ICARE medlab Laboratório de Análises	**STUDY PLAN OF SUBCHRONIC SYSTEMIC TOXICITY+IMPLANT REFERENT TO THE TEST ITEM SMART PRINT BIO BITE SPLINT CLEAR**	**Nº: 12920-1/2024.0**

1. INFORMATION ABOUT THE SPONSOR AND THE TEST FACILITY

Sponsor	*Name:*	MMTECH PROJETOS TECNOLOGICOS IMPORTACAO E EXPORTACAO LTDA
	Address:	Doutor Procopio Toledo Malta Street, 62– Morada dos Deuses – São Carlos – SP– Zip Code: 13562-291

Test Instalation	*Name:*	MEDLAB PRODUTOS DIAGNÓSTICOS LTDA.
	Address:	Rua Octávio Teixeira Mendes Sobrinho, 35 - Vila Santa Catarina - São Paulo – SP CEP: 04376-070

Study Director	*Name:*	Andrea da Costa – CRBio 072416
	Address:	Rua Octávio Teixeira Mendes Sobrinho, 35 – Vila Santa Catarina -São Paulo – SP CEP: 04376-070

2. TEST ITEM IDENTIFICATION*

Test item:	**SMART PRINT BIO BITE SPLINT CLEAR**		
Category:	Health Products		
Date of manufacture:	February, 2024	**Expiration date:**	February, 2026
Batch:	PBSF 007/24	**CAS:**	NA
Declared composition:	METHACRYLIC MONOMERS >45% OLIGOMERS< 50%; DISPERSANT<2%;PHOTOINITIATOR <2%; ADDITIVE <.01%;PIGMENTS<1%		
Other information:	ND		

**Information provided by the Sponsor; ND: not declared; NA: not applicable.*

3. STATEMENT OF NATURE / PURPOSE OF THE STUDY

Subchronic systemic toxicity is the assessment of a possible health risk and adverse effects caused by repeated or continuous exposure to a substance. These studies provide information on systemic and target organ toxic effects and serve as a basis for estimating the safety of the substance. The implantation test consists of evaluating the local effects after the implantation of a material in an animal species. The objective of the method is to characterize the history and evolution of the tissue response after the implantation of a medical device, evaluating its biological safety. The present study aimed to evaluate the systemic and local effects of the **SMART PRINT BIO BITE SPLINT CLEAR** test item implanted in subcutaneous tissue of rats for 3 months.

*The evaluation of the mechanical or functional performance of the material is not part of the objective of the test.

4. PLANNED DATES (SUBJECT TO CHANGE)

Start date of the experimental phase (start of the in vivo part)	End date of the experimental phase (end of the in vivo part)	End date of the experimental phase (complementary exams)
November 18th, 2024	*February 17th,2025*	*April 04th, 2025*

5. CRITICAL STAGES OF THE STUDY

Test Item Implantation, Clinical Assessments, Necropsy, and Specimen Collection.

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6. METHOD

MET-TOX-009 e MET-TOX-010 *current version*

Reference Standards:

ISO 10993-11: *Biological evaluation of medical devices – Tests for systemic toxicity (2017)*

ISO 10993-6: *Biological evaluation of medical devices – Tests for local effects after implantation (2016).*

7. TEST SYSTEM

7.1 Justification for use

Rats will be used, a species widely used to evaluate systemic and local effects and indicated in the reference method.

7.2 Characterization

Species: Rattus norvegicus (rats)
Lineage: Wistar
Number: 30 animals - 20 test and 10 control. Additional animals may be used, for safety reasons, and will only be reported in the final report if a death unrelated to the effects of the test item occurs.
Sex: males and females
Origin: the animals will be purchased from a qualified supplier.
Acclimation: the animals will be acclimatized in the vivarium for a minimum period of 5 days.

7.3 Maintenance

The test system will be housed in boxes suitable for the species in accordance with current standards and legislation, ensuring animal integrity and well-being. They will be kept in a room with a temperature between 19 and 25ºC, relative humidity between 30 and 70% and a 12/12-hour photo period. In the case of records outside the stipulated ranges, the study director will assess their relevance and impact on the study. The test system's feed will consist of conventional feed for the species and drinking water.

8. METHOD OF ADMINISTRATION AND REASON FOR CHOICE

The test item will be applied to the subcutaneous tissue, as it is a representative tissue for the use of the material.

9. REFERENCE ITEM

High-density polyethylene will be used as a negative control. The reference item will be cut into a shape that allows implantation into the subcutaneous tissue of rats. Each animal will receive one unit of the reference item.

10. TEST ITEM PREPARATION/APPLICATION DOSES

The test item was provided by the Sponsor and is cylindrical in shape with a diameter of ≅∅2 mm x 6 mm in length. The test item will be implanted in the subcutaneous tissue of rats. Each animal will receive 01 unit of the test item.

11. EXPERIMENTAL DESIGN

The animals will be randomly divided into two groups, control and test, anesthetized and treated with analgesics, and will have their backs shaved. After the medication has taken effect, the animals will be placed on a surgical table, their skin will be

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antisepsised, and they will be covered with a sterile surgical field, exposing only the area necessary for the surgery. An incision will be made in the back region, and after the material is inserted into the subcutaneous tissue, the skin will be sutured, and the wound will be cleaned and protected with a dressing. Each animal in the test group will receive 1 implantation site for the test item, and each animal in the control group will receive 1 implantation site for the reference item. After the procedure, the animals will be treated with anti-inflammatory drugs for at least 3 days to minimize pain and the risk of infection of the surgical wound. The animals will be observed in the first hours of recovery after implantation and will be clinically evaluated weekly for signs of toxicity. Body weights will be recorded weekly.
After the 3-month period, the animals will be anesthetized and euthanized by exsanguination. An autopsy will be performed and blood and organs will be collected and sent to laboratory for additional tests such as blood count and blood biochemistry, and histopathological analysis of the main organs (*liver, spleen, kidney, adrenal, lung, heart, brain, muscle, lymph node, testicle/ovary, femur and implantation sites - skin*). The *liver, kidney, spleen, heart and adrenal* will be weighed to calculate the relative weight of the organs.

12. RECORDS

12.1. Records accompanying the study dossier

- *Study Plan*
- *Raw data form and annexes, where applicable*
- *Copy of the final report*
- *Study Plan inspection reports and final report*

12.2. Records that remain in the test installation

- *Master Schedule*
- *Records of qualifications, training, and job descriptions of staff involved.*
- *Equipment maintenance and calibration records and reports.*
- *Test item chain of custody*
- *Records of receipt and use of the test system*
- Relatório de inspeções de estudo/processo | *Study/process inspection report*

13. VERIFICATION

I declare that study plan has been checked and complies with requirements of Good Laboratory Practices.

Paula Renata Bezerra
Garantia da Qualidade

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Quality Assurance

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14. APPROVAL

The undersigned responsible parties declare that they approve and agree with the information described and that the study will be conducted in accordance with Good Laboratory Practices.

Roberta dos Santos Machado
Coordenadora de Laboratório
CRQ:04152702

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Test Facility Manager

Sponsor

Andrea da Costa, M.Sc, PhD
Diretor(a) de Estudos Toxicológicos *in vitro*
Supervisor(a) Laboratório de Toxicologia *in vitro* / *in vivo*
Bióloga CRBio/SP – 072416/01-D

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Study Director

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