citoxlab
Safety and Health Research

SYN548121

SYN548121 - Acute Oral Toxicity Study in Rats (Up and Down Procedure)

Final Report

DATA REQUIREMENT(S): OECD 425 (2008)
EPA 870.1100 (2002)

AUTHOR(S): Ádám Appl, M.Sc.

COMPLETION DATE: 24 October 2018

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

LABORATORY PROJECT ID: Report Number: 18/133-001P
Study Number: 18/133-001P
Task Number: TK0346294

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

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, authorized by the Sponsor and Citoxlab Hungary Ltd. Management, and followed applicable Standard Operating Procedures.

No chemical analysis of the dose formulation was performed as part of this study. Traceability (equipment used, quantities of test item weighed) of dosing form preparations were checked and revealed no abnormalities of consequences. Furthermore, for this study, the formulations were prepared just before the treatment. Consequently, the absence of dose formulation analysis data was considered not to prejudice the overall GLP status of the study and the scientific reliability of the study conclusions.

The study was conducted by Viktória Zelenák, M.Sc. up to 22 August 2018. Following the departure of the originally appointed Study Director, I took responsibility for the study.

Signature: _____ Date: 24 October 2018

Ádám Appl, M.Sc.
Study Director

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

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Number: 18/133-001P

Study Title: SYN548121 - Acute Oral Toxicity Study in Rats (Up and Down Procedure)

Test Item: SYN548121

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
22 May 2018	Study Plan	22 May 2018	22 May 2018
24 May 2018	Treatment	24 May 2018	24 May 2018
01 August 2018	Draft Report	01 August 2018	01 August 2018
11 September 2018	Amendment 1 to the Study Plan	11 September 2018	11 September 2018
13 October 2018	Final Report	13 October 2018	13 October 2018

Signature: Schleicher Ivett

Ivett Schleicher, Ph.D.
QA Inspector

Date: 24 October 2018

MANAGEMENT STATEMENT

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 "SYN548121 - Acute Oral Toxicity Study in Rats (Up and Down Procedure)" has been performed in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 24 oct 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 (from 23 August 2018)
Viktória Zelenák, M.Sc.	Study Director (until 22 August 2018)
Zsolt Tarcai, M.Sc.	Assistant Scientist
Szabolcs Gáty, M.Sc	Senior Director of QA
Ivett Schleicher, Ph.D.	Quality Assurance
Leila Merazga, M.Sc.	Quality Assurance
László Székelyhidi, DVM	Veterinary Control
Peter Maslej, DVM, Ph.D.	Director of Pathology
Gábor Boros, DVM	Histopathologist
Tamás Mészáros, Ph.D.	Pharmacy
William Masinja, M.Sc.	Syngenta Study Manager

Study dates

Study Initiation Date	22 May 2018
Experimental Starting Date	24 May 2018
Experimental Completion Date	14 June 2018
Receipt of Animals	03 May 2018
Acclimatisation	At least 20 days
Treatment	24 May 2018 (female no. 3827) 29 May 2018 (female no. 3828) 31 May 2018 (female no. 3829)
Observation	24 May – 07 June 2018 (female no. 3827) 29 May – 12 June 2018 (female no. 3828) 31 May – 14 June 2018 (female no. 3829)

Deviations from the Study Plan

Due to a technical reason, relative humidity values (maximum of 74 %) outside the expected range of 30-70 % were recorded during the acclimation period. However, these minor differences of the environmental parameters were considered not to adversely affect the results or integrity of the study.

The dose volume was 20 mL/kg bw due to the practical reason instead of 10 mL/kg bw as it was indicated in the Study Plan.

The temperature and relative humidity were recorded twice daily during the acclimatisation and experimental phases of study exception on 29 May 2018 where was recoded only once due to the technical oversight.

These deviations were considered not to adversely affect the results or integrity of the study.

Performing laboratory test substance reference number

180156

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 of 15 years 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

An acute oral toxicity (up and down procedure) study was conducted with 3 female Crl:WI rats. Animals were treated with a single oral (gavage) dose of SYN548121, at a dose level of 5000 mg/kg body weight (bw) followed by a 14 day observation period. The animals were fasted overnight prior to treatment and food was returned 3 hours after dosing.

Animals were observed individually after dosing at 30 minutes, then 1, 2, 3, 4 and 6 hours post treatment and once each day for 14 days thereafter. Body weight was measured on Day -1, just before dosing and weekly thereafter. All animals were examined macroscopically at the end of the observation period.

1.2 Results

There was no mortality during the study.

Treatment with SYN548121 at the dose level of 5000 mg/kg bw did not cause any adverse clinical signs.

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

There was no evidence of the macroscopic observations at a dose level of 5000 mg/kg bw.

1.3 Conclusion

Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of the test item, SYN548121, was found to be greater than 5000 mg/kg bw in female Crl:WI rats.

2.0 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the oral toxicity of the test item SYN548121 when administered as a single oral gavage dose to female rats at one or more defined dose levels.

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.

2.2 Guidelines

The study was performed according to the following guidelines:

- OECD Guidelines for the Testing of Chemicals, Section 4, Test No. 425 Acute Oral Toxicity: Up-and-Down Procedure. OECD Publishing, 2008.

- United States Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.1100 Acute Oral Toxicity EPA 712-C-02-190, December 2002.

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 authorized the conduct of the study.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The following information was provided by the Sponsor.

Name:	SYN548121
Batch number:	SMU7FP17006
Design code:	SYN548121 tech.
Appearance:	Yellow solid
Purity*:	98.2% (w/w)
Recertification date:	31 July 2021
Storage conditions:	Room temperature (<30°C)
Safety precautions:	Routine safety precautions (lab coat, gloves, goggles, face mask) for unknown materials were applied to assure personnel health and safety.

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

The Certificate of Analysis is presented in Appendix 2.

The integrity of supplied data relating to the identity, purity and stability of the test material is the responsibility of the Sponsor.

3.1.1 Identification and receipt

The test item of a suitable chemical purity together with all precautions required in the handling and disposal of the test item were supplied by the Sponsor. The identification of the test item was made in the Pharmacy of Citoxlab Hungary Ltd. on the basis of the information provided by Sponsor.

3.1.2 Formulation

Test item was freshly formulated with the vehicle (distilled water), in the Pharmacy of Citoxlab Hungary Ltd. on the day of administration. The formulation was stirred with a magnetic stirrer up to finishing the treatment. The 500 mg/mL concentration (10 ml/kg dose volume) was not achievable during the formulation process due to the characteristic of the test item (the formulation was inhomogeneous and was not suitable for oral gavage); therefore, formulations with lower concentration (250 mg/mL) were used during the study and the dose volume has been increased to 20 mL/kg.

3.1.3 Vehicle selection

The selection of the vehicle was made during trial formulations with the test item. The final choice of vehicle was approved by the Sponsor. On the basis of the trial formulations with the test item, the vehicle used was distilled water.

Name:	Distilled water
Batch number:	8070318/ 8020118
Expiry Date:	26 September 2018/ 29 July 2018
Manufacturer:	Hungaro-Gal Kft., Hungary
Storage condition:	Room temperature

3.2 Experimental Design

3.2.1 Animals

Species and strain:	Crl:WI rats
Source:	Charles River Laboratories, Research Models and Services, Germany GmbH, Sandhofer Weg 7, D-97633 Sulzfeld
Hygienic level:	SPF at arrival, standard housing conditions during study.
Justification of strain:	Recognized by international guidelines as a recommended test system.
Number of animals:	3
Sex:	Female rats, nulliparous and non-pregnant.
Age when treated:	Young adult rats, 10-11 weeks old.
Body weight (at dosing):	226 – 241 g
Identification:	The animals were identified by numbers written on the tail with an indelible marker. 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.
Acclimatization time:	At least 20 days

3.2.2 Husbandry

Animal health:	Only healthy animals were used for the test. The health status was certified by the Veterinarian.
Room number:	522/4
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" nest building material produced by J. Rettenmaier & Söhne GmbH + Co.KG (D-73494 Rosenberg, Germany) were available to animals during the study. Copies of the Certificate of Analysis are retained in the archive at Citoxlab Hungary Ltd.
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	22 ± 3 °C
Relative humidity:	36 - 74 %
Ventilation:	15-20 air exchanges/hour

The temperature and relative humidity were recorded twice daily during the acclimatisation period and throughout the study exception on 29 May 2018 where was recorded only once due to the technical oversight.

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 *ad libitum*. The batch number of the lot used in the study was Lot number: 883 29966, Expiry date: 31 October 2018. The food was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study. Details of the diet are archived with the raw data at Citoxlab Hungary Ltd.

3.2.4 Water supply and quality control

Animals received tap water from the municipal supply from 500 mL bottles *ad libitum*. The water was fit for human consumption and was 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 A. street 36., Hungary). The quality control results are retained in the archive at Citoxlab Hungary Ltd.

3.3 Administration of the Test Item

3.3.1 Dosages

Justification of the doses:

A limit test with a starting dose of 5000 mg/kg bw was selected by the Sponsor. A total of 3 animals were treated with a single oral (gavage) dose of SYN548121at a dose level of 5000 mg/kg body weight (bw). The dose volumes for the animal were 20 mL/kg bw. The individual dose volumes used are shown below.

Animal Number	Dose [mg/kg body weight]	Volume Dosed [mL]	Bodyweight [g]	Mortality
3827	5000	4.6	227	Survived
3828	5000	4.6	226	Survived
3829	5000	4.8	241	Survived

Rationale:

Oral administration was considered to be an appropriate dose route as it is a possible route of human exposure.

3.3.2 Procedure

A single oral (gavage) dose was followed by a 14-day observation period. The animals were fasted overnight prior to treatment. Water was still available, *ad libitum* overnight. Animals were weighed before dosing and the food was returned 3 hours after the treatment.

Individual animals were dosed sequentially following an interval of at least 48 hours.

3.4 Observations

3.4.1 Clinical observations

Animals were observed individually after dosing at 30 minutes, then at approximately 1, 2, 3, 4, and 6 hours after dosing and once each day for 14 days thereafter. Individual observations were performed on the skin and fur, eyes and mucous membranes and also respiratory, circulatory, autonomic and central nervous system, somatomotor activity and behaviour pattern.

Particular attention was directed to observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

3.4.2 Body weight measurement

The body weights were recorded on Days -1(prior to removal of food), 0 (before treatment), 7 and 14.

3.5 *Post Mortem* Investigations

All animals were subjected to gross macroscopic evaluation. All animals were euthanised under pentobarbital anaesthesia (Euthanimal, details in 3.5.1) at the end of the observation period. After examination of the external appearance, the cranial, thoracic and abdominal cavities were opened and the appearance of the tissues and organs were observed. All gross pathological changes were recorded for each animal on the post mortem record sheets and the animals were discarded.

3.5.1 Material used for euthanasia

Name:	Euthanimal 40% (Pentobarbital sodium, 400 mg/mL)
Lot No.:	1609291-03
Expiry Date:	31 October 2019
Produced by:	Alfasan Nederland BV, Kuipersweg 9, Woerden, The Netherlands

3.6 Data Evaluation

Type, severity and duration of clinical observations are described. Body weight and body weight changes are summarised in tabular form. Necropsy findings are described and summarised in tabular form.

The LD_{50} was calculated using the AOT425StatPgm program. This program was prepared for the US Environmental Protection Agency by Westat, May 2001 and updated by the US EPA June 2003. This program was constructed using the most appropriate method to estimate the LD_{50}.

4.0 RESULTS AND DISCUSSION

4.1 Mortality

No mortality occurred during the study.

4.2 Clinical Signs

Treatment with SYN548121 at the dose level of 5000 mg/kg bw did not cause any adverse clinical signs.

Individual clinical observations and mortality results are presented in Table 1.

4.3 Body Weights

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

4.4 Macroscopic Findings

A single oral gavage of SYN548121 to the Crl:WI rats at a dose level of 5000 mg/kg bw with a 14 day observation period, was not associated with any macroscopic findings.

Macroscopic findings are presented in Table 3. The pathology report is presented in Appendix 1.

5.0 CONCLUSIONS

Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of the test item, SYN548121, was found to be greater than 5000 mg/kg bw in female Crl:WI rats.

TABLES SECTION

TABLE 1 Individual Findings – Clinical Sign

INDIVIDUAL CLINICAL OBSERVATIONS
STUDY CODE: 18/133-001P
TEST SYSTEM: CRL: (WI) rats
TEST ITEM: SYN548121

DOSE LEVEL: 5000 mg/kg bw, Treatment on Day 0 **SEX: FEMALE**

Cage No.	Animal Number	Observations	Observation days																		Frequency
			0						1	2	3	4	5	6	7	8	9	10	11	12	13	14	
			30'	1h	2h	3h	4h	6h															
1	3827	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
2	3828	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
3	3829	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20

Remarks: + = present

h = hour (s) ' = minute

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

TABLE 2 Body Weight and Body Weight Gain

INDIVIDUAL BODY WEIGHT AND BODY WEIGHT GAIN
STUDY CODE: 18/133-001P
TEST SYSTEM: CRL: (WI) rats
TEST ITEM: SYN548121

DOSE LEVEL: 5000 mg/kg bw, Treatment on Day 0 **SEX: FEMALE**

Cage No.	Animal Number	Body weight (g) Days				Body Weight Gain (g)			
		-1	0	7	14	-1-0	0-7	7- 14	-1 - 14
1	3827	248	227	246	255	-21	19	9	7
2	3828	244	226	246	255	-18	20	9	11
3	3829	253	241	268	270	-12	27	2	17
Mean:		248.3	231.3	253.3	260.0	-17.0	22.0	6.7	11.7
Standard deviation:		4.5	8.4	12.7	8.7	4.6	4.4	4.0	5.0

TABLE 3 Macroscopic Findings

INDIVIDUAL INTERNAL AND EXTERNAL MACROSCOPIC OBSERVATIONS
STUDY CODE: 18/133-001P
TEST SYSTEM: CRL: (WI) rats
TEST ITEM: SYN548121

DOSE LEVEL: 5000 mg/kg bw, Treatment on Day 0 **SEX: FEMALE**

Cage No.	Animal Number	Necropsy Date/ Necropsy Day	External Observations	Internal Observations	Organ/Tissue
1	3827	07 June 2018 Day 14	No external observations recorded	No internal observations recorded	Not applicable
2	3828	12 June 2018 Day 14	No external observations recorded	No internal observations recorded	Not applicable
3	3829	14 June 2018 Day 14	No external observations recorded	No internal observations recorded	Not applicable

APPENDICES SECTION

APPENDIX 1 Pathology Report

Citoxlab Hungary Ltd. Study code 18/133-001P

PATHOLOGY REPORT

INTRODUCTION

The objective of the study was to assess the acute oral toxicity of the test item SYN548121, when administered via a single oral gavage dose to female rats. Three rats were dosed at 5000 mg/kg bodyweight with the test item.

METHODS

All animals were euthanized upon completion of the observation period on Day 14. Rats were anaesthetized 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 macroscopic observations at a dose level of 5000 mg/kg bw.

CONCLUSION

A single oral gavage of SYN548121 to the Crl:WI rats at a dose level of 5000 mg/kg bw with a 14-day observation period, was not associated with any macroscopic findings.

Gábor Boros, D.V.M.
Histopathologist

22. Oct. 2018.
Date

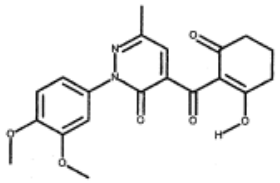
APPENDIX 2 Certificate of Analysis

syngenta

Syngenta Crop Protection AG
GLP Testing Facility WMU
Analytical Development & Product Chemistry
Breitenloh 5
4333 Münchwilen, Switzerland

Certificate of Analysis

SYN548121 tech.



Batch: SMU7FP17006
Purity: 98.2 %

Batch Identification	**SMU7FP17006**
Other Batch ID	995901
Product Code	**SYN548121 tech.**
Other Product Code(s)	---
ISO Common Name	---
CA Reg. No.	---
CA Index Name	---
IUPAC Name	2-(3,4-dimethoxyphenyl)-4-(2-hydroxy-6-oxo-cyclohexene-1-carbonyl)-6-methyl-pyridazin-3-one
Molecular formula	$C_{20}H_{20}N_2O_6$
Molecular mass	384.38
Chemical Analysis	
– **Identity of SYN548121***	**confirmed**
– **Content of SYN548121***	**98.2 % w/w** The detailed results of the characterization are listed in the final report
Methodology used for Characterization / Recertification	HPLC, NMR, headspace GC, coulometric Karl-Fischer Titration, Fraunhofer diffraction
Physical Analysis	
– **Appearance***	**yellow solid**
– **Particle size distribution* (Fraunhofer diffraction method)**	**d(50): 23.62 µm, d(90): 41.20 µm**
Stability:	
– **Storage Temperature**	**< 30 °C**
– **Recertification Date**	**End of July 2021**

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 AG, Switzerland.

Study number of batch characterization: CHMU170402
Study number(s) of batch recertification: ---

Authorization: 24-July-2017

Dr. Christopher Heppel
Analytical Development & Product Chemistry

APPENDIX 3 GLP Certificates

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-egészségügyi Intézet"): ("National Institute of Pharmacy and Nutrition")

APPENDIX 3 GLP Certificates (Continued)

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: OGYÉI/22762-5/2018
Admin.: Dr. Juhász Uzonka
Date: 03 August 2018

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, mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, analytical and clinical chemistry, pathology studies, preparation of microscopic tissue sections, reproduction toxicology, in vitro studies, inhalation toxicology, 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: **07-11 May 2018.**

Tarjáni Ibolya
Head of Inspectorate

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