

## Biological Safety: More Than Just Test Data

*Hazards of new medical devices must be studied so the risks are clear.*

Toxicology Profiles for Evaluation of Medical De-vices, May 1, 1995 (G95-1)” cannot address the wide range of medical devices that are being introduced into the mar-

**T**wenty-five years ago, when I was in charge of biocompatibility at a global manufacturer that specialized in medical devices, my biocompatibility test data package could fit comfortably in a standard-size manilla folder. However, our biocompatibility process was probably more comprehensive than what many manufacturers have today.

ket today. There is a need to also research vertical standards, guidance documents and literature with regard to the types of devices on the market. Any totally novel device must be studied so that the biological hazards of use are well understood and the risk of those hazards occurring are well characterized. Add to this the need to address the requirements of various international markets, and planning for biocompatibility becomes a business necessity, not just a regulatory requirement.



**Permanent tissue implants, such as this device, warrant a biological safety evaluation plan. Photo courtesy of NAMSA.**

What we used in 1983 was a biocompatibility plan that we developed for every product, material, manufacturing material and component that we used. ISO 10993-1: 2003,

*Biological evaluation of medical devices—Part 1: Evaluation and Testing*, states, “The biological evaluation shall be planned, carried out and documented ...” The reason for planning is that even a standard such as ISO 10993-1: 2003 and guidance provided by the U.S. Food and Drug Administration (FDA) such as the G95 Memorandum, “Required Bio-compatibility Training and

### Document Process

In our biological safety program, each material was qualified and characterized using a consistent documented process. Internal acceptance criteria were developed as a result of examining comparative data on various materials. We also requalified the material after we molded components, taking into account process variability, both in terms of specifications and material condition and storage.

In situations where solvent bonding was employed, we examined the chemicals under consideration and their impact on safety. By this stage, a sizable evaluation file had been

# BIOCOMPATIBILITY

established, and we had yet to conduct any biological testing, except for perhaps *in vitro* studies such as cytotoxicity or hemolysis. All of this preliminary work was designed to characterize the material for suitability for use.

## Evaluation Conditions

“Use” implies both biological safety and GMP processing. Surprisingly, lengthy evaluation usually was not required to discover interesting features of the device that impacted its use. The key to evaluating materials early in the process is that evaluation conditions should be exaggerated and in many cases driven to exhaustion. Since risk looks at potential hazards, evaluation of these hazards should take place under exaggerated protocols, whether we are talking about extraction conditions or test design.

When we finally got to the finished device, we chose The United States Pharmacopeia (USP) Class II, a practice to prequalify a material, as the basis for our biological testing, which was a common practice at that time. In the end, our evaluation was probably as extensive, and I dare say more comprehensive than, some I review today, even though USP requirements pale in comparison with ISO 10993-1. However, USP guidelines were sufficient to understand the potential risk and in most cases eliminated risky materials and components before they were actually incorporated into the bill of materials for the product.

ISO 10993-1: 2003 states, “Evaluation may include both a study of relevant experience and actual testing. Such an evaluation may result in the conclusion that no testing is needed if the material has a demonstrable history of use in a specified role that is equivalent to that of the device under design.”

What we had back in 1983, and

## BIOCOMPATIBILITY TEST MATRIX

Specific safety evaluation programs follow Food and Drug Administration (FDA) guidance (May 1, 1995) and International Organization for Standardization (ISO) 10993 standards. The table is based on ISO 10993-1 Evaluation and testing, 3rd edition 8/01/03.

DEVICE CATEGORIES		BIOLOGICAL EFFECT												
BODY CONTACT	CONTACT DURATION A = Limited (<24 Hours) B = Prolonged (24 Hours - 30 Days) C = Permanent (>30 Days)	Cytotoxicity	Sensitization	Irritation/Intraocular	Acute Systemic Toxicity	Subchronic 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		
EXTERNALLY 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 <sup>1</sup>	A	x	x	x	o								
		B	x	x	x	x	x	x						
		C	x	x	x	x	x	x	x		x	x		
	Circulating Blood	A	x	x	x	x		o <sup>2</sup>		x				
		B	x	x	x	x	x	x	x	x				
		C	x	x	x	x	x	x	x	x	x	x		
IMPLANT DEVICES	Tissue/Bone	A	x	x	x	o								
		B	x	x	x	x	x	x						
		C	x	x	x	x	x	x	x		x	x		
	Blood	A	x	x	x	x			x	x				
		B	x	x	x	x	x	x	x	x				
		C	x	x	x	x	x	x	x	x	x	x		

X = Tests per ISO 10993-1

O = Additional tests that may be applicable in the U.S.

Note<sup>1</sup> - Tissue includes tissue fluid and subcutaneous spaces

Note<sup>2</sup> - For all devices used in extracorporeal circuits

**The ISO materials biocompatibility matrix categorizes devices based on the type and duration of body contact. It also presents a list of potential biological effects. For each device category, certain effects must be considered and addressed in the regulatory submission for that device. ISO 10993-1 does not prescribe a specific battery of tests for any particular medical device. Rather, it provides a framework that can be used to design a biocompatibility testing program. Source: NAMS 4 Stage Biocompatibility Approach Matrix, developed per guidance from Tables 1 & 2 of ISO 10993-1 and the FDA Blue Book Memorandum G-95.**

what NAMS Advisory Services still promotes today is a plan for biological evaluation for the product we are studying. While it was rare for companies to develop plans like this in 1983,

it is an absolutely critical step in the process today. Biological safety evaluation plans are an essential tool in:

1. Communicating the plan to

team members, company associates and medical device regulators

2. Leveraging information that is known about the constituents of the device

3. Identifying and characterizing biological and toxicological hazards associated with the product in an effort to characterize risk

4. Defining a plan for assuring biological safety

5. Explaining how your company uses the requirements of ISO 10993-1: 2003 to assure biological safety

The goal of safety evaluation can be summarized in the five principles listed above. Team members or other associates need to examine and challenge the plan in order to assure that it is comprehensive and that it achieves what is necessary to assure safety. Although test data is often seen as the consummate information required for demonstrating safety, why do regulatory agencies often challenge such data? Frequently it is because they don't understand the overall rationale behind the device manufacturer's submission.

They also fail to understand why certain tests were performed a certain way. (Submitting biocompatibility data to regulatory agencies, including the FDA, without a biological safety evaluation plan risks a page (or so) of questions and clarifications from the regulatory agencies.)

## Leveraging

In today's competitive environment, leveraging information can help reduce cost, and, more importantly, time. Twenty-five years ago, we spent a lot of time developing systems that leveraged information. For example, once the use of a specific thermoplastic in the development of a portion of a hip implant has been qualified, if that same thermoplastic now becomes part of a shoulder implant,

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it would behoove the manufacturer to leverage the information that has been acquired in the development of the hip implant. Use of this information for both therapeutic applications not only allows you to leverage test results, it also allows you to influence actual clinical use of the material as a shoulder implant.

## Hazard IDs

Hazard identification is an essential step in assuring safety. For many of us, this process begins and ends with Tables 1 and 2 of ISO 10993-1 or the tables that appear in the FDA Blue Book Memorandum G-95. It is indeed inappropriate to rely on either document to define the risk associated with your product. I can assure you the FDA does not solely evaluate biological risk based on the tables in the blue book memorandum. For example, the agency has published its guidance for evaluating immunotoxicity

in which it provides guidance on evaluation of such risk for medical devices. In this guidance, it does not require testing (Note: It has been and continues to be FDA's policy not to mandate testing), but suggests that certain immunotoxic risks be further evaluated. Also consider situations in which a device is coming in contact with the patient's central nervous system. The risk of neurotoxicity must be considered even though tests that evaluate such toxicity are not part of any of the tables previously mentioned.

The range of effects of potential biological hazards is wide and can include short-term effects, such as acute systemic toxicity, irritation, hemolysis, and throm-

bogenicity, as well as long-term effects, such as chronic toxicity, sensitization, genotoxicity, carcinogenicity and teratogenicity. Most orthopedic devices need to be evaluated for both short-term and long-term effects. This is because intended use drives hazard identification.

The use of a skin electrode to help record an electrocardiogram presents little hazard to a patient compared to a knee implant, which will remain with the patient for the rest of his/her life. Current knowledge of the material or device provided by scientific literature, previous clinical experience, and other relevant data can either mitigate the hazard or enhance it.

An example of the latter is in the manufacture of tissue heart valves where both formaldehyde and glutaraldehyde can be used in the processing of this device.

In the orthopedic industry, the

processing of metal parts often increases the risk of biological reactivity, as these parts must be formed and machined, which inherently creates particulate matter.

In addition, such processes may use manufacturing materials that could increase biological risk to the patient.

Therefore, information characterizing the chemical identity and biological response of materials is useful in assessing a medical device for its intended use.

## Safety Plan

Most importantly, the biological safety evaluation plan defines how the firm will assure the safety of its product. An effective plan starts with material selection, as ours did back in 1983. The principles here were to pick materials whose properties were most suitable for the performance of the device. Given those requirements, materials were characterized and qualified so that the risk of an adverse biological effect arising from the use of that material would be negligible.

After qualifying the material, the component was qualified. We then examined the molding process—specifications such as molding cycle time, generations of regrind permitted, melt flow range and other parameters that could have an effect on the material and whether the processed material could change the safety profile of the material. Once completed, we had a tremendous amount of confidence in the safety of that component and material. We could now apply that information across a range of devices and uses. Combining the information from the raw material supplier and final product test results assured device safety by mitigating the biological risk previously identified. This is exactly what the FDA desires.

Part of communicating the biological safety plan to team members is the

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definition of tasks, milestones and key events in the schedule of bringing this device to market or in advancing the project schedule. Gantt charts and timelines drive schedules. Yet most companies wait to communicate with the regulatory agencies, like the FDA, until late in the process, and when they do, they are less than clear. The plan also can be used in preliminary discussions with these agencies, so they can better understand the firm's thought process.

If the firm wants to work closely with FDA, they can use the test plan as an effective communication tool with the agency.

Even if the company passes on the opportunity to work with FDA early on, this evaluation plan is the perfect instrument for proper communication of the firm's rationale for assuring safety.

In addition, the plan acts as documentation of prevalent thought within the firm, the firm's vendors and the firm's consultants.

In conclusion, the next time your needs turn to biological safety don't

initiate testing until you have documented a plan for ensuring biological safety. A biological test plan is working paper, not paperwork. ♦

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