The Expanding Role of Contract Research Organizations

Written by Paul Upman and Terry Langenderfer
Contract research organizations (CROs) used to be considered premarket- or biocompatibility-testing houses. But over the years, it has become clear that the medical device industry expects a testing laboratory to be involved in the research and development, nonclinical testing, clinical testing, and postmarket quality assurance phases as well. Although CROs are primarily involved with testing devices, device materials, and components, they can play a much larger role in product development. Some 25 years ago, manufacturers typically needed help understanding when to do specific kinds of testing. It was not unusual for a manufacturer or supplier to conduct expensive and complex animal studies, only to discover later that the materials used were not suitable because of chemical, physical, or toxicological properties. Although manufacturers and raw-material suppliers have become more testing savvy, it is important that they understand the preclinical and clinical testing requirements. To this end, this article places these testing activities within the context of a generic product development process that is generally represented by the stages shown in Figure 1.

Each stage consists of many activities. For the sake of simplicity, the stages are condensed into four groups; however, adjacent stages often overlap. The research and development stage is primarily concerned with the generation of concepts and discovery. Design and validation involves product refinement and proof of application. Manufacturing has the clearest definition of the four stages—it is interested in the efficient production of the final product. Finally, ongoing quality control measures are implemented to ensure adherence to specifications.

There are five major categories under which medical device testing fall:

- Analytical chemistry and materials characterization.
- Efficacy.
- Biocompatibility.
- Clinical trials.
- Sterility assurance.

Figure 2 aligns these five categories, or test phases, with the stages of product development. In order to understand what generally occurs during each of the test phases, we will follow a relatively common device, a vascular graft, through the process. However, it is important to remember that the unique properties of any device must be addressed within each testing program.

Analytical Chemistry and Materials Characterization

This phase includes screening and qualification tests that chemically characterize raw materials or medical device components. This initial phase is driven by ISO 10993, Parts 1, 13, 14, 15, and 18.1 (Part 18 is currently in the final draft stage.) There is a wealth of analytical equipment and methods...
Efficacy

Efficacy, or functionality testing, usually involves surgical studies that evaluate how well the device performs the intended treatment. As quickly as possible, the manufacturer needs to see how the new device will work under clinical-like conditions. CROs offering this service must maintain adequate facilities to test and house a variety of animals required for these studies. Typically, there is no regulation or guideline leading this phase. Therefore, manufacturers often rely on the scientific and surgical expertise of the CRO for protocol development.

A functionality study of a vascular graft would involve implanting it at the clinical site or a similar vascular site that would allow evaluation in an animal model under use conditions. Although no animal model perfectly mimics human reaction, these studies have high predictive value and are often required for new and unique devices. Prior to designing a clinical investigation, animal functionality studies are also useful in screening for any use-related hazards. For more information, see FDA’s guidance document titled Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management.²

Biocompatibility

Sometimes referred to as safety testing, biocompatibility testing uses both in vitro and in vivo models to ensure that the device or component material is biologically safe for its intended use. The biocompatibility phase is driven by a wealth of guidance documents available from FDA, ISO, ASTM, and ANSI/AAMI. In some cases, all four sources provide identical protocols or standards based on the ISO 10993 series. The degree of testing will depend on the amount of relevant data available and what the data report for the identifiable chemicals leached from the device under simulated-use conditions.

When designing the testing program, it is important to consider body contact (placement of the device) and the duration of contact. So our example of a vascular device is classified as a permanent implant that will require testing for biological effects including cytotoxicity, sensitization, acute toxicity and irritation, implantation, genotoxicity and long-term systemic toxicity. Because there is blood contact, hemocompatibility testing will also be required. Hemocompatibility tests usually involve hemolysis and thrombogenicity studies.

Clinical Trials

The next step for many devices is clinical investigations. These scientific studies are employed to evaluate a drug, device, or biologic on patients in the treatment, prevention, or diagnosis of a disease or condition. Clinical investigation results are determined by the product’s benefits relative to its risks. In the United States, clinical investigations can only be conducted with the approval of an ethics committee, called an institutional review board (IRB), and the competent authority, FDA. Compliance with EN 540 and GCPs is required throughout the European Union.³,⁴ ISO 14155 Parts 1 and 2 provide special requirements for the design and conduct of a medical device study, as a well as the final study report.⁵

Moving our vascular device through the process, the clinical investigation plan should be designed by the CRO in close cooperation with the sponsor. Key factors in determining the number of patients and investigation centers include regulatory strategy, methodology (open, randomized, controlled, etc.), ethics, and timelines.

In this situation, a clinical trial for a vascular graft could include 4–12 investigation centers and 100–300 patients. Many U.S. sponsors prefer to first initiate their studies in Europe. Clinical trials can often be started earlier and are sometimes less expensive to perform in Europe.

Sterility Assurance

Although sterility assurance should be considered early in the design stage of the development process, it is sometimes overlooked until the manufac-

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**Figure 2. The five major categories under which medical device testing fall can be aligned with the stages of product development. This figure is adapted from NAMSA’s Medical Device Process and Testing Guide.**
turer approaches mass production. For medical devices, the three major com-
ponents of a comprehensive sterility assurance program are sterilization val-
idation, environmental monitoring, and packaging validation with shelf-
life testing. Release and audit testing ensures product uniformity and com-
pliance with label claims. Each com-
ponent has a variety of assays to con-
sider and a number of sources for regulatory and methods guidance, such as certain ISO standards. ASTM and the United States Pharmacopeia also have similar standards.

A vascular graft is an invasive de-
vice, so the sterilization process must be able to achieve a sterility assurance level (SAL) of $10^{-6}$. This means that the sterilization process must be validated to ensure sterility to a probabil-
ity of one nonsterile device in a sam-
ping of 1 million. This does not mean that we literally expect to find non-
sterile devices every million pieces or so. Rather, the point is that the proba-
bility of finding a nonsterile device is very remote and within the tolerance of risk to the patient.

Ethylene oxide (EtO) is the most popular sterilization method, followed by radiation. EtO has very few effects on materials used to construct a vas-
cular graft but, by itself, is toxic, a car-
cinogen, and a mutagen. Therefore, it is important to use enough gas to achieve the desired SAL but also de-
vise a process that can remove residues of the gas to safe levels. The validation process involves processing sublethal cycles on a process-challenge de-
vice. This process-challenge device (PCD) represents a worst-case treat-
ment of the product. By using sublethal cycles, it is possible to sterility test a quantity of PCDs and measure an SAL somewhere between $10^{-1}$ and $10^{-2}$. From there, a CRO can then extrapo-
late a process that will result in an SAL of $1:1,000,000$.

Finally, a package will not remain sterile unless its primary packaging is capa-
bale of doing so. Faulty pack-
aging is the number one reason for sterility-related recalls, so package validation must not be overlooked in a medical device’s testing program.

Taking Testing Outside

Several large medical device OEMs have some of the capabilities offered by CROs available internally. How-
ever, many are finding it advantageous to outsource these services while con-
centrating their resources on research and development and marketing.

Working with a CRO that provides all of these services can be especially beneficial to small and medium-sized manufacturers. Cost savings in labor and overhead are the most obvious benefits, but additional efficiencies can be realized when the CRO is engaged at the early stages of the development process. Working with the same CRO from the start of a project through production creates a knowledge base. That way, the CRO is in a good posi-
tion to make recommendations and respond to design modifications or changes in the manufacturing process. Helping establish a regulatory ap-
proval strategy at the outset of the de-
volution process is another advanta-
ge of this relationship.

Conclusion

Although it is presented here in a linear sequence, some testing can be per-
formed simultaneously. Also, data in one area can sometimes be leveraged to minimize testing in another area. Prior to the deployment of a testing pro-
gram, a review of existing, relevant data should take place, and an assess-
ment of risk should be performed.

References

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