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Pharmaceutical Sciences
Volume 4 Issue 1, 2024
eISSN No.: 2582-8371

Current Practices in Biocompatibility Assessment of Medical Devices

Tirumala Devi. K[1*], Prasada Rao. M[2], M. Charishma Padma Priya[3]
[1]Associate Professor, Department of Pharmaceutics, MAM College of Pharmacy, Narasaraopet, Palnadu (Dt), Andhra Pradesh, India-522601.
[2]Professor cum Principal, Department of Pharmaceutical Analysis, MAM College of Pharmacy, Narasaraopet, Palnadu (Dt), Andhra Pradesh, India-522601.
[3]Research Scholar, Department of Pharmaceutical Regulatory Affairs, MAM College of Pharmacy, Narasaraopet, Palnadu (Dt), Andhra Pradesh, India-522601.

****Corresponding Author***
Email Id: bobby.indlamuri@gmail.com

ABSTRACT
Medical device safety is guaranteed by biocompatibility testing, which evaluates a device's suitability for biological systems as well as its potential for injury or unfavourable reactions. As a result, it is essential to the process of overall safety evaluation for medical equipment. Almost all medical devices require one of three main types of biocompatibility tests: cytotoxicity, irritation, or sensitization assessment. However, depending on the type of device and how it will be used, more biocompatibility testing, like genotoxicity, systemic toxicity, hemocompatibility, and implantation studies, might also be required. Although some of the testing is done in vitro, animal studies are still used extensively in this business. The use of alternatives in medical device biocompatibility testing has progressed noticeably more slowly than in other industrial areas. The lack of customized validation procedures is the reason for this delay.

Keywords: *Medical device, hemocompatibility, sensitisation, irritation, cytotoxicity.*

INTRODUCTION
To guarantee the safety and compatibility of medical devices with biological systems, biocompatibility testing is an essential part of the development and regulatory approval processes. The "Big Three" assessments- cytotoxicity, irritation, and sensitization testing are essential to this testing and are required for practically all medical devices that are released onto the market. The "Big Three" continue to be the mainstay of the biocompatibility assessment, while additional tests may be required depending on the type of medical device and its intended application.

In order to determine the safety and effectiveness of pharmaceuticals and medical equipment before they are used on humans, animals have been employed in medical research throughout history. However, animal testing raises a number of ethical concerns and is still a contentious issue in the public eye. The medical device industry understands the possibility of new methodologies that could expedite and streamline the safety testing process, even though these established procedures remain essential for safety assessment.

The ISO 10993-1:2018 standard states that animal testing is only warranted in cases when in vitro research and current scientific data are insufficient to allow for a thorough evaluation of a medical device's safety (ISO 10993-1:2018, 2018) [1-2]. Additionally, when conducting

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Volume 4 Issue 1, 2024
eISSN No.: 2582-8371

required animal testing, ISO 10993-2:2022 specifies the minimal conditions required to guarantee and justify the ethical treatment and care of animals (ISO 10993-2:2022, 2022) [3-4].

Regretfully, the adoption of alternative methods in medical device biocompatibility testing has been noticeably sluggish in comparison to other industrial sectors. The lack of specific validation procedures designed for medical devices and the ensuing regulatory doubt and hesitancy about these alternatives' ability to predict outcomes, even in spite of their successful use in other fields, are to blame for this delay.

The Big Three biocompatibility tests for medical devices are examined in detail in this paper, along with the advancements and difficulties in using alternate approaches for cytotoxicity, irritation, and sensitization testing. Our goal is to clarify the rationale behind this cautious approach and discuss possible ways to speed up the medical device industry's adoption of alternative biocompatibility testing methods.

Regulatory Frame Works

Adherence to both domestic and global biocompatibility testing mandates is crucial for regulatory clearance and the secure operation of medical devices in healthcare facilities, hospitals, or by unsuspecting end users. Each nation or region has different laws governing biocompatibility testing and medical devices. Nonetheless, industry widely acknowledges and abides by a number of common worldwide standards and laws. The following are important laws and guidelines pertaining to the biocompatibility assessment of medical devices:
Medical device biocompatibility evaluation guidelines and requirements are provided by the worldwide standardized ISO 10993 series of standards, which were created by International Organization for Standardization Technical Committee 194 (ISO/TC 194) [5].

The ISO 10993 standards address a number of biocompatibility testing topics, such as genotoxicity, cytotoxicity, sensitization, irritation, and more. These standards are frequently referred to by manufacturers when performing biocompatibility testing and evaluating the safety of their medical equipment

The OECD test guidelines (TGs) can be applied in certain situations.
The extensive set of guidelines known as OECD TGs is largely intended to evaluate the safety of chemicals and mixtures, and it is a crucial component in the assessment of some medical device features. Although these recommendations provide a standardized method for safety assessments, according to ISO standards, medical devices frequently need extra, more focused studies [6-9].

Food and Drug Administration

The Food and Drug Administration (FDA) is the American regulatory body in charge of managing medical devices. Though it does not fully recognize all ISO 10993 standards, the FDA does have particular laws pertaining to biocompatibility testing, including guidelines documents and standards that correlate with ISO 10993 [10].

In order to receive FDA clearance or approval for their regulatory submissions, manufacturers are required to include biocompatibility data.

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Volume 4 Issue 1, 2024
eISSN No.: 2582-8371

European Medicine Device Regulation

The European Medicine Device Regulation (MDR) is a thorough regulatory framework that oversees medical devices inside the European Union. It includes specifications pertaining to biocompatibility testing. In order for manufacturers to get CE markings for their equipment, they have to follow this law. The MDR describes the standards for biocompatibility assessment and makes reference to ISO 10993 standards [11].

Pharmaceuticals and Medical Devices Agency

Japan's PMDA, or Pharmaceuticals and Medical Devices Agency, is in charge of regulating medical devices. The PMDA complies with worldwide rules and standards when it comes to biocompatibility testing criteria. Manufacturers who want to get their gadgets approved in Japan have to follow these rules and submit biocompatibility information. Health Canada Regulations: In Canada, medical devices are subject to regulation by Health Canada. To have their devices approved, manufacturers have to comply with the Medical Devices Regulations (MDR) and provide biocompatibility information. These rules comply with ISO 10993 and other international standards.

Numerous additional nations own their own regulatory bodies and mandates concerning medical devices and biocompatibility testing.

In order to guarantee that their gadgets comply with local laws, manufacturers should speak with the appropriate regulatory bodies in each nation where they plan to sell their products. Manufacturers of medical devices are required to be aware of and abide by the particular laws and guidelines that apply to their goods.

To comply with these regulations, manufacturers usually collaborate closely with regulatory specialists and contract research organizations (CROs) that specialize in biocompatibility testing. Unfortunately, despite several attempts, the lack of consensus in the sector has led to misunderstandings and some degree of uncertainty in the testing of requirements and final evaluations.

The terms "Big Three" pertain to tests for cytotoxicity, irritation, and sensitization. Regardless of category, patient contact, or length of use, testing for these three biological impacts is necessary for the majority of medical devices [6].

Most medical gadgets are examined as prepared extracts. Simply submerging the apparatus or its parts in a suitable extraction solvent, such as vegetable oil, physiological saline, or cell culture medium, in the given circumstances. The extraction procedure is a conventional technique used to determine whether or not medical devices are biocompatible by analyzing the possible release of chemicals that may interact with biological systems. You can find information on extract preparation in ISO 10993-12 [3].

Cytotoxicity Testing

The primary purpose of cytotoxicity testing is to assess whether a medical device’s materials and components can potentially cause harm to living cells. This testing helps determine whether the device or its extracts are safe for use in contact with biological systems, such as human or animal tissues and cells. It is crucial to ensure that the device does not harm cells when it contacts the body, as this can lead to adverse effects and complications. Cytotoxicity testing, as specified in ISO 10993-5:2009 is essential for biocompatibility assessment of

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eISSN No.: 2582-8371

medical devices. The standard provides guidance and requirements for evaluating the cytotoxic potential of materials used in medical devices [12].

***In vitro* test methods and protocols:** ISO 10993-5 provides specific test methods and protocols for conducting cytotoxicity testing. These methods typically involve exposing cultured mammalian cells to extracts of the medical device or its materials for approximately 24 h. Commonly used cell lines for cytotoxicity testing include Balb 3T3 (fibroblasts), L929 (fibroblasts) and Vero (kidney-derived epithelial cells). Cytotoxicity testing evaluates various endpoints to assess cell viability and adverse cellular reactions. The primary endpoints include:

1) Cell viability: This measures the extent to which cells exposed to the device extracts survive and proliferate compared to control cells.
2) Morphological changes: Any changes in cell shape or structure are noted.
3) Cell detachment: The degree of cell detachment from the culture substrate is assessed.
4) Cell lysis: The presence of cellular debris or cell membrane damage is evaluated.

Based on these endpoints, cytotoxicity is typically categorized as non-cytotoxic, mildly cytotoxic, moderately cytotoxic, or highly cytotoxic. The following methods are commonly used to determine quantitative cell viability for these categories: MTT (3-(4,5-dimethylthiazol- 2-yl)-2,5-diphenyl-2Htetrazolium bromide), XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)- 2H-tetrazolium-5-carboxanilide), and neutral red uptake. Other less frequently used methods are the Bradford protein, Chrystal violet, Resazurin dye, and Trypan blue assays [13].

Acceptance Criteria

ISO 10993-5 does not define specific acceptance criteria for cytotoxicity testing; however, its Annex V provides guidance for data interpretation, where protocols are detailed. This ISO standard emphasizes that the acceptance criteria should be defined based on the nature of the medical device, its intended use, and potential patient exposure. If cytotoxicity is observed, further testing should be conducted to better understand the influence of the test conditions on the result. Any cytotoxic effect can be of concern; however, the medical device cannot necessarily be determined unsuitable for a given clinical application based solely on cytotoxicity data. On the other hand, 70% cell survival (cell viability) and above can be seen as a positive sign, especially when testing neat extract.

Relevance to Regulatory Compliance

According to ISO 10993-5, cytotoxicity testing is a fundamental component of the biological evaluation of medical devices. It is the primary test required by regulatory authorities such as the US FDA, European Medicines Agency (EMA), PMDA, and other national agencies. Manufacturers use the results of cytotoxicity testing to support regulatory submissions and demonstrate the safety of their devices.

While ISO 10993-5 does include in vitro cytotoxicity testing as a central component of biocompatibility evaluation, it is part of a broader framework that considers various aspects of biocompatibility, including other in vitro and in vivo tests, as well as risk assessment. The specific tests and evaluations conducted for a given medical device will depend on its characteristics and intended use to ensure its safety and compatibility with biological systems.

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IRRITATION TESTING:

The ISO 10993-23:2021 standard provides updated guidance for assessing the skin irritation potential of medical devices [3]. A key aspect of this standard is its strong support for the in vitro reconstructed human epidermis (RhE) assay as the preferred method over traditional in vivo animal tests. This shift aligns with ethical efforts to reduce animal testing and reflects a combined industrial and regulatory commitment to advancing biocompatibility evaluation methods. Based on the old ISO 10993-10:2010 standard, which concerned skin irritation and sensitisation, ISO 10993-23:2021, was developed thanks to over a decade of collaborative effort by industry partners validating the RhE assays for medical devices.

This collaboration led to the ISO/TC 194s decision to update and separate these two endpoints into distinct standards – ISO 10993-23:2021 for irritation and ISO 10993-10:2021 for sensitization testing needs of the medical device industry [3].

ISO 10993-23:2021's in vitro test methods: *In vitro* test methods and protocols within ISO 10993-23:2021 describe specific procedures for skin irritation assessments using advanced models (ISO 10993-23:2021, 2021). The standard endorses validated RhE models EpiDerm and Skin Ethic RHE. These three-dimensional, cultured skin models closely replicate human epidermal tissue's barrier properties and structure, making them highly relevant for irritation and intracutaneous testing. Their applications extend to various regulatory domains, including skin corrosion, irritation, and phototoxicity evaluations for chemicals, cosmetics, and drugs, as delineated in OECD TG 431, 439, and 498 and ICH S10 [7-9,11].

The potential for RhE models to replace traditional animal testing was highlighted by Casas *et al* [14] which demonstrated their ability to identify chemical irritants in medical device extracts. This work spurred ISO/TC 194 to encourage further development and validation of these methods. A key initiative was a global round robin study designed to assess the RhE models' predictive capability in identifying irritating properties of medical device extracts. For this study, three organisations provided positive and negative samples of medical device polymers; in addition, human patch tests were conducted alongside for comparative analysis.

The comprehensive results of this study, conducted by 23 laboratories worldwide between 2015 and 2017, along with other related scientific findings, and were published in a special medical device issue of Toxicology In vitro (2018). These results led to the creation of ISO 10993- 23:2021 by ISO/TC 194s Working Group 8 for Irritation and Sensitization [15-19].

The validated testing protocols of ISO 10993-23:2021 involve an 18–24 h exposure of the RhE models to medical device extracts, followed by assessments of cellular damage and inflammatory responses. These assessments are typically conducted using cell viability assays, such as the MTT test, and cytokine release profiling, ensuring a robust and comprehensive evaluation of a material's irritation potential.

Acceptance Criteria: The assessment of tissue viability via cytotoxicity testing plays a pivotal role in determining the irritation potential of medical device extracts or topically applied formulations. The primary indicator of irritation is the reduced viability of cells within the RhE model. A decrease in cell viability below 50% is considered a sign of irritation.However, a significant decrease in viability, when coupled with a notable increase in interleukin-1 alpha (IL-1α), can also indicate tissue inflammation. In addition, the reliability of RhE models was further confirmed by parallel testing conducted with human

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Volume 4 Issue 1, 2024
eISSN No.: 2582-8371

volunteers and comparative analysis with existing rabbit data which demonstrated that RhE models closely mirrored the predictions of traditional rabbit intracutaneous skin tests (Kandarova et al., 2018b). This agreement underscored the high sensitivity and predictive accuracy of RhE models in assessing the irritation potential of medical devices, making them a robust alternative in biocompatibility testing.

Relevance to Regulatory compliance

For the vast majority of medical device manufacturers, complying with ISO 10993-23:2021 has become critical for achieving regulatory compliance in major international markets. Consequently, this new standard has been rapidly adopted CROs. However, the regulatory landscape is not uniform. While Europe and Asia have embraced in vitro testing, the US FDA has yet to recognize the in vitro testing sections of the standard and still requires irritation data from rabbits (FDA, 2021). The medical device industry is working with FDA to satisfy its request for dual data from the in vitro RhE assays and in vivo rabbit tests, along with data from previous validation studies for chemicals and cosmetics (De Jong et al., 2020). This divergence in regulatory requirements between Europe, Asia and the U.S. presents a significant challenge for the medical device industry, creating a situation of dual testing. Such discrepancies not only complicate the global compliance process, but also have significant impacts on the costs and efficiency of testing. This situation underscores the need for global harmonisation in medical device testing standards, which is crucial for streamlining the approval process and reducing unnecessary financial and procedural burdens.

Sensitization Testing

Sensitisation testing is critical in evaluating medical devices and their materials for potential allergic or hypersensitivity reactions. This testing aims to determine if a device can sensitise the immune system, leading to allergic responses upon subsequent exposures. The standard animal-based sensitisation tests are the Guinea Pig Maximization Test (GPMT), Buehler assay, and murine Local Lymph Node Assay (LLNA). Of these, the GPMT is recognised as the most sensitive method. Despite significant advancements in the chemical industry, and incorporation of various methods into OECD Test Guidelines based on knowledge of key events leading to sensitisation, the medical device industry has not yet incorporated these in vitro and in chemico methods into the ISO 10993 standards, but still relies on animal testing for decision making[20] acknowledges that alternative approaches for neat chemicals have been developed, utilising a combination of assays to identify skin sensitizers. These methods are included in OECD Test Guidelines or are part of the ongoing OECD test guideline evaluation program. An overview of the methods can be found in Annex C of the ISO 10993-10: 2021. However, the applicability of these alternative approaches for medical devices remains uncertain, and validation studies are necessary to demonstrate the reliability and relevance of these tests for the medical device industry. This issue is being addressed by ISO/TC 194s Working Group 8 that recently published ISO/TS 11796:2023, which provides detailed guidance on conducting an in vitro sensitisation validation study for medical devices. In 2024, Working Group 8 plans to begin preliminary work on a global round robin study of *In-vitro* sensitization methods.

Obstacles to implementing additional in vitro tests for other toxicity endpoints:

A range of *in vitro, in silico,* and *in chemico* assays have been developed for assessing biological endpoints, including skin and eye irritation, as well as skin sensitisation, for cosmetics, pharmaceuticals, and chemical substances. However, their validation and acceptance for medical device use remain pending because the medical device testing field

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Volume 4 Issue 1, 2024
eISSN No.: 2582-8371

has been reluctant to adopt new approach methodologies. A review of the reasons for the slow validation and implementation of in vitro testing methods is presented below.

Technical Difficulties of Testing Materials by In vitro Methods

Degradation of medical devices: Over time, both chemical and mechanical degradation can lead to delayed cytotoxic or inflammatory responses. This process presents a significant challenge for current in vitro testing methods which are typically designed for short-term assessment. *In vitro* assays may not adequately simulate prolonged, repeated exposure, and the cumulative effects that medical devices experience under real-life conditions. Capturing these long-term and repeated toxicity effects in vitro is a complex task.

One potential avenue to address this challenge is using microfluidic systems combined with advanced cell culture models. These systems have the potential to culture cells over extended periods, thereby providing a more realistic simulation of long-term device usage and its effects. Furthermore, addressing the issue of material degradation–whether mechanical or chemical–is essentially an engineering challenge. It requires the integration of interdisciplinary teams in the design of testing methods. By involving experts from various fields, including material science, bioengineering, and toxicology, more comprehensive and predictive in vitro models can be developed. These models would assess immediate cytotoxic effects and evaluate the long-term biocompatibility and safety of medical devices. Low concentration of toxic compounds: Medical device extracts are often complex chemical mixtures, wherein harmful components might be present at low concentrations. Although trace levels can pose significant risks over long-term exposures, accurately assessing these risks in short-term in vitro acute toxicity tests is difficult. Challenges in sample preparation: The methodology for preparing extracts from medical devices needs more standardization and harmonization. Recent studies evaluating the
variability of ISO 10993-5:2009 cytotoxicity methods have highlighted the substantial impact of the extracting solution—such as medium with or without serum—on test outcomes. Even minor protocol modifications can significantly alter the predicted cytotoxicity effects [21].

There is a need for more comprehensive guidance on handling materials that absorb solvents, as they can alter the osmolarity of the cell culture medium, adversely affecting the cell lines. Testing poorly soluble materials in submerged cell cultures, in general, poses technical challenges and may lead to false-negative results. In addressing these issues, epithelial 3D tissue models emerge as a promising solution. These models are capable of sustaining materials extracted in both polar and non-polar solutions, offering a more versatile and potentially accurate testing framework. The development and implementation of such advanced models
could significantly enhance the reliability of cytotoxicity assessments for medical devices, particularly for those with low-level toxic components that are poorly soluble in polar vehicles. This approach would ensure a more accurate long-term safety and efficacy prediction, aligning in vitro testing more closely with real-world device usage scenarios.

Slow Adaptation of Existing Protocols

Protocol adjustment delays: The medical device industry has been slow in adapting and validating existing testing protocols from other sectors to suit the unique properties of medical devices. This delay is partly due to the lack of well-characterised medical device materials that can serve as positive controls for specific toxicity endpoints.

Limited validation expertise: The complexity of medical device testing necessitates specialised expertise for validation projects. However, only a few CROs and medical device manufacturers possess the necessary skills and resources (financial and personal) to design and conduct such validation projects effectively, leading to bottlenecks in broader validation and consequent implementation. Although there are test methods and models that could be included in ISO 10993-23:2021 for other endpoints (e.g., eye, oral, and vaginal irritation), validation studies have yet to be completed.

Other Issues include were as follows;
1) Regulatory distrust and lack of public interest.
2) Cross-sectorial harmonisation, open access to the information.
3) Training of regulators along with contract research organizations

CONCLUSION

The slow progression in validation and implementation of in vitro testing methods in the medical device sector is multifaceted. It is influenced by technical challenges, the inherent complexity of medical devices, regulatory hesitancy, limited advocacy for alternative methods, the specialised nature of the required testing, and a lack of industry-wide harmonisation. The language in the ISO 10993-1:2018 standard acknowledges the possibility of a tiered approach, emphasizing the importance of in vitro data (ISO 10993-1:2018, 2018). However, there is a notable gap between recognition and practical application in regulatory decision-making. Nevertheless, implementing this approach comprehensively across the “Big Three” endpoints presents a substantial challenge, particularly given the unique complexities associated with sensitisation testing.

Addressing these issues requires concerted efforts by industry stakeholders, regulatory bodies, and the scientific community to advance towards more efficient, ethical, and reliable testing methodologies.

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