Evaluating Biocompatibility of Dental Medical Devices

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Biocompatibility refers to a material's ability to perform its intended function without causing significant adverse effects to the patient. Dental materials must be safe and nontoxic for patients, as well as for dentists and staff, and should not cause irritation, allergic reactions, or be carcinogenic. However, biocompatibility also refers to a material's ability to promote a beneficial cellular or tissue response while optimizing the therapy's clinical performance. Therefore, when assessing a material's biocompatibility, it is essential to consider both the reaction of the host tissue to the material and the material's effect to the host tissue.

The assessment of biocompatibility, also sometimes referred to as biological evaluation, is an interdisciplinary undertaking which draws on knowledge from fields such as materials science, bioengineering, biochemistry, molecular biology, and tissue engineering. At iFyber, we recognize the importance of this multidisciplinary approach and have a diverse team of scientists prepared to evaluate the biocompatibility of dental materials. By leveraging expertise from multiple fields, we are able to provide a comprehensive and robust assessment of any dental material's biocompatibility.

What is a medical device? What is a dental medical device?

In biocompatibility testing standards, two terms are used: "device" and "drug."

Device refers to a material, instrument, or occasionally a substance that achieves its intended use without requiring chemical reactions in the patient's body.

Drug refers to a substance that requires chemical and biochemical reactions in the patient's body for efficacy.

A dental medical device is any medical device that is used in dentistry.

For example, an anesthetic syringe is a medical device, but the contents of the anesthetic syringe are a drug. In some cases, a substance might be regulated as either a drug or a medical device, depending on its primary mode of action. For example, the U.S. Food and Drug Administration (FDA) classifies oral rinses as either cosmetic or therapeutic.

If the primary mode of action of an oral rinse is to create a physical barrier rather than to act chemically, it is considered a cosmetic rather than a therapeutic product and is regulated as a medical device. Medical devices are subject to specific regulatory requirements, but the regulatory requirements for drugs are more stringent.

What factors must be considered when evaluating dental materials' biocompatibility?

When evaluating the biocompatibility of dental medical devices, or dental medical device materials, the same basic principles apply as when evaluating the biocompatibility of any material. The properties of the material itself, as well as the host and the material's intended function, are all essential factors to consider.

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Material

A crucial aspect to grasp regarding biocompatibility is that there are no biomaterials that can be considered completely inert. When a material is placed inside living tissue, it interacts with the complex biological system around it, which leads to specific biological responses. The material affects the host, and the host also affects the material. Additionally, biocompatibility is dynamic, as the body may change through disease or aging, and the material itself may also change over time.

Host

When evaluating biological responses to dental materials, dentists must consider how various patient health factors and habits can become sources of variation for the same material.

For example, if a patient is diabetic or a smoker, their gingival responses to restorative materials could vary from the gingival responses of patients who are not diabetic or who do not smoke. High consumption of acidic drinks can also affect the properties of a material that comes into contact with a patient. Additionally, if a patient has a fully osseointegrated implant, it may not remain osseointegrated in their bone indefinitely.

The host's response to a material can change as well over time due to factors such as disease or aging. Changes to dental occlusions can also alter the forces applied to a dental material, which can result in the material's inability to maintain its desired biological response within the host.

Furthermore, a patient not allergic to nickel today may develop an allergy to it in the future. It's critical to consider the dynamic nature of biocompatibility and to account for changes that may occur over time to ensure each dental material's continued safety and efficacy.

Expected Function

It is important to remember that the biocompatibility of a dental material cannot be evaluated without considering its intended function.

For instance, a titanium implant used for replacing missing teeth gradually integrate with the bone over time, which enables the implant to function properly. However, if a cobalt-chromium alloy is placed in the exact same situation as the titanium implant, osseointegration will not occur; this does not mean that cobalt-chromium alloy is non-biocompatible or that titanium is always biocompatible. Rather, it simply means that titanium is a more biocompatible material than a cobalt-chromium alloy as a dental implant.

By contrast, a cobalt-chromium alloy has optimal biocompatibility compared to titanium when used as an orthopedic implant for hip arthroplasty because it is much harder than titanium and can perform well in orthopedic application.

Similarly, the expected function of one medical device might be to aid in the repair of the dentinal bridge (calcium hydroxide) or to aid in remineralization (CPP-ACP), while another medical device might be expected to have antibacterial properties (fluoride-releasing restorative materials). A biomaterial might be expected to be recellularized and degrade gradually (dermal graft), while another should maintain its solid structure (dental implant).

Overall, a dental material may be suitable for one application but not for another, so making a careful evaluation of its properties for each unique situation is critically important.

What are the current biocompatibility evaluation standards for dental medical devices?

The ISO 10993 series is the overarching set of ISO standards for evaluating medical device biocompatibility and applies to all medical devices, regardless of type or specialty.

ISO 7405, "Dentistry — Evaluation of biocompatibility of medical devices used in dentistry", describes biocompatibility tests specific to dental medical devices, which account for dentistry-specific needs.

Section 3.3 of ISO 7405 emphasizes,

"Many dental materials are used in a freshly mixed state, and evaluation of the materials in both freshly mixed and set conditions should be considered."

ANSI/ADA Specification 41, "Evaluation of Biocompatibility of Medical Devices Used in Dentistry", provides additional detailed guidance for United States dental professionals, scientists, and manufacturers on how to apply the guidance in ISO 7405 to dental products intended for distribution in the US. Both ISO 7405 and ANSI/ADA Specification 41 cross-reference ISO 10993 in many sections, and the introduction to ISO 7405 and ANSI/ADA Specification 41 states that they were designed to be used in conjunction with ISO 10993 series of standards.

The priority of minimizing the use of animals was considered when recommending test methods. To promote the development of *in vitro* and *ex vivo* test methods that reduce the reliance on animal testing for evaluating the biocompatibility of medical devices used in dentistry, Annexes B and C were added to the ANSI/ADA Specification 41. When all three standards are considered together, the completion of biocompatibility testing is just one component of an overall biocompatibility evaluation.

Why is it essential to use biocompatibility evaluation standards?

Due to the complexity of biocompatibility testing, it is essential to use standards. The outcome of a biocompatibility test is highly dependent on the design of the test, and different variables should be considered and controlled.

ISO 7405 encourages

"the development of *in vitro* and *ex vivo* test methods which will further reduce the use of animals in evaluating the biocompatibility of medical devices used in dentistry."

For instance, the result of a cytotoxicity test can be influenced by changing the ratio of the number of cells to the quantity of substance being tested. Standardization of biocompatibility testing enables reliable comparisons to be made between materials by specifying the exact test parameters while controlling for other relevant variables. Since important decisions about material safety and performance are made based on the results of these tests, standardization is necessary for minimizing errors and achieving accurate results.

For example, standardization of biocompatibility testing makes it possible to objectively assess the biocompatibility of a new device compared to a gold standard or predicate device and thereby determining the suitability of the new device for its intended applications.

How should you use the standards to evaluate the biocompatibility of your dental medical device?

Whereas ISO 7405 and ANSI/ADA Specification 41 focused primarily on which dentistry-specific tests need to be done based on the nature and duration of body contact, ISO 10993 takes a broader approach of completing a whole series of prerequisite steps and gathering numerous pieces of prerequisite data, prior to tackling the question of what biocompatibility testing needs to be done and how it will be performed.

Therefore, in terms of an end-to-end, chronological process flow for using ISO 10993 and ISO 7405 together, iFyber recommends first starting with answering one question as shown in Figure 1 (ISO 10993 decision flowchart): "Does the device contact the body directly or indirectly?"

If the answer is YES, you must obtain physical/chemical data (ISO 10993-18&19) and determine if the new device has the same material formulation, manufacturing process, geometry or physicochemical properties, and same body contact and clinical use as the marketed device.

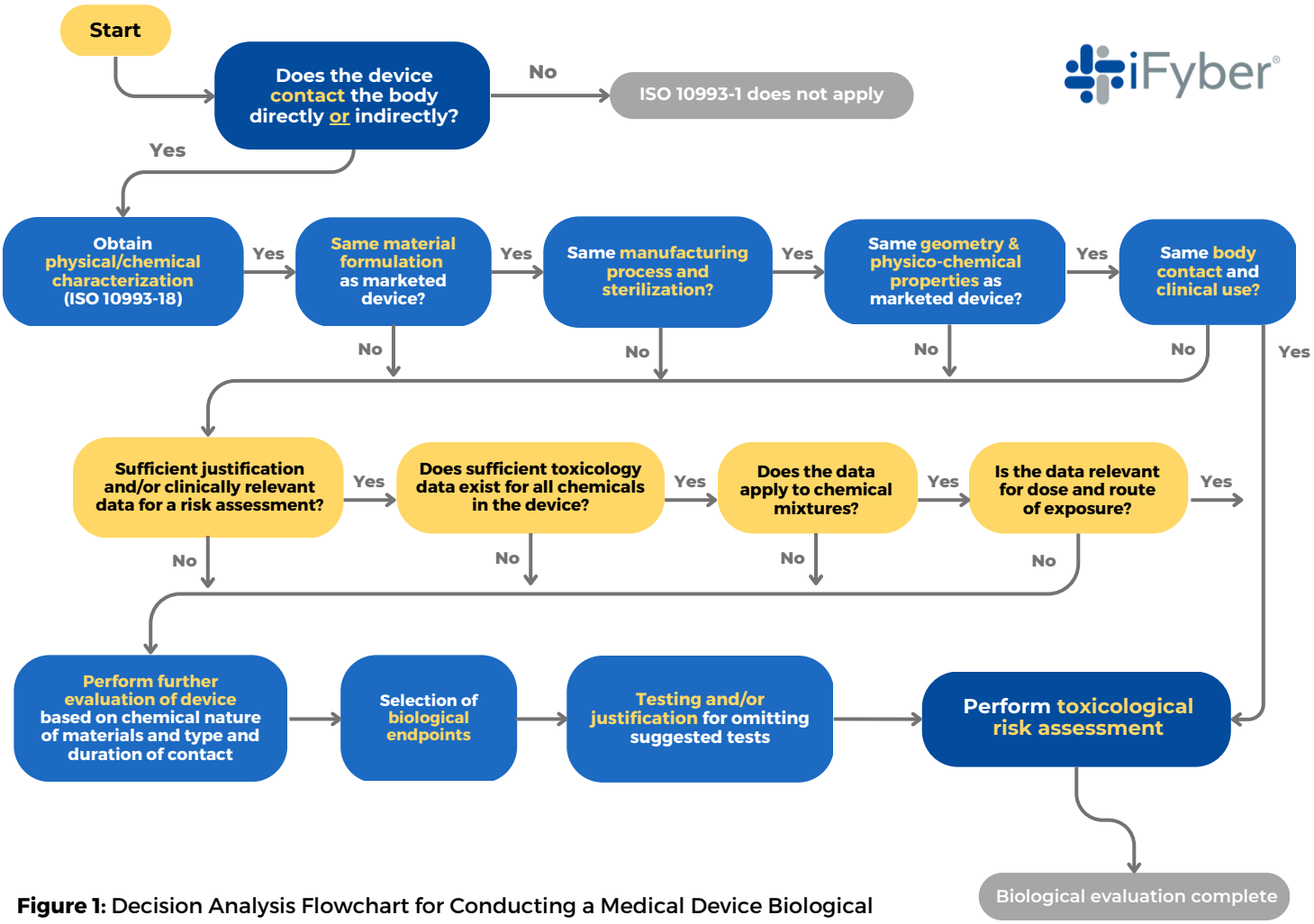

Figure 1: Decision Analysis Flowchart for Conducting a Medical Device Biological Evaluation as Part of a Risk Management Process (ISO 10993-1:2018).

To determine body contact, you need to go through Table 1.

Determine nature of body contact:

The standard categorizes medical devices based on the nature of body contact as follows: 1) devices in contact with the external surface of tissues (pit and fissure sealants, orthodontic wires, or fluoride-containing varnishes); 2) devices that can penetrate hard or soft tissues but are exposed to the oral environment (dental restorative materials); and 3) implanted devices that are entirely enclosed in the tissue (dental implants, bone substitutes, endodontic materials). Also, the type of tissue with which the substance is in contact is crucial. For example, a headgear device is in contact with the skin, while acrylic retainers are in contact with the mucous membrane, and composites are in contact with dentin.

Determine the duration of body contact:

The requirements of the tests also depend on the duration of the contact with the body. Contact duration is divided into 1) Limited (less than 24 hours, such as impression materials); 2) Prolonged (24 hours to 30 days, provisional restorations); and 3) Permanent (more than 30 days; restorative materials).

Table 1: Biocompatibility Evaluation Endpoints to be Addressed in a Biological Risk Assessment (ISO 10993-1:2018).

Medical Device Categorization by			Biological Effect														
Nature of Body Contact		Contact Duration	Physical/Chemical Information	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Material-Mediated Pyrogenicity	Acute Systemic Toxicity	Subacute Toxicity	Subchronic Toxicity	Chronic Toxicity	Implantation	Hemocompatibility	Genotoxicity	Carcinogenicity	Reproductive/Developmental Toxicity	Degradation
Category	Contact	A – Limited (≤ 24 h) B – Prolonged (24 h to 30 days) C – Permanent (> 30 days)															
Surface Device	Intact skin	A	X	E	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal Membrane	A	X	E	E	E											
		B	X	E	E	E		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or Compromised Surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		
External Communicating Device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/bone/ dentin	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
Implant Device	Tissue/bone	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

NOTE 1: X indicates prerequisite information needed for a risk assessment.

NOTE 2: E indicates endpoints to be evaluated in the risk assessment (either using existing data, additional endpoint-specific testing, or a rationale for why assessment of the endpoint does not require an additional data set). If a medical device is manufactured from novel materials, not previously used in medical device applications, and no toxicological data exists in the literature, additional endpoints beyond those marked "E" in this table should be considered. For particular medical devices, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated.

As shown in Figure 1, if the new device has the same material formulation, manufacturing process, geometry or physicochemical properties, and same body contact and clinical use as the marketed device, you just need to perform the toxicological risk assessment. If there is some difference in one of the above mentioned processes or characteristics, you need to answer several more questions to figure out if performing a toxicological risk assessment is enough or if you need to perform further evaluation of the device based on the chemical nature of the product and type and duration of contact.

Based on the type and duration of contact, section 5 of ISO 7405 determines which tests you need to perform to assess the biocompatibility of your dental material (Table 2).

Group I

Group I are *in vitro* tests of cytotoxicity, including 1) agar diffusion test; 2) filter diffusion test; 3) direct contact or extract tests in accordance with ISO 10993-5; and 4) dentine barrier cytotoxicity test.

Group II

Group II includes 1) acute systemic toxicity — oral application — in accordance with ISO 10993-11; 2) acute systemic toxicity — application by inhalation — in accordance with ISO 10993-11; 3) subacute and subchronic systemic toxicity — oral application — in accordance with ISO 10993-11; 4) skin irritation and intracutaneous reactivity in accordance with ISO 10993-10; 5) delayed-type hypersensitivity in accordance with ISO 10993-10; 6) genotoxicity in accordance with ISO 10993-3; and 7) local effects after implantation in accordance with ISO 10993-6.

Group III

Finally, Group III considers 1) pulp and dentine usage test; 2) pulp capping test; 3) endodontic usage test; and 4) endosseous dental implant usage test.

Table 2: Types of Biocompatibility Tests to be Considered for Evaluation of Dental Medical Devices (ISO 7405).

	Contact Duration	General	Group I			Group II					Group III				
Nature of Body Contact	A – Limited (≤ 24 h) B – Prolonged (24 h to 30 days) C – Permanent (> 30 days)	Physical and chemical data ISO 10993-18 ISO 10993-19	Cytotoxicity ISO 7405, 6.2 and 6.3	Cytotoxicity ISO 10993-5	Cytotoxicity ISO 7405, Annex B	Delayed-type Hyper-Sensitivity ISO 10993-510	Irritation or Intra-Cutaneous Reactivity ISO 10993-10	Acute Systemic Toxicity ISO 10993-11	Subchronic (Subacute) Toxicity ISO 10993-11	Genotoxicity ISO 10993-3	Implantation ISO 10993-6	Pulp and Dentine Usage Test ISO 7405, 6.4	Pulp Capping Test ISO 7405, 6.5	Endodontic Usage Test ISO 7405, 6.6	Endodontic Usage Test ISO 7405, Annex C
Surface Device	A	X	X	X		X	X								
	B	X	X	X		X	X								
	C	X	X	X		X	X		X	X					
External Communicating Device	A	X	X	X	X	X	X					X			
	B	X	X	X	X	X	X	X	X	X	X	X			
	C	X	X	X	X	X	X	X	X	X	X	X			
Implant Device	A	X	X	X		X	X						X		
	B	X	X	X		X	X	X	X	X	X		X	X	X
	C	X	X	X		X	X	X	X	X	X		X		X

NOTE 1: X indicates test shall be considered for use.
NOTE 2: This table is a framework for the development of an assessment program and is not a checklist.

Overall, the extent to which a dental medical device requires biocompatibility testing depends on the type(s) of material(s) the device is made of, the end use of the medical device, and the availability of existing biocompatibility data for similar devices.

How can iFyber help with the biocompatibility evaluation of your dental medical device?

The FDA relies on ISO standards to evaluate the safety and efficacy of dental medical devices, while the ADA requires an independent body of scientific experts to assess a dental medical device objectively to determine which devices meet the criteria for the ADA Seal of Acceptance. We will assist you in evaluating the biocompatibility of your novel dental material, whether it is a device developed with osteogenic/odontogenic functions, remineralization or antibacterial properties, membranes for GTR/GBR, or any other dental innovation.

Communicate your goals, and we will work with you to ensure your device testing meets the required standards. Our iFyber scientists and services team is ready to partner with you to help your product achieve FDA approval and the ADA Seal of Acceptance, as well as better patient outcomes.

At iFyber, we also provide comprehensive data packages covering all stages of material development, from initial front-end design input testing to animal and clinical studies evaluating the material's final performance characteristics.

Let us know what your goal is, and we will work with you to meet it.

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3. *ANSI/ADA Specification No. 41, Recommended Standard Practices for Biological Evaluation of Dental Materials*
4. *ISO 10993-1:2018, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.*