Rethinking the Standard Device Pre-Clinical Testing Paradigm for Combination Products

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Traditional testing procedures are satisfactory for the majority of today's medical devices. However, with combination products, testing can become a significantly greater challenge. This article looks at the background of testing practices and examines how changes need to be introduced for the newer combination product technologies.

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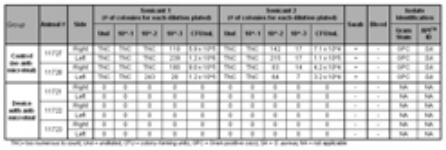
Regulated medical devices undergo a rigorous examination process before human use, with 98% of all medical devices available for clinical use in the U.S. going through a 510(k) review process–the U.S. FDA's single largest pre-market program at 3,000 to 4,000 submissions a year. The 510(k) review process by law (21 CFR 860.7) requires the submission of valid scientific evidence, which, in most cases, is the pre-clinical data comprising *in-vitro* and *in-vivo* studies. The data should be risk based and data driven, with a focus on use and performance.

Pre-clinical testing (or nonclinical testing, the term used in 21 CFR part 58) has historically been used in the evaluation of medical devices for a number of endpoints.

- Biocompatibility testing
- Component testing to ensure product safety
- Selection and qualification of materials
- Final testing of the device design prior to regulatory submissions

For companies submitting products to the FDA for consideration, federal regulations regarding pre-clinical testing–as found in the Code of Federal Regulations Title 21-Food and Drugs, Part 58[1] (also known as the "GLP Document")–are laws that must be followed. 21 CFR Part 58 defines a non-clinical laboratory study for medical devices as an *in-vivo* or *in-vitro* experiment used to test articles prospectively in a laboratory setting to determine safety. It does not include exploratory studies or studies utilizing human subjects, clinical studies, or field trials in animals. It also does not include basic studies used to determine whether a test article has any potential utility (efficacy). Manufacturers may often mistakenly assume that GLP studies are used for testing the safety and efficacy of a medical device. However, per 58.3 Section D, efficacy is clearly excluded.

Current Testing Paradigm



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Most devices in the category of a 510(k)-type product do not require clinical data for regulatory review. (Approximately 10% of 510(k) submissions contain clinical data to meet a performance requirement.) If biocompatibility testing of well-known materials is required for regulatory review, what testing can be performed on combination products when clinical studies are either not practical (unable to define usable clinical endpoints or unknown statistical outcomes) or immoral (no one wants to infect a patient post implant)?

The normal paradigm–pre-clinical testing for safety data, and clinical testing for efficacy–does not support the evolution that is now driving the combined product market where clinical testing for efficacy and supporting claims are not practical.

The current pre-clinical testing paradigm–employing pre-clinical studies to prove that a device is safe and biocompatible prior to clinical use–is driven by the general essence of the language in applicable FDA documents (such as G95-1), and recognized standards from ISO (such as ISO 10993 parts 1-20) and ASTM (American Society for Testing and Materials). In fact, it is quite common for regulatory submissions to include pre-clinical studies (compliant to these standards) as a demonstration of the safety of the device. It should be noted, though, that these documents are guidelines and not law, which means there can be varied interpretations of the documents and the specifics of the testing.

Medical device companies should employ a systematic process of testing new devices in pre-clinical studies prior to human use because it provides the optimum "wet" research usage and evaluation. These studies typically are designed for single safety endpoint determinations only. For example, a skin sensitization test does not evaluate the potential for the same device to cause skin irritation even though the scoring methods are almost identical. While it is true that these reactions are caused by different immunological reactions, the question then arises, "Can this testing be combined?" The simple answer today is no because of the current study protocols in use. In reality, medical devices today are as they were 50 years ago in terms of:

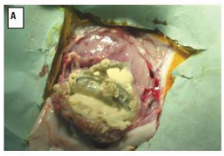
- Base materials
- Cleaning processes
- Sterilization processes
- Packaging

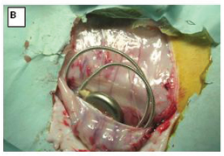
Why then is this testing still performed? There are two reasons: 1) Most pre-clinical

specialists have learned that if it "fails" in a pre-clinical test, the device will likely have the same issues in the field, and 2) Regulatory personnel have learned that devices have little-to-no chance of getting approved without this data for submissions performed in compliance with GLP.

So it appears–at least by the current pre-clinical testing paradigm, which is designed to prove safety–that product efficacy can be demonstrated only by the use of clinical testing. However, what is to be done with combination products in which the device is the active ingredient and a drug or biologic is a component? Pre-clinical studies are ideal to address performance differences when clinical studies are not practical, and, as a result, a shift has recently started to emerge–the use of pre-clinical study designs to evaluate efficacy and make regulatory claims.

Challenges of Combination Product Testing





Combination products have been around since the medical devices amendments act of 1976. But according to the FDA's website, "Differences in regulatory pathways for each component can impact the regulatory processes for all aspects of product development and management, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, and post-approval modifications." Because combination product safety and efficacy testing is not easily support by the normal testing paradigm of the regulatory process, a new paradigm needs to be created. In fact, the regulatory agencies have been open to discussions about broader approaches to pre-clinical data to support both safety and labeling claims when clinical studies may not be appropriate. How has this changed the pre-clinical testing environment? The new testing paradigm should now be considered to include:

- Biocompatibility testing
- Component testing to ensure product safety
- Selection and qualification of materials
- Final testing of the device design prior to regulatory submissions
- Efficacy claims

Preclinical studies designed to meet either singular or multiple endpoints can be an effective means to demonstrate that a product has a provable performance difference from a predicate device. Such studies also allow the collection of valid scientific evidence to support efficacy. Efficacy claims can be important to demonstrate to a variety of data consumers the utility and importance of the

combination product. Following is a case study that presents a unique approach to this new testing paradigm.

Case Study: Antimicrobial Efficacy (AME) Testing

One combination product area experiencing increased focus is the development of products aimed at preventing device-related infections. It is estimated that 1-5% of device implants in the U.S. result in device implant site infections.[2,3] This is a huge clinical challenge due to the resistance of such infections to systemic antibiotic therapy. Plus, the actual source of the infection may be unknown as many of these infections can take place months or even years after the implant. Often, the medical options are limited to revision surgery for device removal, tissue debriding, and replacement of the infected device, which is likely to be a costly and risky procedure. In addition to these clinical concerns, recent changes in Centers for Medicare and Medicaid Services' reimbursement policies can result in hospitals being forced to incur the high costs of treating device-related infections.

Products aimed at preventing device infection may take many different forms, but they often involve a device coating designed to release one or more antimicrobial drugs at the site of implantation. In addition to the usual safety and pharmacokinetic testing required for regulatory approval of such combination drug/device products, efficacy testing is also a necessary step to acquire the desired label claims.

While the FDA has been understandably reluctant to specify detailed protocol requirements for general *in-vivo* AME testing due to the diversity of devices and clinical settings, certain parameters are desired for all such testing. These parameters include:

- Clinically relevant implant models
- Reproducibility of positive and negative controls
- The use of low passage, clinically relevant bacterial strains to create the infection
- Quantifiable methods to assess bacterial burden following treatment

Using these parameters, WuXi AppTec designed studies to assess the antimicrobial efficacy of different products implanted with devices, such as cardiac pacing devices in a subcutaneous implant model in rabbits.[4] In these studies, a pacemaker or similar device is implanted in a dorsal subcutaneous pocket, with or without an antimicrobial treatment, and a specific dose of a clinically-relevant bacterial strain is infused into the surgically closed pocket. After recovery and in-life periods ranging from three days to six weeks, the devices are aseptically removed (Figure 1) and assessed for residual, viable bacteria using both swabbing techniques and a vortex/sonication procedure. This approach results in quantifiable counts of bacteria removed from the device following serial dilutions of the sonication solution and culture on agar plates. Complementary endpoints may also include histopathology assessment of local reaction and microbial infection; blood culture and differential counts; microbial and residual drug analysis of surrounding tissue; and scanning electron and confocal microscopy imaging of explanted samples to directly visualize

residual biofilm on the explanted samples. Results from treated samples are then compared directly to results from non-treated positive (infected) controls (Table 1).

Depending on the antimicrobial treatment being tested, results can range from no effect seen (i.e., equivalent levels of recovered bacteria on the treated and non-treated devices) to complete eradication of viable bacteria from the explanted device and surrounding tissue. These types of results have been used directly by manufacturers to receive approval for efficacy claims on their antimicrobial containing devices. Though this approach has been successful, challenges remain for specific labeling claims, and it is strongly recommended that clients have initial meetings with the FDA to review their desired claims along with their proposed pre-clinical efficacy study outlines.

Discussion and Implications

When standard device testing–such as performance testing and biocompatibility–is being conducted on combination products, the testing lab should be informed as to the specific components of the test article. The release of biologicals or drugs from the combination product can be problematic with the more sensitive tests, such as cell cytotoxicity and sensitization assays. These tests are required by the agencies, but forethought and proper test designs can deal with some issues that may arise. Before any combined testing is performed, it is highly recommended that biocompatibility testing be concluded, as the addition of a chemical or biological material can alter the data. For example, many chemicals and some biological materials will induce an immune response when presented chronically in tissue verses acute dermal contact.

Efficacy testing for a combination product that has the device as the main active component can buy the manufacturer a potentially faster review process and the ability to make claims, as it makes efficacy data available and demonstrates a performance difference. It may buy a reduced or more effective clinical study in that the pre-clinical data can help define study design and endpoints. And, it may help identify unique device claims that would not be practical using any other testing methods.

Study designs, such as the examples provided in the previously illustrated case study, have been expanded for use beyond cardiac pacing devices to include such devices as spinal implants, hernia mesh materials, dural/brain implants and orthobiological devices. As the number of combination products grows, along with the need for preclinical testing that demonstrates both safety and efficacy, a change is occurring in the pre-clinical testing paradigm from what has existed over the last 35 years.

References

[1]Code of Federal Regulations, 21 CFR part 58: Good Laboratory Practice for Non Clinical Laboratory Studies.

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[4]Hansen, LK, et al. In Vivo Model of Human Pathogen Infection and Demonstration of Efficacy by an Antimicrobial Pouch for Pacing Devices. PACE 2009; 32:898-907.

Online

For additional information on the technologies and products discussed in this article, see *MDT* online at www.mdtmag.com [4] or WuXi AppTec at www.wuxiapptec.com [5].

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