

1-2-3: Development and regulation of

“Medical TEXnology”

Steps you'll have to take to bring your new product to the medical market.

By Elaine Duncan

Current medical textile technology is the backbone of the lucrative and highly effective medical device industry. Can you even imagine a surgical procedure that would not involve barrier drapes, gowns, masks, bandages, wound care treatments and filters that scrub the water, the air and even the blood? Without fabrics, fundamental asepsis could not be practiced. Sterilized products might not be possible, and keeping them clean and sterile would be impossible, as medical textiles make up the sterile packaging. Many implantable devices today rely on specialty medical textiles: everything from heart valve sewing rings to hernia mesh.

Medical textiles are leading the continuing innovation in “Medical TEXnology.” New devices are announced on a regular basis, including wearable electronic sensors that not only detect a physiological parameter, but report it to a computer or tracking technology. Using Medical TEXnology, researchers are going beyond “tissue engineering”—known for taking cells from the body and culturing them on a substrate for re-implantation—to engineering the response to the textile right in the body, by altering the

cellular response to the biosynthetic textile. Textile devices already deliver drugs; but consider the time, coming soon, when a medical textile will serve as the temporary host to nano-pharmacology, specifically designed to alter the surrounding tissues to grow new bone or rejuvenate damaged nerve cells.

How can we expedite the development of new medical TEXnology using the least amount of time, money and resources, yet assure that a safe product reaches the user? No medical device is without risk, but we can follow some basic steps that help the developer and the regulator meet on common ground. Regardless of which part of the global medical textiles market you're after and what regulatory schemes may be enforced, three basic steps serve as the foundation for developing a medical device that suits the needs of the user *and* the regulator.

Design Control and Review: baby steps

Two forms of Quality Systems dominate the regulatory approaches worldwide today. The two systems are essentially harmonized, with a few notable exceptions. Both the ISO 13485-2003 and the U.S. Food and Drug Administration's (FDA) Quality System Regulation (21 CFR §820) require the practice known as Design Control and Review, or DCR. Although the specific requirements

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may vary, the principles are the same: Control the development process in a systematic manner, with methodical reviews to assure that the device meets user needs.

Even though the regulations in the United States have been enforced since the mid-1990s, new medical device companies often find this to be an awkward program to adopt. Some believe that the process inhibits creativity. In fact, DCR assures that creative energies will be directed where they are needed. Others believe that it will slow down the development process and that they don't have the time or money needed. But in fact, companies that do not implement DCR more frequently find themselves redesigning their product before it even makes it to the marketplace.

Although the FDA does not require (except for certain circumstances) review of the Design Control and Review documentation prior to acceptance of a 510k application, it is often apparent to FDA reviewers when a company has not "done its homework." Certainly there are some critical documentation steps, but here I will review the first three "baby steps" to Design Control and Review, and then discuss briefly how these tie into successful product submission and regulatory compliance.

Step 1: Inputs

Even if your small medical device manufacturing company has not implemented a formalized standard operating procedure and quality manual which spell out the steps for Design Control and Review, you can start with Input Requirements.

Design Inputs are the physical and performance requirements of a device that are used as the basis for the device design. These inputs come from many sources; it's up to the development team to sort through these input requirements and come up with a product specification. One way to look at "inputs" is through the customer's eyes: If the customer could have what she or he wanted from the product, how would it behave, and what would it do?

These are fundamental questions that can be gathered from literature, interviews, field evaluations and direct observations. One of the most critical inputs is the consideration of human factors and ergonomics. One product

that comes to mind where inputs were ignored was a device meant to be used by a female, but that turned out to be too large for a woman's hands. It fit the male engineer's hands perfectly.

International and national standards are an obvious source of input requirements. In fact, you could say that ignoring the input from such standards assures that the device will have regulatory difficulties, because there may not be any evidence to support compliance with the requirements of the standards adopted by the regulatory agency. These inputs must be part of the user requirements from the beginning of development. The number of standards in any given specialty or application is vast, but you can narrow your focus by starting with those that the FDA indicates on its Web site for your product type. Go to www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm to search for standards that may be applicable and recognized by the FDA.

For certain products, the FDA permits an "Abbreviated 510k" with which the sponsor may certify conformity to the recognized standard and not be required to submit all of the data from testing.

Some regulatory agencies, like the FDA, have sponsored guidance documents specifically for a particular product's submission requirements. Anyone undertaking the development of a new

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medical device must understand the impact of both the specific and general FDA guidance documents as "input requirements" for the device. U.S. FDA Guidance documents can be a bit more difficult to follow than international standards, because terminology and applicability can be buried in regulatory custom and practice; but as a start, go to: www.fda.gov/opacom/morechoices/industry/guidedc.htm.

Another source of input requirements can be the predicate medical devices to which the company must demonstrate substantial equivalence (required for U.S. Class II devices.) Even for a Class III device, where safety and efficacy is required through a Premarket Approval Application (PMA), knowing the state of the art of the competition is critical. A great deal of information on the performance of a product is available on the manufacturer's own Web site, but the FDA has some basic information on most 510k products, and Summary of Safety and Efficacy on the Web for PMA products. These are available by searching on the product name or company name at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmnm.cfm, or www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm for PMA products.

The development team has the responsibility of synthesizing all of the input requirements and dealing with conflicting requirements to create a rational requirements document for the product. Conflicting requirements that often creep into the development equation can be: cost versus features, portability versus battery life, customizing to user needs versus controlling user risks, and functionality versus simplicity, just to name a few. Making sure that the team appreciates the key "unmet

needs" can play an important role in the winnowing process. Sometimes designers want to have certain features, but the unmet need of the user may lie in a totally different direction. And, of course, reimbursement can play a major role in the success of a product in the field. Having features that are "cool" but that no one can afford to buy can sink a new product very quickly.



Step 2: Hazard analysis and risk assessment

The next area that seems to confuse new start-up medical device innovators is the concept of risk analysis. The international standard ISO 14791 takes a total product life-cycle view of risk management. But buried in the detail is the first step: design risk analysis. Stripping away all of the complex tasks that must be done eventually, there's a fundamental task that must be accomplished in the early phases of development: hazard analysis and risk assessment.

The first step in a good design-based risk analysis is the input requirements discussed earlier. Some teams refer to

the finished list as the "performance requirements" and distinguish this document from the final "device specification," which is generally the final document describing the finished device. Performance requirements generally describe what the product is expected to do, but not necessarily how it is accomplished, or the components within the device.

With a good performance list, the task of analyzing hazards can begin. A hazard should be thought of as the failure of a device to meet expected performance requirements. There can be multiple hazards, and it's important to employ a systematic and analytical method to document these

potential hazards. They can often be derived from literature or from the experience of clinical practitioners; sometimes only the designer will appreciate a particular potential hazard, based upon incidents observed from early prototypes.

The best hazard analysis is a process that involves a team of people knowledgeable in the product requirements, which can include potential users, healthcare professionals who are advisers to the company, and any staff functions in the company, such as manufacturing and quality assurance. Sometimes a product developer wants to "phone it in"—but when a hazard analysis is written in the absence of the team, the analysis can be pedantic and ultimately meaningless. Both the potential customer and the medical device developer will suffer from any short-cuts.

Although an important part of the process of risk analysis may be the "scoring" of the potential severity of the hazard, its potential for occurrence and the potential for detection, it truly is the discussion process about the hazard and its impact on the user that has the greatest benefit to the development process. From this group endeavor, the manner in which the potential risk may be mitigated is developed from the knowledge base of the entire team. Skipping the working meetings to pass around the spreadsheet developed by a sole author to have everyone "just sign off" can spell disaster.

The most important outcome of the risk analysis process is the description of the intended mitigation for the potential risk. Usually, teams employ a spreadsheet and identify the mitigation for each combination of potential hazard, potential cause and associated potential harm. There can be multiple mitigations for each combination, or each potential cause may have a unique mitigation. These mitigations (controls) should be defined in terms of "tasks," or actions that the company needs to take to assure the best possible outcome. In some cases, the hazard can be mitigated only by warning the potential user—which becomes a statement on the labeling. In other cases, the hazard can be detected during verification testing and performance qualification.

By creating a spreadsheet with the analytically derived requirements, potential hazards and potential mitigation, the developer has laid out the plan for step three: verification and validation.

Step 3: Verification and validation

Development teams can become confused quickly in trying to develop the testing plan for their product. Engineers storm the regulatory agency (or their own regulatory team members) with a demand to know what testing must be done to satisfy the submission requirements. This is too little too late. The requirements from the FDA should be firmly imbedded in the input requirements, since the FDA is also one of the customers.

A good risk analysis with a list of mitigations will form the basis for the verification and validation. As a start, take the risk analysis spreadsheet and code the mitigations as “labeling or user manual” and “V & V.” Before proceeding, take a last check of the mitigation and make sure that mitigation can be accomplished and is appropriate to the risk. Those risks that require testing can generally be characterized in two groups: verifiable, or requires validation. (Don’t forget you may need to validate the labeling, too. When a complex user manual is required, validation of this portion of the labeling is vital.)

Generally speaking, verification can be measured or monitored as a discrete event. For example, the pore

size can be measured on a medical textile. However, to determine if a material is capable of incorporating a specific type of tissue into its structure in a given time period, a validation is necessary. In this case, that validation could be a pre-clinical trial in an animal, or a clinical trial in a human. As is obvious in this example, the validation would involve multiple parameters in making the assessment of suitability for the intended use. Most of the time, if an assessment is done correctly, the team will make a determination of the proper testing (verification and validation) that will be acceptable to the regulatory agency. When in doubt, or when a lot of time and money is required to meet these test requirements, the developers can use the mitigation plan as a basis for discussion with the FDA in what is known as a “pre-IDE” meeting. These meetings are not just for devices that require an investigational device exemption, but are used as a formal structure for discussions between the FDA and the developer, to assure each party that the appropriate level of testing and the right kind of data will be available to the FDA for review and approval (or 510k clearance) of the device.

To manufacturing, to market

Certainly the product developer must have a system of change control for design requirements that includes control over materials, components and design throughout the various

stages of the device development. A Design Plan should be in place early enough in the program to lay out the critical milestones at which Design Review is required. However, Design Review should become a natural part of the sequencing of the design through the development and testing, documenting through team minutes and as needed when critical decisions need to be made. Design Transfer, then, is the fine art of taking the developed device to the manufacturing floor.

Often this is not done all at once, but rather in a series of builds; but at some point, the device leaves the womb of design development and is a released product. Design History File is merged into Device Master Record, and the requirements for device performance are formally transferred into the language of product specification. This process comes naturally (or at least much more easily) for the medical device developer who has followed all the basics steps.

Most medical textiles will clear under the Class II designation, and in the United States, require a 510k submission to demonstrate substantial equivalence to a product that is already cleared by the FDA. Quite a few medical textiles are Class I devices, and the manufacturer needs only to register and list. Of course, unless the regulation for that device specifically exempts it from following Quality System Regulations, the manufacturing site will be subject to FDA inspection.

For many products sold to Europe and countries with similar regulatory strategies, the manufacturer may even be able to self-declare to conformity to the regulations and essential requirements. But regardless of the classification of the device or the regulatory submission requirements, following the basic 1-2-3 steps of product development will help to assure that you will make it to your market with a safe, reliable product that meets the customers’ needs. **R**

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