WHITEPAPER

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Biological Equivalence and the EU MDR

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Table of Contents

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Executive Summary

In connection with biological equivalence, the MDR states, "the device uses the same materials or substances in contact with the same human tissues or body fluids for a similar kind and duration of contact and similar release characteristics of substances, including degradation products and leachables." The intent behind using an equivalence strategy in the EU is to leverage the clinical data from the equivalent device via an assessment of risks arising out of any potential similarities or differences that may have an impact of the established safety/performance profile of the equivalent device.

Manufacturers have found this to be a mysterious aspect of the MDR and are compiling their technical documentation with much uncertainty around the acceptability of their biological equivalence strategies.

This paper, authored by a leader in notified body BSI through Jan 2021, provides insight into the notified body review process and expectations for biological equivalence. It begins with an overview of the EU MDR requirements for biological safety evaluation, and practical approaches to establishing biological equivalence. A very detailed table of potential methodologies to demonstrate biological equivalence is presented. For each of the common scenarios of material differences, the author estimates the likelihood of acceptance by the notified body and suggests actions to take to increase the likelihood of acceptance, including rationales, testing, design documentation.

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Introduction

Typically, medical devices comprise multiple components, each with mutually exclusive physical and chemical profiles. To address this inherent varying complexity, risk of injury and toxic effects to the human, notified bodies (NBs) expect a biological safety evaluation process under the aegis of the manufacturer's risk management process and QMS with application of the recommendations of ISO 10993 series.

However, blind adherence to the matrix of tests listed in Figure 1 of ISO 10993-1:2018 per device categorization, tends to be a less targeted, sub optimal approach. For example, for a non-implantable device, strict adherence to only the test matrix of biocompatibility tests may result in lack of quantitative and qualitative chemical characterization addressing the presence of colorants, fillers, plasticizers, etc., risks due to direct/indirect contact with users may lead to incorrect, time consuming, extensive biological endpoints-based biocompatibility testing without providing a comprehensive understanding of the safety profile of the device.

Thus, it is important to bear in mind that while the test matrix is a useful tool for endpoint selection, it is not a conclusive set of activities when it comes to biological safety evaluation. Consequently, the latest version of ISO 10993-1 has been revised to lay emphasis on material physical and chemical characterization (Annex A).

Per the MDR, biological safety evaluation by way of physical and chemical characterization and the relevant biological endpoint-based biocompatibility testing is expected to establish the overall biological safety profile of any subject device under review. This testing is also important when a manufacturer wants to claim biological equivalence to another device. Please bear in mind, that the NB reviewer will only progress towards assessing biological equivalence once they are convinced of the objective evidence supporting the biological safety profile of the subject device. In connection with biological equivalence, the MDR (Annex XIV (3)) states, "the device uses the same materials or substances in contact with the same human tissues or body fluids for a similar kind and duration of contact and similar release characteristics of substances, including degradation products and leachables."

MDCG 2020-5, Clinical Evaluation – Equivalence, notes that "the exceptions, outlined in the MEDDEV 2.7/1 rev 4, to not use the same materials are NOT acceptable under the MDR." MDCG 2020-5 also provides additional guidance and importantly states, "The distinction between "same materials or substances" and "similar release characteristics of substances" is made to account for the fact that processing, design and the use environment may introduce small changes even when the raw materials are the same."

Therefore, it is important to consider chemical characterization testing when evaluating biological equivalence. It is also worth noting that having different materials that are considered biologically safe does not mean they automatically satisfy the requirements of biological equivalence.

Approach to Equivalence in the EU

The intent behind using an equivalence strategy in the EU is to leverage the clinical data from the equivalent device via an assessment of risks arising out of any potential similarities or differences that may have an impact of the established safety and performance profile of the equivalent device.

Please note that the EU's process of evaluating equivalence is very different from a typical US FDA 510K style equivalence table, which typically stops with an identification of same/similar (sometimes manufacturing related differences tend to be ignored). Irrespective of device classification, NB reviewers approach equivalence (all three aspects of technical, clinical, and biological) in three phases:

Phase 1 is a review of items that are identical with the equivalent device

Phase 2 is a review of items that are similar (but not identical)

Phase 3 is where the reviewer seeks to identify the risks arising out of differences between the devices and the impact of these risks on successfully leveraging the clinical data of the equivalent device.

To this end, the approach to biological equivalence must be focused on discussing the most relevant material-based device performance parameters and their impact on corresponding device performance parameters and eventually the clinical outcomes. Ideally, the focus should be on specific material-related biological equivalence items that have an impact on clinical outcomes and not on every 'cyanoacrylate glue' that may be different (which will have been comprehensively addressed via the overall biological safety evaluation reviewed prior to the biological equivalence discussion) but most importantly on clinically relevant items.

To infer, such an approach is critical to ensure that we focus on specific material-related biological equivalence items that have an impact on clinical outcomes.

Approach to Equivalence in the EU

The table that follows provides a general overview of ways to approach biological equivalence and the potential likelihood of success. The key considerations behind creating this table are:

- **What role does the different material / component have with respect to device safety and performance?**
- **What is the expected impact of the material differences on leveraging the clinical data of the equivalent device?**

Where applicable, the manufacturer should provide a risk assessment based on a scientific justification/experimental evidence comprising chemical and physical characterization data (sometimes to the extent of toxicology risk assessment outcomes).

Potential Methodologies to Demonstrate Biological Equivalence

This table assumes all the relevant items are patient contacting materials

Material difference	Likelihood of acceptance and potential considerations for demonstrating biological equivalence of a transient/short term device Note: "transient" intended as MDD/MDR classification (i.e. less than 60 mins), different from "transitory contact" per ISO 10993-1:2018 (see closing comments further below)	Likelihood of acceptance and potential considerations for demonstrating biological equivalence of an implant
Different grade/formulation of the same material (e.g., different durometers or different degrees of crystallinity)	May be acceptable if the manufacturer follows the principles stated in ISO 10993-17/18:2020 Annex C and address (scientific justification/objective evidence) any differences in the following: • Source, supplier, supplier location, material specification • Chemical formulation, processing, primary packaging, or sterilization of the product • Storage considerations, e.g., changes in shelf life and/or transport • Adverse effects profile in humans • Functional performance of the device • Biological safety evaluation at the end of the device shelf life	May be acceptable, if the manufacturer can provide evidence showing that the composition and processing do not result in additional or different toxicological concerns. Specifically, the release characteristics of substances should be similar and the resulting margin of safety (MoS) values from the tox assessment should be like those obtained for the claimed equivalent device. Note: When extractables & leachables (E&L) testing results are available and there are many non-identified compounds (usually referred to as "unknowns" in extraction studies), these should be evaluated within the toxicology assessment against acceptable toxicological thresholds (see paragraphs below). To claim equivalence between materials and therefore conclude on biological equivalence between devices, there should not be a higher risk of unknown substances potentially leaching from the subject device compared to the claimed equivalent one.

Potential Methodologies to Demonstrate Biological Equivalence

This table assumes all the relevant items are patient contacting materials

Material difference	Likelihood of acceptance and potential considerations for demonstrating biological equivalence of a transient/short term device	Likelihood of acceptance and potential considerations for demonstrating biological equivalence of an implant
Different type of the same material (e.g., varying densities of polyethylene, or different types of Nylon or Polyurethanes or cyanoacrylate glues or resins)	May be acceptable, based on outcomes of the risk assessment and objective evidence comprising chemical and physical characterization data along with toxicology assessment outcomes. Special focus should be placed on the risks arising out of differences in material specifications, overall chemistry, surface area, surface morphology, processing/ cleaning aids, sterilization, and biological safety evaluation at the end of the device shelf life.	May be unacceptable unless the manufacturer can show that despite the different chemical and physical properties the local tissue response and long term effects are not different.
Same material, different processing (e.g., different passivation or different degrees of crosslinking, same material)	May be acceptable with evidence of the following items: • The release characteristics of substances remain similar (quantitative and qualitative material characterization through analytical testing will most likely be required regardless of duration of contact since there is no better way to address processing differences). The resulting toxicology assessment must conclude that there are no additional toxicological concerns or significant difference in MoS. • The final device and blood contacting surface-chemistry, area and morphology are unchanged. • The items impacting material interactions within the same device and lifetime considerations are unchanged, such as polymer glass transition temperatures, oxidative degradation products (e.g., Laurolactams that show up as Pebax and Nylon undergo oxidative degradation thus raising the toxicity profile over time), degradation kinetics, and resorption rates • Biological safety evaluation at the end of the device shelf life	May be acceptable along with all the adjacent items (assuming that biological safety has been established)

Potential Methodologies to Demonstrate Biological Equivalence

This table assumes all the relevant items are patient contacting materials

Material difference	Likelihood of acceptance and potential considerations for demonstrating biological equivalence of a transient/short term device	Likelihood of acceptance and potential considerations for demonstrating biological equivalence of an implant
Different material Note: Difference/s in material/s should be discussed in detail unless the component involved clearly has a minor / negligible role in terms of safety and performance.	May be acceptable. Importantly, the justification should not rely solely on biological endpoint-based biocompatibility tests, and must address considerations of chemical composition, release characteristics and consequent toxicological risk. The manufacturer should discuss the risk assessment focused on the following items: • Where in the body is the material going to be used? Typically, a large animal study designed to gather data around the typical relevant biological endpoints is sufficient. • How long is the material going to be in contact with the body? The animal data is expected to be at least 2 times the expected duration. • How much of the material is going to be in contact with the body or body fluids? For example, most vascular devices are blood contacting bringing quantitative and qualitative material characterization, especially, E&L prominently into focus. • What effect is the material going to have on the body? As stated above, E&L and toxicological assessment must be considered. • Any evidence that the materials are acceptable for the intended use along with any historical use of material in this intended use/application?	Unacceptable

Potential Methodologies to Demonstrate Biological Equivalence

This table assumes all the relevant items are patient contacting materials

Material difference	Likelihood of acceptance and potential considerations for demonstrating biological equivalence of a transient/short term device
Different processing agent or cleaning agent	May be acceptable. Discuss the risk assessment and risk mitigation for any potential impact on the final device morphology, surface chemistry and/or potential residues. If the overall biological safety assessment demonstrates that the material/chemical differences have no impact on the final device morphology, chemistry and no difference in residuals (chemical characterization testing outcomes like the claimed equivalent device or significantly high MoS in tox assessment).
Different "minor" component	May be acceptable if you are able to demonstrate the component is truly minor with no impact on device performance and safety. The definition of a "minor" component can be very tricky. This item would only be discussed for biological equivalence if it has a significant impact on the expected device function from a material perspective and therefore, the eventual clinical outcome. Otherwise, it can be sorted under technical equivalence.However, please note that such an item can become critical when it comes to evaluating significant changes as opposed to initial CE marking reviews. Note: Justifying biological equivalence based on the component involved being "minor" might be considered in contrast with MDCG 2020-5, which states that the exceptions in MedDev 2.7/1 rev.4 for skin contacting and "minor components" are NOT acceptable under MDR. This should be carefully evaluated on a case-by-case basis.
Different colorant	May be acceptable if the quantitative and qualitative chemical characterization data associated with the E&L profile and the related toxicological risk assessment of the proposed new colorant is not worse than the clinically established material.
Change to any non-patient contacting parts of the device	May be acceptable but should be considered on a case-by-case basis depending on the interactions with the patient contacting device components, potential impact of sterilization and degradation over time and relevant lifetime considerations.

Comment on Devices with Extremely Limited Contact with Patients

Categorization per duration of contact is slightly different between MDD/MDR and ISO 10993-1. The most recent version of ISO 10993-1 now defines "transitory contacting devices" as medical devices with very brief/transitory contact with the body (e.g., lancets, hypodermic needles, capillary tubes that are used for less than one minute). It is stated that these generally would not require testing to address biocompatibility unless they are made with coatings or lubricants that could be left in contact with body tissues after the medical device is removed. This suggests that release characteristics are generally considered less relevant when contact duration is so limited. Based on this, one could consider the release characteristics of materials less relevant when assessing biological equivalence for the transitory contacting devices.

About the Author

Dr. Jaishankar Kutty presents a unique blend of expertise combining cardiovascular product development and CE marking (technical & clinical) leadership with a keen appreciation for the rapidly evolving cardiovascular device and medical device regulations landscapes. His comprehensive cardiovascular device experience spans product development, advanced biomechanical testing, preclinical model development, physician training, FDA interactions, implantable device commercialization and patents.

Over the past seven years he has held CE marking technical and clinical leadership roles at BSI. He has been involved in biological safety evaluations via chemical characterization and biological endpoint-based biocompatibility testing, both as part of industry and as a CE marking technical expert at BSI. His industry experience involving biological safety evaluations spans chemical characterization activities in St. Jude Medical Inc.'s (now Abbott Medical) analytical chemistry lab and the development of biocompatibility strategies supporting regulatory submissions for heart valve repair/replacement products, across multiple geographies. At BSI, he has reviewed numerous submissions involving biological safety evaluations and has trained several technical team members on the nuances of biocompatibility assessments and the ever-evolving ISO 10993 standards.

In January of 2021, Jai joined RQM+ as the VP of Clinical Services. In this role, Jai provides leadership and technical support to both RQM+ clients and internal teams with the interpretation and implementation of EU medical device regulations. Jai's deep technical and clinical understanding of devices combined with his extensive regulatory knowledge and notified body insight make him a fantastic leader in the RQM+ Clinical Regulatory Affairs Team.

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