citoxlab
Safety and Health Research

Isopyrazam/Difenoconazole

Isopyrazam/Difenoconazole SC (A21295D) - Acute Dermal Toxicity Study in Rats

Final Report

DATA REQUIREMENT(S): OECD 402 (1987)
EPA 870.1200 (1998)
EC 440/2008 (2008)
Guidance Document on Toxicology for Registration of Pesticides in India (2014)

AUTHOR(S): Ádám Appl, M.Sc.

COMPLETION DATE: 05 January 2018

PERFORMING LABORATORY: CiToxLAB Hungary Ltd.
H-8200 Veszprém, Szabadságpuszta
Hungary

LABORATORY PROJECT ID: Report Number: 17/135-002P
Study Number: 17/135-002P
Task Number: TK0296435

SPONSOR(S): Syngenta Ltd.
Jealott's Hill International Research Centre
Bracknell, Berkshire, RG42 6EY, United Kingdom

VOLUME 1 OF 1 OF STUDY

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study has been performed in accordance with the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.).

This study was conducted in accordance with a written Study Plan, authorised by the Sponsor and CiToxLAB Hungary Ltd. Management, and followed applicable Standard Operating Procedures.

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study.

Ádám Appl, M.Sc.
Study Director

05 January 2018
Date

Performing Laboratory: CiToxLAB Hungary Ltd.
H-8200 Veszprém, Szabadságpuszta
Hungary

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Code: 17/135-002P

Study Title: Isopyrazam/Difenoconazole SC (A21295D) - Acute Dermal Toxicity Study in Rats

Test Item: Isopyrazam/Difenoconazole SC (A21295D)

This study has been inspected, and this report audited by the Quality Assurance Unit in compliance with the Principles of Good Laboratory Practice. As far as it can be reasonably established the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in written form to the Study Director and to Management. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to	
		Management	Study Director
24 May 2017	Study Plan	24 May 2017	24 May 2017
13 June 2017	Treatment	13 June 2017	13 June 2017
07 August 2017	Draft Report	07 August 2017	07 August 2017
05 January 2018	Final Report	05 January 2018	05 January 2018

Signature: Schleicher Ivett Date: 05 January 2018

Ivett Schleicher, Ph.D.
On Behalf of QA

STATEMENT OF THE MANAGEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and CiToxLAB Hungary Ltd. (as Test Facility) the study titled "Isopyrazam/Difenoconazole SC (A21295D) - Acute Dermal Toxicity Study in Rats" was performed, in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 05 Jan 2018

Alyson Leyshon, M.Sc.
Managing Director

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Ádám Appl, M.Sc.	Study Director
Máté Weisz, M.Sc.	Assistant Scientist
Ivett Schleicher, Ph.D.	Quality Assurance Unit
László Székelyhidi, D.V.M.	Veterinary Care
Peter Maslej, D.V.M., Ph.D.	Pathology
Tamás Mészáros, Ph.D.	Pharmacy
William Masinja, M.Sc.	Syngenta Study Manager

Other trained, competent personnel worked on the study.

Study dates

Study initiation date:	24 May 2017
Experimental starting date:	13 June 2017
Acclimatization period:	08 June – 12 June / 14 June 2017
Treatment date:	13 June / 15 June 2017
Observation period:	13 June – 27 June / 15 June – 29 June 2017
Experimental completion date:	29 June 2017
Draft report:	07 August 2017

Deviations from the Study Plan

Due to technical reason, temperature values (maximum of 26.2°C) outside the expected range of 19-25°C were recorded occasionally during the study.

This minor difference of the environmental parameters was considered not to adversely affect the results of integrity of the study as confirmed by the Clinical Veterinarian

Performing laboratory test substance reference number

170120

Other

The study documents and samples:
- Study Plan,
- all raw data,
- sample of the test item,
- original Study Report and any amendments,
- correspondence

will be archived according to the Hungarian GLP regulations and to applicable SOPs in the archives of CiToxLAB Hungary Ltd. 8200 Veszprém, Szabadságpuszta, Hungary. This is for a period of 15 years.

After the retention time has elapsed, all the archived materials listed above will be returned to the Sponsor or retained for a further period if agreed by a contract. Otherwise the materials will be discarded.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

1.1 Study Design

Five male and five female Crl:WI rats were treated with a single dermal application of Isopyrazam/Difenoconazole SC (A21295D) at the limit dose of 2000 mg/kg body weight (bw). The application period was 24 hours, followed by a 14-day observation period.

Clinical observations along with a check of viability and mortality were performed on all animals at 1 and 5 hours after dosing and daily for 14 days thereafter. Body weight was measured on Day 0 (prior to dosing) and on Days 7 and 14 (before necropsy). All animals were examined macroscopically at necropsy at the end of the observation period.

1.2 Results

No mortality occurred during the study.

There were no adverse clinical signs noted in any animals throughout the study.

No local dermal signs were observed after treatment with the test item during the 14 day observation period.

There were no treatment related body weight changes. Body weights were within the range commonly recorded for this strain and age.

There was no evidence of the any macroscopic changes at a dose level of 2000 mg/kg bw at necropsy.

1.3 Conclusion

Under the conditions of this study, the median lethal dose (LD_{50}) of Isopyrazam/Difenoconazole SC (A21295D) after a single dermal administration was greater than 2000 mg/kg bw in male and female Crl:WI rats.

2.0 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the acute dermal toxicity of the test item Isopyrazam/Difenoconazole SC (A21295D) when administered to Crl:WI male and female rats by a single dermal application, followed by an observation period of 14 days.

This study was performed with vertebrate animals as no *in vitro* alternative is available. The study was designed such that the minimum numbers of animals were used.

This study should provide a rational basis for hazard assessment.

2.2 Guidelines

The study was performed according to the following guidelines:

- OECD Guidelines for Testing of Chemicals, Section 4, Number 402 "Acute Dermal Toxicity", adopted February 24, 1987
- United States Environmental Protection Agency Health Effects Division Test Guidelines, OPPTS 870.1200 Acute Dermal Toxicity EPA 712-C-98-192, August 1998
- Commission Regulation (EC) No 440/2008, B.3 (L 142, 30 May 2008)
- Guidance Document on Toxicology for Registration of Pesticides in India (2014). Ministry of Agriculture Department of Agriculture & co-operation Central Insecticides Board & Registration Committee Directorate of Plant Protection Quarantine & Storage. NH-IV, Faridabad

This study was being performed to meet safety assessment requirements outside the EU, hence the Commission regulation (EU) 2016/863 of 31 May 2016 restricting the performance of acute dermal toxicity studies does not apply.

2.3 Test Facility

This study was performed in an AAALAC-accredited laboratory. The Institutional Animal Care and Use Committee (IACUC) of CiToxLAB Hungary Ltd. reviewed the Study Plan and authorised the conduct of the study.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The following information was provided by the Sponsor.

Name:	Isopyrazam/Difenoconazole SC (A21295D)
Batch number:	JHU002-109-004
Active ingredient content*:	CGA169374 (difenoconazole), 11.9 % w/w corresponding to 129 g/L CGA185882 (cis isomer of difenoconazole), 6.97 % w/w corresponding to 76.0 g/L CGA185883 (trans isomer of difenoconazole), 4.89 % w/w corresponding to 53.3 g/L SYN520453 (isopyrazam) 11.9 % w/w corresponding to 130 g/L SYN534969 (syn isomer of isopyrazam) 10.1 % w/w corresponding to 110 g/L SYN534968 (anti isomer of isopyrazam) 1.82 % w/w corresponding to 19.9 g/L
Density:	1091 kg/m^3
Appearance:	Off-white liquid
Recertification date:	30 November 2018
Storage conditions:	Room temperature (<30°C)
Safety precautions:	Enhanced safety precautions were applied considering the supplied safety datasheet to assure personnel health and safety.
Hazards:	May cause an allergic skin reaction. Causes serious eye irritation. Suspected of damaging the unborn child.

**No correction for purity of the test item was applied.*

The Certificate of Analysis is presented in Appendix 2.

3.1.1 Identification and receipt

The test item of a suitable chemical purity was provided by the Sponsor. All precautions required in the handling and disposal of the test item were outlined by the Sponsor. The test item was identified by the Pharmacy of CiToxLAB Hungary Ltd. on the basis of the information supplied by the Sponsor.

3.1.2 Formulation

The test item was administered as a single dose, as supplied by the Sponsor.

3.2 Experimental Design

3.2.1 Animals

Species and strain:	Crl:WI Wistar rats
Source:	Charles River Laboratories, Research Models and Services, Germany GmbH, Sandhofer Weg 7, D-97633 Sulzfeld, Germany
Hygienic level:	SPF at arrival, standard housing condition during the study
Justification of strain:	Recognized by international guidelines as a recommended test system
Number of animals:	5 animals/sex
Sex:	Male and female, female rats were nulliparous and non-regnant.
Age of animals at dosing:	Young adult rats
Body weight at dosing:	Between 237 g and 269 g
Identification:	Animals were identified by numbers written on the tail with an indelible pen. The cages were marked with individual identity cards with information about study number, sex, cage number, dose group and individual animal number.
Randomization:	Selected by hand at time of delivery
Acclimatisation time:	5 or 7 days

3.2.2 Husbandry

Animal health:	Only healthy animals were used for the study. The Veterinarian certified health status.
Room number:	242/4
Housing / Enrichment:	Animals were housed individually in Type II. polypropylene/polycarbonate cages. Rodents were housed with deep wood sawdust bedding to allow digging and other normal rodent activities.
Bedding / Nesting:	"Lignocel 3/4-S" Hygienic Animal Bedding and "Arbocel crinklets natural" nesting material (produced by J. Rettenmaier & Söhne GmbH + Co.KG, Germany) were available to animals during the study.
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	20.2 – 26.2 °C
Relative humidity:	30 – 60%
Ventilation:	15-20 air exchanges per hour

The temperature and relative humidity were recorded twice daily during the acclimatisation and experimental phases of the study.

3.2.3 Food and feeding

Animals received ssniff® SM R/M "Autoclavable complete diet for rats and mice – breeding and maintenance" produced by ssniff Spezialdiäten GmbH, D-59494, Soest, Germany (Lot number: 285 17890, Expiry date: 31 August 2017), *ad libitum*. The food was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study. A detailed description of the contents of the lot used is archived with the raw data at CiToxLAB Hungary Ltd.

3.2.4 Water supply and quality control

The animals received tap water, from the municipal supply, provided in 500 mL bottles, *ad libitum*. The tap water is suitable for human consumption and considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study.

Water quality control analysis is performed once every three months and microbiological assessment is performed monthly by Veszprém County Institute of State Public Health and Medical Officer Service (ÁNTSZ, H-8201 Veszprém, József Attila utca 36., Hungary). The quality control results are retained in the archives at CiToxLAB Hungary Ltd.

3.3 Experimental Design

3.3.1 Doses

A limit dose of 2000 mg/kg bw was chosen by the Study Director after discussion with the Sponsor.

3.3.2 Experimental design

Dose Group	Number of cages	Number of animals
Sentinel animal 2000 mg/kg bw male	Cage 1	1
2000 mg/kg bw males	Cages 2-5	4
Sentinel animal 2000 mg/kg bw female	Cage 6	1
2000 mg/kg bw females	Cages 7-10	4

A single administration was performed by the dermal route and was followed by a 14-day observation period.

One male and one female rats were dosed initially and the remaining four male and four female rats were dosed 48 hours later when it was clear there were no adverse effects.

3.3.3 Procedure

The back of the animal was shaved (approximately 10% area of the total body surface) approximately 24 hours prior to the treatment. Only those animals without injury or irritation on the skin were used in the test.
On Day 0, the test item was applied as a single dose of 2000 mg/kg bw, and distributed as uniformly as possible over the skin and remained on the skin throughout a 24-hour exposure period. Sterile gauze pads were placed on the skin of rats at the site of application. These gauze pads were kept in contact with the skin by a patch with adhesive hypoallergenic plaster. The entire trunk of the animal was then wrapped with semi occlusive plastic wrap for 24 hours. At the end of the exposure period, residual test item was removed, using body temperature water.

3.4 Observations

3.4.1 Clinical observations

A clinical examination was performed on the day of treatment (Day 0), at 1 and 5 hours after the application of the test item, and once each day for 14 days thereafter.

Observations included the skin and fur, eyes and mucous membranes, and also respiratory, circulatory, autonomic and central nervous system, and somatomotor activity and behaviour pattern. Particular attention was directed to the observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

3.4.2 Skin irritation

Adverse skin reactions at the site of application were recorded daily following the removal of the dressing.

3.4.3 Measurement of body weight

The body weight of all animals was recorded on Day 0 (day of treatment), and on Days 7 and 14 (before necropsy).

3.5 *Post Mortem* Investigations

All animals were subjected to gross macroscopic examination. All animals were anaesthetised with Release® (Pentobarbital sodium, details in 3.5.1.) and exsanguinated. After examination of the external appearance, the cranial, thoracic and abdominal cavities were opened and the appearance of the tissues and organs were observed. Any gross macroscopic findings were recorded.

3.5.1 Material used for euthanasia

Name:	Release® (Pentobarbital sodium)
Lot No.:	106075
Expiry Date:	31 July 2018
Produced by:	Wirtschaftsgenossenschaft deutscher Tierärzte eG Siemensstr. 14, 30827 Garbsen, Germany

3.5.2 Data evaluation

The type, severity and duration of clinical observations were described. Body weight and body weight changes were summarised in tabular form. Necropsy findings were described and summarised in tabular form.

4.0 RESULTS AND DISCUSSION

4.1 Mortality

No mortality occurred during the study.

4.2 Clinical Signs

There were no adverse clinical signs noted in any animals throughout the study. Individual clinical observations are presented in Table 1.

4.3 Local Dermal Signs

No local dermal signs were observed after treatment with the test item during the 14-day observation period.

4.4 Body Weight

There were no treatment related body weight changes. Body weights were within the range commonly recorded for this strain and age. Individual body weights are presented in Table 2.

4.5 Necropsy

No macroscopic changes were observed (Table 3). Pathology Report is presented in Appendix 1.

5.0 CONCLUSIONS

Under the conditions of this study, the median lethal dose (LD_{50}) of Isopyrazam/Difenoconazole SC (A21295D) after a single dermal administration was greater than 2000 mg/kg bw in male and female Crl:WI rats.

TABLES SECTION

TABLE 1 Clinical Observations

DOSE LEVEL: 2000 mg/kg bw **SEX: MALE**

Cage No.	Animal No.	Observations	Observation days																Frequency
			0		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
			1h	5h															
1	9604	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16
2	9605	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16
3	9606	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16
4	9607	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16
5	9608	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16

DOSE LEVEL: 2000 mg/kg bw **SEX: FEMALE**

Cage No.	Animal No.	Observations	Observation days																Frequency
			0		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
			1h	5h															
6	9609	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16
7	9610	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16
8	9611	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16
9	9612	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16
10	9613	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16

Remarks: + = present

h = hour (s) Treatment day = Day 0

Frequency of observation = number of occurence of observation / total number of observations

TABLE 2 Body Weight and Body Weight Gain

DOSE LEVEL: 2000 mg/kg bw **SEX: MALE**

Cage No.	Animal No.	Body weight (g) Days			Body Weight Gain (g)		
		0	7	14	0-7	7-14	0-14
1	9604	247	282	313	35	31	66
2	9605	261	299	348	38	49	87
3	9606	259	281	316	22	35	57
4	9607	269	306	346	37	40	77
5	9608	261	298	336	37	38	75
Mean:		259.4	293.2	331.8	33.8	38.6	72.4
Standard deviation:		7.9	11.1	16.5	6.7	6.7	11.4

DOSE LEVEL: 2000 mg/kg bw **SEX: FEMALE**

Cage No.	Animal No.	Body weight (g) Days			Body Weight Gain (g)		
		0	7	14	0-7	7-14	0-14
6	9609	241	248	271	7	23	30
7	9610	245	258	272	13	14	27
8	9611	247	271	274	24	3	27
9	9612	257	260	271	3	11	14
10	9613	237	257	271	20	14	34
Mean:		245.4	258.8	271.8	13.4	13.0	26.4
Standard deviation:		7.5	8.2	1.3	8.7	7.2	7.5

TABLE 3 Macroscopic Findings

DOSE LEVEL: 2000 mg/kg bw **SEX: MALE**

Cage No.	Animal No.	Necropsy Date/ Necropsy Day	External Observations	Internal Observations	Organ/ Tissue
1	9604	27 June 2017 Day 14	No external observations	No internal observations	Not applicable
2	9605	29 June 2017 Day 14	No external observations	No internal observations	Not applicable
3	9606	29 June 2017 Day 14	No external observations	No internal observations	Not applicable
4	9607	29 June 2017 Day 14	No external observations	No internal observations	Not applicable
5	9608	29 June 2017 Day 14	No external observations	No internal observations	Not applicable

DOSE LEVEL: 2000 mg/kg bw **SEX: FEMALE**

Cage No.	Animal No.	Necropsy Date/ Necropsy Day	External Observations	Internal Observations	Organ/ Tissue
6	9609	27 June 2017 Day 14	No external observations	No internal observations	Not applicable
7	9610	29 June 2017 Day 14	No external observations	No internal observations	Not applicable
8	9611	29 June 2017 Day 14	No external observations	No internal observations	Not applicable
9	9612	29 June 2017 Day 14	No external observations	No internal observations	Not applicable
10	9613	29 June 2017 Day 14	No external observations	No internal observations	Not applicable

APPENDICES SECTION

APPENDIX 1 Pathology Report

Study code. 17/135-002P

PATHOLOGY REPORT

INTRODUCTION

The objective of the study was to assess the acute dermal toxicity of Isopyrazam/Difenoconazole SC (A21295D) when administered in a single 24-hour dermal application to male and female rats at a dose level of 2000 mg/kg bw followed by 14 days observation.

METHODS

All rats survived until the scheduled termination of the study.

All animals were euthanised upon completion of the treatment period on Day 14. Rats were anaesthetised with pentobarbital, followed by exsanguination. Gross pathology consisted of an external examination, including identification of all clinically-recorded lesions, as well as a detailed internal examination. Histopathological examination was not performed.

TERMINAL (DAY 14)

Macroscopic Findings

There was no evidence of the any observations at a dose level of 2000 mg/kg bw at necropsy.

CONCLUSION

A single 24 hour dermal application of Isopyrazam/Difenoconazole SC (A21295D) to male and female Crl:WI Wistar rats at a dose level of 2000 mg/kg bw followed by 14 days observation, was not associated with any macroscopic findings.

Peter Maslej, D.V.M., Ph.D.
Director of Pathology

19 Dec 2017
Date

APPENDIX 2 Certificate of Analysis

syngenta

GLP Testing Facility WMU
Analytical Development &
Product Chemistry GS2131

Syngenta Crop Protection
Münchwilen AG
Im Breitenloh 5
4333 Münchwilen, Switzerland

Certificate of Analysis

A21295D
CGA169374/SYN520453 SC (125/125)
JHU002-109-004

Batch Identification	**JHU002-109-004**
Product Code	**A21295D**
Other Product Code(s)	CGA169374/SYN520453 SC (125/125)

Chemical Analysis
(Active Ingredient Content)

– **Identity of the Active Ingredients***	**Confirmed**
– **Content of CGA169374 (difenoconazole)***	**11.9 % w/w corresponding to 129 g/l**
– **Content of CGA185882 (cis isomer of difenoconazole)***	**6.97 % w/w corresponding to 76.0 g/l**
– **Content of CGA185883 (trans isomer of difenoconazole)***	**4.89 % w/w corresponding to 53.3 g/l**
– **Content of SYN520453 (isopyrazam)***	**11.9 % w/w corresponding to 130 g/l**
– **Content of SYN534969 (syn isomer of isopyrazam)***	**10.1 % w/w corresponding to 110 g/l**
– **Content of SYN534968 (anti isomer of isopyrazam)***	**1.82 % w/w corresponding to 19.9 g/l**

The Active Ingredient(s) content is within the FAO limits.

Methodology used for Characterization	HPLC, OECD 109 (oscillating density meter)

Physical Analysis

– **Appearance**	**Off-white liquid**
– **Density***	**1091 kg/m^3**

Stability:

– **Storage Temperature**	**< 30 °C**
– **Recertification Date**	**End of November 2018**

If stored under the conditions given above, this test substance can be considered stable until the recertification date is reached.

This Certificate of Analysis summarizes data which originates either from a single study or from several individual studies. Tests marked with an asterisk (*) have been conducted in compliance with GLP. Raw data, documentation, study plans, any amendments to study plans and reports pertaining to this/these study/studies are stored under the study number(s) referenced below within the archives of the GLP Testing Facility WMU at Syngenta Crop Protection Münchwilen AG, Switzerland.

APPENDIX 2 Certificate of Analysis (Continued)

syngenta

GLP Testing Facility WMU
Analytical Development &
Product Chemistry GS2131

Syngenta Crop Protection Münchwilen AG
Im Breitenloh 5
4333 Münchwilen, Switzerland

Certificate of Analysis

Study number of batch characterization: CHMU151002
Study number(s) of batch recetification: ---

Authorisation: 14-Dec-2015

Elke Ebi
Analytical Development & Product Chemistry

APPENDIX 3 GLP Certificate

OGYÉI
National Institute of
Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Ref. no: OGYI/19440-7/2015
Admin.: Szatmári Andrea
Date: 22 September, 2015

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility

CiToxLAB Hungary Ltd.

H-8200 Veszprém, Szabadságpuszta

is able to carry out

physico-chemical testing, toxicity studies, in vitro studies and mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, reproduction toxicology, inhalation toxicology, analytical chemistry and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **02-04. June 2015.**

Dr. József Reiter
Deputy Director-General

Note: Translation of the Stamp on the official document ("Országos Gyógyszerészeti és Élelmezés-egészségügy Intézet"): ("National Institute of Pharmacy and Nutrition")