

SATISFYING MEDICAL DEVICE BIOCOMPATIBILITY REQUIREMENTS: WHAT'S A SUPPLIER TO DO?

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Abstract

Since the early 1990's, the medical device industry biocompatibility programs have been driven by the international standard (ISO) 10993. This series of standards is now approaching 20 subparts. Demands on the device manufacturer in time and money have become substantial. This can be softened by suppliers of raw material resins and component parts that address some of these testing requirements in advance. Attention to testing requirements by the supplier often prevents duplication by the device manufacturer, and can eliminate surprising results that appear when various companies conduct their own biological and chemical testing. Providing results to the manufacturer can take the form of test certificates, formal brochures with data, or a material master file at the FDA. Such additions to the suppliers offerings can improve marketing position and marketing efforts.

Background

From a purely regulatory perspective, the manufacturer of a finished medical device bears the responsibility for satisfying the U.S. Food Drug Administration (FDA) requirements for biocompatibility prior to clinical use of the device. The FDA may approve or clear an Investigational Device exemption (IDE for clinical trials), a Premarket Approval application (PMA), or determine substantial equivalence on a manufacturer notification of intent to market under the 510(k) rule. A similar situation exists in the European Union (E.U.). In most cases, the path to follow to market is clearly defined by domestic or international standards. In many cases, information provided by vendors or suppliers of the raw materials or component parts of a medical device are used as part of the regulatory submission in the U.S. or for CE marking in the E.U. The larger the device manufacturer and the more competitive the market place, the more demands

may be placed on the supplier to provide basic physical, chemical and biocompatibility data.

Typical Device Component

Medical PVC tubing provides a good example of a component part that is used widely by the device industry. Various formulations were subjected to a series of tests that satisfy the requirements for a device in contact directly and indirectly with a patient's blood, over a prolonged period of time. These tests represented a significant undertaking at the supplier level, that eventually provided valuable information to the device manufacturer. A supplier has the option of conducting testing at one or more levels to satisfy specific customer needs or their own requirements. Such information may be used to satisfy procurement specifications, or shorten the time to FDA or international market approval, as well as enhance marketing position.

Deciding What To Do

Over the last 10 years, the multiple international standards identified as ISO 10993 have emerged as the state of the art in evaluating the biocompatibility of medical devices. Many countries have adopted these standards into their own systems, including the FDA. In the U.S. some minor modifications were made to ISO 10993-Part 1, and the document was reissued with changes under FDA Memorandum #95-1. The matrix of biological effects is a part of the original ISO 10993-Part 1 document¹ and it defines the effects that must be addressed according to the type and duration of patient exposure.

Input from the field identified the fact that many times medical device products are being designed by engineers that have no background in polymer materials or biological testing. They know what function they want the tubing to perform, but are not able to translate that knowledge into exact specifications for selection. This is especially true for many small and start-up device manufacturers.

To address this need, it was decided to develop a collection of information (Validation Binder) that could satisfy both the tubing specifier and an FDA reviewer. This does not entirely eliminate the requirement to conduct tests on the final device, but it can provide assurances to the designer that the biocompatibility of the tubing will not be an issue.

Testing Protocols

One of the first and most important steps for PVC medical tubing formulations was to obtain physical and chemical characterization of the components². Below are some of the characteristics defined for Tygon³ formulations:

Physical Properties

Tensile Strength
Elongation
Durometer Hardness
Bonding Capability
Water Absorption

Chemical Properties

FTIR (fingerprint)
Aqueous Extractables
Non-aqueous Extractables
Trace Metals

After the material was well characterized, biological tests were conducted:

Biological Effects (basic)

Cytotoxicity
Sensitization
Irritation

Systemic Toxicity

Biological Effects (advanced)

Subchronic Toxicity
Genotoxicity
Implantation
Hemocompatibility

Biological Effects (special)

Material Mediated Pyrogen test
Bacterial Endotoxins
Bacteriostasis/Fungistasis

Using the Data

In many cases the supplier will not know exactly how or where their product will be used. As can be seen in the standard, the type and extent of contact with the body dictates how the device is classified.

Body Contact

Surface: Skin, Mucosal, Breached
External Communicating: Indirect blood,
Tissue/Bone, Blood
Implant: Tissue/Bone, Blood

Contact Duration

A-limited (<24h)
B-Prolonged (24h-30 days)
C-Permanent (>30 days)

A supplier would need to make a decision as to the cut off point for general testing. In the case of the Tygon PVC tubing, it was decided to cover all the basic tests:

Cytotoxicity
Sensitization
Irritation

In addition, considering the potential uses as intravenous tubing, it was decided to include blood contact requirements:

Hemolysis
Coagulation
Thromboresistance



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Complement Activation

And to address longer term, or repetitive exposure in patients:

Acute Systemic Toxicity

Muscle Implantation

Subchronic Toxicity

Genotoxicity

The genotoxicity evaluations adhered to the FDA premise that a battery of three assays would be needed for devices falling into category C, longer than 30 days patient contact:

Reverse Mutation Bacterial Assay

Chromosomal Aberration Assay

Sister Chromatid Exchange Assay

formulations and assure relevance of biocompatibility data.

¹Biological Evaluation of Medical Devices - Part 1:

Guidance for the selection of tests. ISO 10993-1:1997

²Biological Evaluation of Medical Devices - Part 18:

Material Characterization. ISO 10993-18 DIS

³Tygon® Medical Grade Tubing, Norton Performance Plastics Corporation, Akron, OH

Conclusion

As indicated at the outset, the responsibility for biocompatibility of the final device lies with the manufacturer. This can be accomplished in several ways, one of which is to profile all components of the device according to ISO 10993 standards for the category in which the device falls. As data becomes available from suppliers for all components, duplicative testing may be avoided for some if not all of the requirements for the device. Some evaluation may still be needed on the entire final sterilized packaged device. These tests, if needed, will be the most sensitive and often the shortest term models, and chemical assays designed to show a lack of leached chemicals, such as sterilant residue, from the assembled device.

Component suppliers who are aware of the biocompatibility requirements their customers must meet, have an opportunity to supply testing data to meet those needs and thus enhance credibility of the product in the eyes of the manufacturer. Previously qualified components provide materials with a known safety profile and can save the manufacturer both time and money. When the supplier conducts the testing, results can be made available to multiple manufacturers, thus avoiding duplicative testing. Characterization tests carried out on a regular basis confirm the consistency of specific polymer