory definition, as you know, was drafted with some constraints.
- Also, as I mentioned earlier, rulemaking considerations must factor in. We believe, as do others in industry, that there must be notice and comment debate on the record, so that all comments receive formal responses, and administrative processes are protected and independently reviewable.

^{7/} Cook press release dated January 24, 2000.

-- Finally, the regulations at Part 3 instruct the Agency that jurisdictional changes must only be for "public health" or other "compelling reasons" -- a standard the Agency has not met in this case.

2. Premarket Review Considerations

You have already heard from Dr. Gentzkow about the many premarket reasons supporting device status. I can add one further premarket comment to what Dr. Gentzkow had to say -- and that is, that the greater flexibility of the device premarket review structure, is more in keeping with the risk-based philosophy initially envisioned by the Agency for cellular and tissue-derived products. Bear in mind, in this regard, that cadaveric tissue and bone products -- also used for wound healing/structural purposes, also local in nature, and with comparable efficacy issues and arguably greater safety concerns -- undergo no premarket review.

3. Manufacture Considerations

There are also manufacture factors supporting device status. As with the premarket device framework, the device quality systems framework allows greater flexibility than manufacture requirements for biologics. For example, the device quality framework is written so as to be amenable to a wide range of technology. This allows, in our case, for product release to be tailored properly to those biological and safety tests deemed appropriate and relevant for tissue-engineered products.

By contrast, manufacture regulations for biological products are structured for a more narrow range of products. They are written so as to be consistent with the statutory definition of biologics, which explicitly lists the products covered by that definition -- virus, therapeutic serum, blood, blood components, and so forth. The regulations then fairly rigidly apply requirements by addressing each of these biological categories.

The marketing experience for not just ATS products, but others in industry, has demonstrated that quality systems under the device framework have not produced postmarket safety concerns. Because the flexibility of the device quality systems better accommodates these device-like products, we urge retention of those device manufacture requirements. Further buttressing these device requirements are the full panoply of existing and proposed federal and state tissue processing regulations, which address tissue-specific quality issues, not squarely addressed by device QSR requirements.

We thus already have a comprehensive and complicated series of manufacture requirements, and any proposed imposition of biologics regulations to this existing matrix would be costly, confusing, and unnecessary.

4. Equitable Considerations

There are also compelling equitable reasons that support continuing device jurisdiction. As stated at the outset of this presentation, ATS' long-standing regulation by CDRH, has led to a well-entrenched device orientation. All of our systems, our people, our development strategies, our compliance programs, and our marketing apparatus -- in

short, our entire business -- has been as a device company. To now attempt to call us a biological-regulated company, would require us to invest substantial funds in the development and implementation of new regulatory systems, and new personnel. It also will cause us to reconsider, and substantially revise and replace, our short and long-term product development plans.

We ask, as a matter of equity, then, that the Agency consider very carefully this potential substantial harm, not only to ATS, but to other companies similarly situated. As part of this process, we also would ask that the Agency consider very carefully whether any perceived administrative benefits from this proposed jurisdictional change, could ever outweigh such significant costs to companies such as ATS.

C. Other Jurisdictional Observations

In conclusion, we offer several comments on possible alternative jurisdictional decisions that the Agency might be considering. In particular, there are several options that we have heard proposed, in our informal discussions with Agency personnel.

One theoretical option that we have heard, is for CBER to have responsibility for regulating these products, but under device authorities. If these products have, as their primary mode of action, that of a device -- as regulations, guidance, and historical practices have supported -- the responsibility for review should be retained within CDRH. In fact, the statute and regulations do not permit leeway on this matter. The statute instructs that, if the Secretary determines that the primary mode of action is that of a device, then CDRH shall be charged with its jurisdiction.^{8/}

Another theoretical option that I have heard in formal discussions with the Agency, is that of "grandfathering" those products that have already undergone approval, or some stage of review, within CDRH.

While we appreciate that FDA would be acknowledging certain of our equitable concerns by this approach, it is important to bear in mind that some of those products that have been, or are being, reviewed by CDRH, represent platform technology that will have a number of applications in the future.

The Dermagraft platform is a good example of this. Given the Dermagraft approval, and the fact that a series of additional applications of this same technology are also under various stages of review by CDRH, CDRH is familiar with the safety of this platform, and with its manufacture/control, performance characteristics, and prior human experience. We do not believe, if site of implant or indication should change, that this platform technology should be split into jurisdictional parts.

The Agency has stated that one of the primary purposes of its jurisdictional regulations is "to enhance the efficiency of Agency management and operations." In this case, the most

^{8/} Section 503(g) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 353(g).

efficient use of Agency resources would be to retain all aspects of the same platform technology within a single Center. To do otherwise would require re-evaluation of the fundamentals of this platform, creating redundancies, rather than efficiencies.

Moreover, two sets of requirements for the same technology would require substantial additional investment of resources, time, and personnel, and would present major logistical challenges for us. For all of these reasons, we request consistency of regulation.

IV. Conclusion

As a closing thought, I would like to reflect on this issue, not only as a Company representative, but as a regulatory professional – a position I view as a bridge between product innovators and patients in critical need. The process presents complex regulatory requirements and lengthy timelines, but I am encouraged by the clinical results we are seeing. We continue to hear how our products have made a difference -- to help treat burned child who had pulled a pot of boiling water onto himself, or a patient with diabetes whose open sore on the bottom of her foot has healed after years of treatment with more traditional methods. From this perspective, we at ATS and Smith & Nephew urge FDA to continue to support that which CDRH historically has sought to do -- that is, to take a least burdensome approach to foster safe and effective tissue engineered products, which hold the promise of redefining the way we treat injury and disease.

With those final comments, I will conclude by thanking you all for your time and answering any questions you might have.

**DERMAGRAFT® PRECLINICAL/
TOXICOLOGICAL/CLINICAL DATA**

1. Examination of pharmacological responses and potential toxicities in animal models for wounds:
 - a. Because it is acknowledged by the Guidance that “there are no ideal animal models for chronic wounds,”^{1/} Dermagraft® was studied in animal models in multiple species (i.e., mouse, rat, mini-pig);
 - b. Performance, safety and biocompatibility were examined in full thickness wounds in mini-pigs, which “are often useful models since their cutaneous architecture is most similar to that of human skin;”^{2/}
 - c. Graft performance was examined in full thickness wounds in rats;
 - d. Healing and re-epithelialization were examined in athymic mice; and
 - e. Angiogenesis was evaluated in the aortic ring assay and chick chorioallantoic membrane, consistent with the recommendation of the draft Guidance.

2. Toxicity studies were also undertaken, consistent with recommendations in the draft Guidance:
 - a. The PMA contained in vitro and in vivo assays for biocompatibility, systemic toxicity and cytotoxicity;
 - b. Cutaneous irritation and hypersensitivity were examined;
 - c. Carcinogenicity testing was performed, including Ames mutagenicity, mouse lymphoma mutagenesis, and tumorigenicity;
 - d. Graft persistence in patients was examined by biopsy; and
 - e. Immunogenic potential was assayed by monitoring antibody response in patients.

3. In addition to two prior studies that were regarded as pilot, a pivotal multi-center, randomized, controlled clinical trial was conducted, consistent with

1/ FDA Draft Guidance: Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment (June 2000), at 6.

2/ Id.

recommendations for wound indication trials in the draft Guidance. In this study, 314 patients were treated with either Dermagraft® plus conventional therapy or conventional therapy alone. The primary endpoint was incidence of complete wound closure, which the Guidance states “is considered the most clinically meaningful of the claims related to improved wound healing.”

4. Beyond this draft Guidance, CDRH also requested additional data and information to further confirm the safety profile of Dermagraft®. For example:
 - a. Concerns with contamination by adventitious agents were addressed by extensive screening of maternal sera, donor cell strain, master cell bank, and working cell bank for HIV-1, HIV-2, HTLV-1, CMV, HBV, and HCV; and
 - b. Characterization of Dermagraft also addressed purity, identity, viability, and sterility of the cellular component of the combination product, as well as karyology, isoenzyme analysis, and DNA profiling.
 - c. Postmarketing study to further confirm immunological safety (i.e., to further confirm that the product elicits no cell mediated response).