Study of Maximized Skin Sensitization for the Test Item

SMART PRINT BIO VITALITY

Report

REFERENCE METHOD:	ISO 10993-10:2021
STUDY DIRECTOR:	Andrea da Costa
DATE OF COMPLETION OF THE STUDY:	November 11th, 2024
CONTRACT LABORATORY:	**MEDLAB PRODUTOS DIAGNÓSTICOS LTDA.** Octávio Teixeira Mendes Sobrinho Street, 35 Vila Santa Catarina - Zip Code: 04376-070 São Paulo, SP - Brazil
IDENTIFICATION:	Study code: **BSDM2** Study Number: **12916-1/2024.0**
SPONSOR:	MMTECH PROJETOS TECNOLOGICOS IMPORTACAO E EXPORTACAO LTDA Rua Doutor Procopio Toleto Malta, 62 Zip Code: 13562-291 – São Carlos - SP – BRAZIL.

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

Study title: Study of Maximized Skin Sensitization for the Test Item SMART PRINT BIO VITALITY
Study number: 12916-1/2024.0

This study was conducted under my responsibility in accordance with NIT-DICLA-035 (INMETRO, Oct/19, Rev. 04) and its complementary documents, which meets the principles of Good Laboratory Practice as published by the OECD (N° 1 [ENV/MC/CHEM (98) 17]).
This study was conducted in accordance with the study plan, approved by the Sponsor and Test Facility Manager and to the standard operating procedures. This report represents a true and accurate record of the results obtained. There were no major known circumstances that may have affected the quality or integrity of the study.
All original raw data, including electronic records, documentation, signed study plan, possible additions to the study plan, final report and test item rate will be retained in the GLP files of Medlab Produtos Diagnósticos Ltda.

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

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Study Director
Medlab Produtos Diagnósticos Ltda

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STATEMENT OF QUALITY ASSURANCE

Study title: Study of Maximized Skin Sensitization for the Test Item SMART PRINT BIO VITALITY
Study number: 12916-1/2024.0

Based on the Quality Assurance review, this final report was considered an accurate and true record of the data generated during the study.

This final report has been inspected for the respective study plan, standard operating procedure and raw data. Study procedures were monitored through process inspection.

The inspections were conducted in accordance with the standard operating procedures of the Quality Assurance of Medlab Produtos Diagnósticos Ltda.

Inspection dates and respective reporting dates to the Study Director and Test Facility Manager are presented below. These inspection reports are kept in the GLP files of Medlab Produtos Diagnósticos Ltda.

Inspection	Date of Inspection	Reporting dates	
		Study Director	Test Facility Manager
Study plan	08/30/2024	08/30/2024	08/30/2024
Experimental phase*	06/17 and 06/21/2024	07/05/2024	07/05/2024
Raw data	11/11/2024	11/11/2024	11/11/2024
Final Report	11/11/2024	11/11/2024	11/11/2024

* Process inspection performed at least every 12 months

Emine Sakaue
Garantia da Qualidade

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Quality Assurance
Medlab Produtos Diagnósticos Ltda

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GENERAL INFORMATION

Contributors

Andrea da Costa	Study Director
Roberta dos Santos Machado	Test Facility Manager
Emine Oshiro Sakaue	Quality Assurance
Suellen Karoline Moreira Bezerra	Technical Support
Paloma Oliveira	Technical Support
Mariucha Soares	Technical Support
Victoria Ferreira Cravo	Technical Support

Study dates

Study start date:	September 12th, 2024
Experimental phase start:	September 20th, 2024
Experimental phase end:	October 18th, 2024
Study completion date:	November 11th, 2024
English version:	November 11th, 2024

Performing laboratory

This study was conducted at Medlab Produtos Diagnósticos Ltda, located at Rua Octávio Teixeira Mendes Sobrinho, 35 – CEP:04376-070, São Paulo – SP, Brazil.

Study plan adherence

No deviations from the study plan were recorded.

Amendment 01: In item 11.1 of the Study Plan, information about the steps of days 5-7 was not included: "*approximately 24 hours before induction by topical application, if there is no dermal irritation, the tested area (after being properly shaved) should be exposed to 0.5 mL of Sodium Lauryl Sulfate 10% to create local irritation. The remaining SDS will be removed before the 2nd induction*". There is no impact on the study, since the experimental steps were followed according to the methodology and reference related to the Study.

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Archives

All raw data and original study records are the property of the Sponsor. The data will be correctly registered, signed and kept at Medlab Produtos Diagnostics Ltda for five years. Upon completion of all studies, unused/damaged test items will be retained until the expiration date and then will be discarded.

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INDEX

PAGE
GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT 2
STATEMENT OF QUALITY ASSURANCE 3
GENERAL INFORMATION 4
1. ABSTRACT 8
2. INTRODUCTION 9
2.1. Study objective 9
2.2. Reference 9
2.3. Weight of evidence analysis 9
2.4. Animal welfare 9
3. MATERIAL AND METHOD 10
3.1. Test item** 10
3.2. Test system 11
3.3. Environmental conditions 12
3.4. Method of administration and reason for choice 12
3.5. Reference item (control) 13
3.6. Material, reagents and equipment 13
3.7. Test item preparation 14
3.8. Experimental design 15
3.9. Results evaluation / Acceptance criterion 16
4. RESULTS 17
4.1. Body weight 17
4.2. Challenge evaluation 17
5. CONCLUSION 17
6. REFERENCES 17
TABLE 1: Individual body weight of the test system – polar extract 18
TABLE 2: Individual body weight of the test system – non-polar extract 19
TABLE 3: challenge evaluation – polar extract 20
TABLE 4: challenge evaluation – non-polar extract 21
TABLE 5: Incidence of positive reactions during challenge evaluation – polar extract 22
TABLE 6: Incidence of positive reactions during challenge evaluation – non-polar extract 22
APPENDIX 1 23

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RECOGNITION CERTIFICATE OF COMPLIANCE WITH THE PRINCIPLES OF GOOD LABORATORY PRACTICES 23

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1. ABSTRACT

The aim of this study was to evaluate the possible sensitizing effects of the test item **SMART PRINT BIO VITALITY** provided by MMTECH PROJETOS TECNOLOGICOS IMPORTACAO E EXPORTACAO LTDA. Skin sensitization is an immunologically mediated skin reaction to a substance, characterized in laboratory animals by the appearance of edema and erythema. The methodology used was ISO 10993-10 (2021).

For each extraction (polar and non-polar), ten guinea pigs (Cavia porcellus) had an immunological response induced through the intradermal injection of the test item in the scapula region, potentiated with the use of an adjuvant, followed by the topical application of the test item over the same location after a week apart. After the 14-day rest period, the animals were challenged with the topical application of the test item in the flank region. The control group of five animals was treated with vehicle during the induction period, and treated with the test item in the challenge period. The animals were weighed at the beginning and at the end of the experimental period, and clinically evaluated throughout the experimental period. No erythema and edema reactions were observed in the challenge assessment. According to the methodology adopted for the study, the test item **SMART PRINT BIO VITALITY** was considered non-sensitizing.

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2. INTRODUCTION

2.1. Study objective

Skin sensitization is an immunologically mediated skin reaction to a substance, characterized in laboratory animals by the appearance of edema and erythema. The maximized method uses an adjuvant capable of stimulating the immune response, to enhance the sensitivity of the method. The present study aimed to evaluate the possible sensitizing effects of the test item **SMART PRINT BIO VITALITY.**

2.2. Reference

The study was conducted according to ISO 10993-10: Tests for skin sensitization, 2021.

2.3. Weight of evidence analysis

For reasons related to animal welfare, prior to conducting the study, an analysis of the evidence was performed, with available and relevant data from the test item. The testing strategy includes an assessment of human and/or animal data related to toxic effects. Test substance known to cause pain and discomfort due to corrosive or severely irritating properties need not be tested.

2.4. Animal welfare

Animals are maintained in the testing facility in accordance with local and international requirements outlined in the Standard Operating Procedures. Animals with ongoing signs of severe discomfort and/or pain at any stage of the study are humanely euthanized and the test item properly evaluated. Animal care procedures and decision criteria for euthanasia of moribund and severely distressed animals are described in detail in the Standard Operating Procedures.

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3. MATERIAL AND METHOD

3.1. Test item**

Identification:	**SMART PRINT BIO VITALITY**
Receiving date at Medlab:	August 6th, 2024
Category:	Medical device
Batch:	PVA3 004/24
Manufacturing date:	April, 2024
Expiry date:	April, 2026
Active ingredient(s):	Not applied
CAS number of active ingredient(s):	Not applied
Declared composition:	Amorphous Silica < 5%; Silanized Silica > 50%; Dispersant <4%; Photoinitiator<4%; Methacrylic Monomers >40%; Pigments <0.07%
Physical state:	Solid
Other information:	Dimensions: 50x50x1,2 mm | Weight: 5g
Provided by:	MMTECH PROJETOS TECNOLOGICOS IMPORTACAO E EXPORTACAO LTDA.

**Information regarding the test item and/or reference item is the responsibility of the Sponsor.

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3.2. Test system

Species:	*Cavia porcellus* (Guinea pigs)
Strain:	Dunkin-Hartley
Source:	Anilab, Paulínia-SP
Justification for the test system:	Guinea pigs are a species widely used in skin sensitization studies, and recommended in the test method
Number and sex:	15 females per extraction, 5 animals in the control group and 10 animals in the test group
Body weight:	Healthy young adults with body weight between 300 and 500 g
Date of birth:	August 11th, 2024
Receiving date:	September 19th, 2024
Acclimatization:	The animals were acclimated to laboratory conditions for 5 days before starting the test; animals with any signs of abnormality were not used in the study
Accommodation:	The animals were kept in conventional cages for the species during the acclimation and testing period, 5 animals per cage
Identification:	The test system was individually identified by marking with a felt-tip pen on the flank; the boxes were identified by labels containing the study number, lot of animals and dates of the experimental phase.

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Feeding:	Commercial feed for the species (Qualy Nutrição Animal – Guinea pigs, batch 234-2, manufacture: 08/21/2024, validity: 12/19/2024) was supplied *ad libitum* during the acclimatization period; the feed is analyzed at each batch to verify the presence of microbiological contaminants. The feed provided did not show contamination that could affect the purpose or integrity of the study.
Water:	Filtered water was provided *ad libitum* in the acclimatization periods; the water is periodically analyzed for the presence of chemical and microbiological contaminants. The filtered water provided did not show contamination that could affect the purpose or integrity of the study.

3.3. Environmental conditions

The environmental conditions of the test room were monitored and recorded during the experimental period. The average temperature was 21.56ºC, and the average relative humidity was 66.79%. The animals were kept under automatic control of the 12/12 hours photoperiod.

3.4. Method of administration and reason for choice

The sample was applied intradermally (1st induction) and later topically in the dermis (2nd induction and challenge) of the test system as described in the methodology.

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3.5. Reference item (control)

The vehicles used for the test item extraction were 0.9% sodium chloride solution (polar vehicle) and cottonseed oil (non-polar vehicle).

The quality assurance control of this assay is provided for in the reliability test carried out periodically (Periodic Positive Control). The last evaluation was carried out in September/2024, using 15 animals (5 animals in the control group and 10 animals in the test group), and the substance α–hexylcinnamaldehyde described in the table below was considered sensitizing (positive reactions grades 1 and 2 in test group animals).

Positive control: **α – Hexylcinnamaldehyde**
CAS number: **101-86-0**
Batch: **A4 30376-QA4**
Manufacturing date: **09/08/2022**
Expiry date: **06/07/2025**

3.6. Material, reagents and equipment

Materials: Bottle with lid, gauze, syringe, sterile needle, felt-tip pen, hypoallergenic tape/ adhesive tape, micropore, scissors, filter paper, cotton, cotton swab.

Reagents: 0.9% sodium chloride solution, cottonseed oil, 10% sodium dodecyl sulfate (SDS), liquid vaseline and complete Freund's adjuvant (FCA).

Equipment: Electronic scale, trimmer machines and incubator.

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3.7. Test item preparation

Extraction of the test item was performed in accordance with ISO 10993-12 (2021). The test item was extracted at 50°C for 72 hours in an incubator in two vehicles (polar and non-polar) in a ratio of 3 cm^2 of test item to 1 mL of vehicle. The extracts were used within 24 hours of preparation.

Polar extraction:

Total prepared for 1st induction: 50 cm^2 of test item for 16,7 mL of 0.9% sodium chloride solution.

Total prepared for 2nd induction: 50 cm^2 of test item for 16,7 mL of 0.9% sodium chloride solution.

Total prepared for challenge: 50cm^2 of test item for 16,7 mL of 0.9% sodium chloride solution.

The liquid resulting from this process (extract) presented a homogeneous and colorless appearance, as per the original color of the vehicle, without the presence of particulates, and was not submitted to any other additional process.

Non-polar extraction:

Total prepared for 1st induction: 50 cm^2 of test item for 16,7 mL of cottonseed oil.

Total prepared for 2nd induction: 50cm^2 of test item for 16,7 mL of cottonseed oil.

Total prepared for challenge: 50 cm^2 of test item for 16,7 mL of cottonseed oil.

The liquid resulting from this process (extract) presented a homogeneous and yellow appearance, according to the original color of the vehicle, without the presence of particulates, and was not submitted to any other additional process.

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3.8. Experimental design

The test system was weighed before the beginning and at the end of the experiment. Trichotomy was performed approximately 24 hours before each application.

At the first induction (day 0), each animal received three pairs of intradermal injections (0.1 mL each injection) in the scapula region, with one injection of each pair being applied on each side of the midline, in a mirror fashion. The contents of the test group injections are described below:

- Injection 1: mixture 1:1(v/v) of FCA + 0.9% sodium chloride solution or cottonseed oil.
- Injection 2: undiluted test item extract.
- Injection 3: extract of the test item undiluted in a 1:1 ratio with the solution from injection 1

The control group received three pairs of intradermal injections of 0.1 mL each, applied in the same sites as the animals in the test group, as described below:

- Injection 1: mixture 1:1 v/v of FCA + 0.9% sodium chloride solution or cottonseed oil.
- Injection 2: 0.9% sodium chloride solution or undiluted cottonseed oil.
- Injection 3: 0.9% sodium chloride solution or cottonseed oil in a 1:1 ratio with injection solution 1.

On day 6, the animals had the scapula area pretreated with 10% SDS massaged into the skin. On day 7, the animals received applications of filter paper soaked in 0.5 mL (0.25 mL on each side) of the test item extract (experimental group) and 0.5 mL (0.25 mL on each side) of cottonseed oil (control group) in the scapula region. The occlusive dressings remained in contact with the animals' skin for 48 hours, and after removal, the area was cleaned with a 0.9% sodium chloride solution.

On the 21st, the challenge period began. Animals (control and experimental groups) received cotton dressings soaked in 0.5 mL of undiluted test item extract. The occlusive dressing was kept in contact with the skin for 24 hours, and after removal, the area was cleaned with a 0.9% sodium chloride solution. Approximately 24 and 48 hours after dressing removal (48 and 72 hours after challenge exposure), skin reactions (erythema and edema) were assessed. Assessments were made according to the Magnusson and Kligman grading scale.

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3.9. Results evaluation / Acceptance criterion

The criteria established for classifying the sample as a potential sensitizing agent were:

a) Within 48 and/or 72 hours, 30% or more of the animals tested had a positive response (grade ≥1), in the absence of similar results in the control group.

b) A positive reaction presented within 48 hours persistent at 72 hours in at least one animal, in the absence of similar results in the control group.

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4. RESULTS

4.1. Body weight

Tables 1 and 2 show the initial and final body weight of the test systems, as well as the body weight variation. All animals showed weight gain at the end of the experimental period.

4.2. Challenge evaluation

Tables 3 and 4 show the evaluation of dermal reactions after challenge. Tables 5 and 6 show the incidence of positive reactions. Erythema and edema reactions were not observed for both polar and non-polar extracts.

5. CONCLUSION

According to the methodology adopted for the study, the test item **SMART PRINT BIO VITALITY** was considered non-sensitizing.

6. REFERENCES

INMETRO: NIT-DICLA-035 - Principles of Good Laboratory Practice – GLP, Rev. 04, October/2019 and its complementary documents.

ISO 10993:10 – Biological evaluation of medical devices. Part 10: Tests for skin sensitization, 2021.

ISO 10993:12 – Biological evaluation of medical devices. Part 12: Sample Preparation and Reference Materials, 2021.

OECD Environmental Health and Safety Publications, Series on Principles of Good Laboratory Practice and Compliance Monitoring. No. 1.,41p., Paris, 1998 (17).

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TABLE 1: Individual body weight of the test system – polar extract

Test group	Body weight (g)		
	Initial	**Final**	**Variation**
01	310	468	158
02	308	412	104
03	346	428	82
04	300	396	96
05	300	398	98
06	352	446	94
07	302	388	86
08	346	410	64
09	316	424	108
10	314	428	114
Control group	**Body weight (g)**		
	Initial	**Final**	**Variation**
01	342	482	140
02	328	420	92
03	300	390	90
04	346	426	80
05	322	404	82

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TABLE 2: Individual body weight of the test system – non-polar extract

Test group	Body weight (g)		
	Initial	**Final**	**Variation**
01	322	416	94
02	304	378	74
03	322	402	80
04	322	414	92
05	318	386	68
06	324	428	104
07	332	432	100
08	316	466	150
09	302	400	98
10	300	408	108
Control group	**Body weight (g)138**		
	Initial	**Final**	**Variation**
01	300	402	102
02	316	420	104
03	300	404	104
04	344	418	74
05	318	400	82

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TABLE 3: Challenge evaluation – polar extract

Test group	Challenge evaluation	
	48 hours	72 hours
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
Control group	**Challenge evaluation**	
	48 hours	**72 hours**
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0

0	No visible alteration
1	Discrete or Irregular Erythema
2	Moderate and Confluent Erythema
3	Intense Erythema and/or Edema

Magnusson and Kligman Scale (reactions ≥ 1 are considered positive)

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TABLE 4: Challenge evaluation – non-polar extract

Test group	Challenge evaluation	
	48 hours	72 hours
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
Control group	**Challenge evaluation**	
	48 hours	**72 hours**
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0

0	No visible alteration
1	Discrete or Irregular Erythema
2	Moderate and Confluent Erythema
3	Intense Erythema and/or Edema

Magnusson and Kligman Scale (reactions ≥ 1 are considered positive)

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TABLE 5: Incidence of positive reactions during challenge evaluation – polar extract

Groups	48 hours	72 hours
Experimental	0/10 = 0%	0/10 = 0%
Control	0/5 = 0%	0/5 = 0%

TABLE 6: Incidence of positive reactions during challenge evaluation – non-polar extract

Groups	48 hours	72 hours
Experimental	0/10 = 0%	0/10 = 0%
Control	0/5 = 0%	0/5 = 0%

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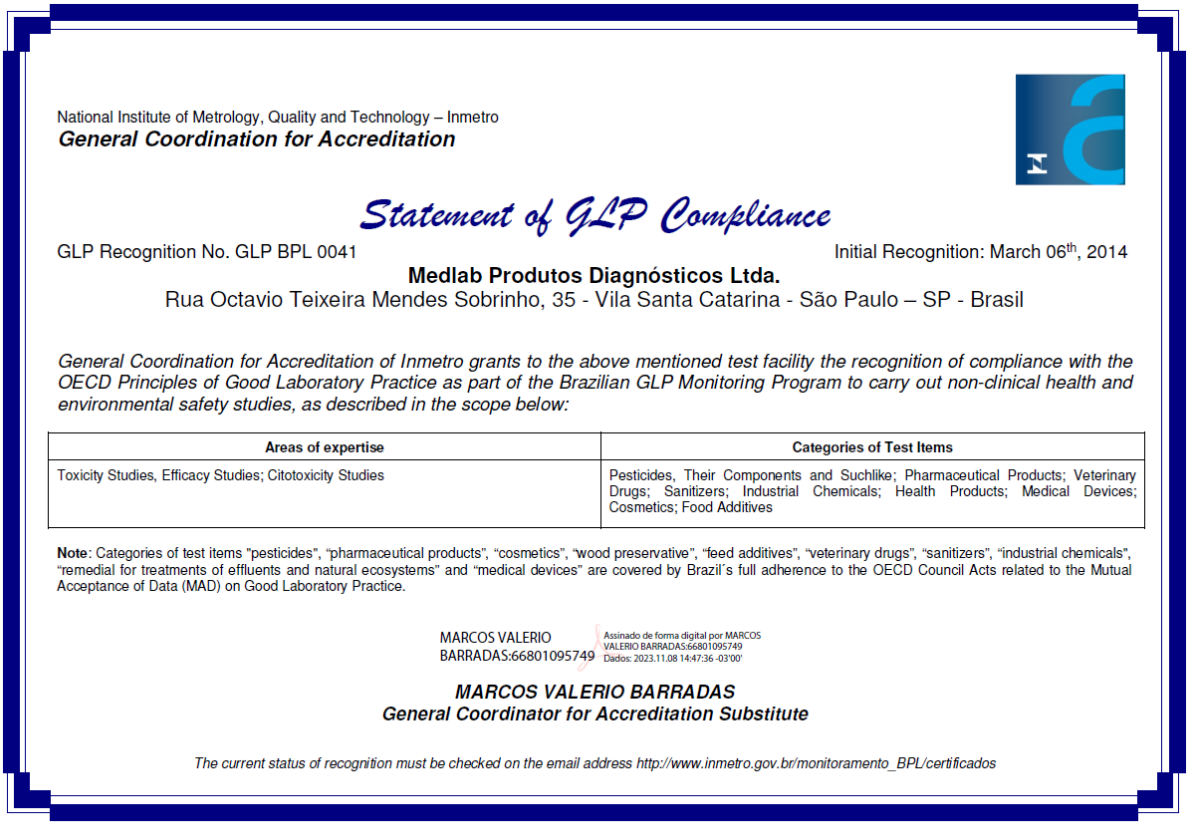
APPENDIX 1

RECOGNITION CERTIFICATE OF COMPLIANCE WITH THE PRINCIPLES OF GOOD LABORATORY PRACTICES



National Institute of Metrology, Quality and Technology – Inmetro
General Coordination for Accreditation

Statement of GLP Compliance

GLP Recognition No. GLP BPL 0041 — Initial Recognition: March 06th, 2014

Medlab Produtos Diagnósticos Ltda.
Rua Octavio Teixeira Mendes Sobrinho, 35 - Vila Santa Catarina - São Paulo – SP - Brasil

General Coordination for Accreditation of Inmetro grants to the above mentioned test facility the recognition of compliance with the OECD Principles of Good Laboratory Practice as part of the Brazilian GLP Monitoring Program to carry out non-clinical health and environmental safety studies, as described in the scope below:

Areas of expertise	Categories of Test Items
Toxicity Studies, Efficacy Studies; Citotoxicity Studies	Pesticides, Their Components and Suchlike; Pharmaceutical Products; Veterinary Drugs; Sanitizers; Industrial Chemicals; Health Products; Medical Devices; Cosmetics; Food Additives

Note: Categories of test items "pesticides", "pharmaceutical products", "cosmetics", "wood preservative", "feed additives", "veterinary drugs", "sanitizers", "industrial chemicals", "remedial for treatments of effluents and natural ecosystems" and "medical devices" are covered by Brazil's full adherence to the OECD Council Acts related to the Mutual Acceptance of Data (MAD) on Good Laboratory Practice.

MARCOS VALERIO BARRADAS:66801095749 Assinado de forma digital por MARCOS VALERIO BARRADAS:66801095749 Dados: 2023.11.08 14:47:36 -03'00'

MARCOS VALERIO BARRADAS
General Coordinator for Accreditation Substitute

The current status of recognition must be checked on the email address http://www.inmetro.gov.br/monitoramento_BPL/certificados

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