Selection of Plastic Colorants for Medical Devices

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Introduction

Plastics play a major role in the design and manufacture of devices for the medical and healthcare field. Many of these applications require coloring of the plastic resin. Coloring often serves an important purpose beyond pure aesthetics. For example, color-coding may be used to distinguish between different sizes of the same device. Thus color can be an important functional element in the device design.

Once the type of resin to be used in a device has been identified, based on criteria such as physical, mechanical, and chemical resistance properties, it usually is fairly straightforward to identify a manufacturer's grade that is suitable for the medical application. Major resin manufacturers make it clear which of their grades have been tested for medical use and what limitations there are on these uses (e.g. "not for implant"). They can provide letters of certification regarding the testing that has been performed on the material and often can provide access to FDA Device Master Files containing extensive toxicological data. However, the situation is less clear-cut for the colorants that will be used and there may be a disconnect between the amount of testing data the device OEM would like to see and what is actually available.

Overview of the Regulatory Environment

Before going further we should review the regulatory climate that the device OEM operates in. The OEM is responsible for submitting a 510K Pre-Market Notification to the FDA for non-exempt Class I and Class II devices, or a Pre-Market Approval Application for higher risk Class III devices. PMA's also are needed where a substantially equivalent predicate device does not exist to support a 510K. Class I applies to low risk devices that have only surface contact with skin or mucosal membranes for periods of 30 days or less. Class II applies to higher risk devices that have indirect blood path contact; communicate with tissue, bone, or dentin; contact circulating blood; or contact liquid drugs or IV solutions, for periods of 30 days or less. Class III devices support or sustain human life or represent a serious risk of illness or injury and include long term implants (contact time > 30 days). Whether done via a 510K or a PMA the FDA expects to see convincing data regarding the safety and suitability of the device. This is also the

case for exempt Class I and II devices. Even if a device is exempt due to low risk the FDA expects that the OEM will develop data to support the intended use.

The bottom line is that the OEM is fully responsible for demonstrating the suitability and safety of the medical device. This includes surface activity, potential extractible materials, and potential effects on the host. If one word must be used to sum this up it would be “biocompatibility”. Note that the term used here is “suitability and safety of the device”, not “the materials” that were used to make the device. This is an important distinction that influences the testing that is performed on the materials.

Testing of Materials for Biocompatibilty

Even though it is the device itself that ultimately must be tested the OEM obviously needs to start with materials that have been vetted for biocompatibility. Historically, materials were tested against the USP Class VI long-term implantation standard. This standard applies to the most demanding type of medical application and it is assumed that any material that passes this level of testing is suitable for less demanding applications. USP Class VI testing includes Acute Systemic Toxicity in mice using extract solutions, Intracutaneous Toxicity in rabbits using extract solutions, and Muscle Implantation in rabbits using the material itself. Many of the materials on the market today, including both resins and colorants, carry USP Class VI status only.

Over the past 15+ years the ISO 10993-1 standard has been supplanting USP Class VI. This standard, in modified form, has been an FDA requirement for medical devices since 1995. The test matrix in ISO 10993-1 lists up to twelve evaluation tests. The specific tests that need to be performed are a function of the nature of body contact expressed in three categories (Surface Contact, External Communicating Devices, or Implant Devices) and the duration of contact (Limited, meaning <24 hours; Prolonged, meaning 24 hours to 30 days; and Permanent, meaning >30 days). See the table below for the full test matrix (table complements of NAMSA, Northwood, OH).

FDA Blue Book Memorandum #G95-1: Biological Evaluation Tests for Consideration

DEVICE CATEGORIES			INITIAL TESTS								SUPPLEMENTARY TESTS			
BODY CONTACT		CONTACT DURATION A= Limited (≤24 hours) B= Prolonged (24 hours - 30 days) C= Permanent (>30 days)	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	System Toxicity (acute)	Sub-Chronic Toxicity (sub-acute toxicity)	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental	Biodegradation
Surface Devices	Skin	A	x	x	x	.	.	.	.	.	.	.	.	.
		B	x	x	x	.	.	.	.	.	.	.	.	.
		C	x	x	x	.	.	.	.	.	.	.	.	.
	Mucosal Membrane	A	x	x	x	.	.	.	.	.	.	.	.	.
		B	x	x	x	o	o	.	o	.	.	.	.	.
		C	x	x	x	o	x	x	o	.	o	.	.	.
	Breached or Compromised Surfaces	A	x	x	x	o	.	.	.	.	.	.	.	.
		B	x	x	x	o	o	.	o	.	.	.	.	.
		C	x	x	x	o	x	x	o	.	o	.	.	.
External Communicating Devices	Blood Path, Indirect	A	x	x	x	x	.	.	.	x	.	.	.	.
		B	x	x	x	x	o	.	.	x	.	.	.	.
		C	x	x	o	x	x	x	o	x	x	x	.	.
	Tissue/Bone/ Dentin Communicating[1]	A	x	x	x	o	.	.	.	.	.	.	.	.
		B	x	x	o	o	o	x	x	.	.	.	.	.
		C	x	x	o	o	o	x	x	.	o	x	.	.
	Circulating Blood	A	x	x	x	x	.	o[2]	.	x	.	.	.	.
		B	x	x	x	x	o	x	o	x	.	.	.	.
		C	x	x	x	x	x	x	o	x	x	x	.	.
Implant Devices	Tissue/Bone	A	x	x	x	o	.	.	.	.	.	.	.	.
		B	x	x	o	o	o	x	x	.	.	.	.	.
		C	x	x	o	o	o	x	x	.	x	x	.	.
	Blood	A	x	x	x	x	.	.	x	x	.	.	.	.
		B	x	x	x	x	o	x	x	x	.	.	.	.
		C	x	x	x	x	x	x	x	x	x	x	.	.

X = ISO 10993 Evaluation Tests for Consideration O = Additional Tests which may be applicable

[1] Tissue includes tissue fluids & subcutanous spaces

[2] For all devices used in extracorporial circuits

The OEM must test the device itself in accordance with the FDA-modified ISO 10993-1 standard. As a result the OEM usually would prefer to see the materials also tested to ISO 10993-1 rather than the older USP Class VI, but in many cases they will accept USP Class VI.

Selection of Biocompatibility Tests

The selection of ISO 10993-1 tests needed for a new medical device itself is done on a case-by-case basis as a function of the nature and duration of body contact. In a perfect world the OEM might want to see the same tests performed on all the materials, including colorants, that are used to make the device, but economic reality prevents this. USP Class VI testing costs approximately $5,000 per sample. The full matrix of ISO 10993-1 tests can approach $100,000 per sample. Given the many permutations and combinations of resins and colorants it is not economically feasible for the color compounder to conduct this level of testing. Nor does it make sense to test the materials to the same degree as the device itself when you consider that (1) this would be redundant and (2) that the FDA is not interested in biocompatibility test data on the materials used in the device; they are interested only in results on the device itself.

What the OEM actually needs is to have enough confidence in the materials they plan to use to justify moving forward with the lengthy and expensive device development process. They do not want to invest considerable time and money in a project only to find months down the road that the device fails biocompatibility testing. The question then is how much testing is needed to provide this level of confidence.

What we find is that testing to USP Class VI or selected portions of the ISO 10993-1 standard usually provides adequate assurance to the OEM for them to move forward. Most commonly, the following parts of ISO 10993-1 are employed at a cost of approximately $11,000 per sample:

Part 5:	Invitro cytotoxicity
Part 10:	Intracutaneous reactivity / sensitization
Part 11:	Systemic toxicity
Part 19:	Physiochemical characterization of plastics

This degree of testing represents a compromise that provides adequate information to the OEM while keeping costs for the colorant supplier or color compounder at a reasonable level.

Other Expectations of the Device OEM

The focus of this article has been on approval and selection of materials used in compounded medical resins, but we would be remiss in not mentioning two other key expectations of the OEM. The first is that the compounder must have a change management procedure in place under which no changes will be made to a formula unless forced to do so by a raw material change or discontinuation. Even when forced to make a change the compounder will take steps to assure supply for 1-2 years to allow the OEM to requalify the change. The second is that the compounder must be able to provide a certification statement regarding biocompatibility testing that was performed on the materials, when so requested.

By providing materials that have undergone adequate biocompatibility testing, backed up by certification statements and combined with good change of management practices and, of course, consistent product that is free from defects, the color compounder can become a valuable supply partner to the OEM and their contract manufacturers.