Israel Laboratory Accreditation Authority

Valid from בתוקף מתאריך
15.02.2021

Effective from מחייב בתאריך
15.02.2021

GLP מדריך

GLP Manual

נוהל מספר: 1-200000

Procedure Number: 1-200000

Signature – חתימה	תאריך – Date	Name – שם	Position – תפקיד
		יקיר ג'אוי Yakir Jaoui	נכתב ע"י מנהל איכות: Written by Quality Manager:
		אתי פלר Etty feller	מאושר ע"י מנכ"ל: Approved by General Manager:

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

הרשות הלאומית להסמכת מעבדות ISRAC (Israel Accreditation) הוקמה בחוק על ידי ממשלת ישראל כארגון ההסמכה הלאומי לבדיקה והסמכה של כשירות מקצועית בתחום כיול ובדיקה.

הרשות מוכרת במסגרת הסכם ההכרה ההדדי של הארגון הבינלאומי ILAC (International Laboratory Accreditation Cooperation) כעובדת על פי הכללים הבינלאומיים להסמכה.

כל זכויות היוצרים והקניין הרוחני, מכל סוג כלשהו, בקשר לכל פרסום, תוכן, כתבה, עיצוב, יישום, קובץ, תוכנה וכל חומר אחר, המתפרסם באתר – שייך לרשות הלאומית להסמכת המעבדות © ISRAC.
אין להעתיק, לתרגם, לשדר בכל אמצעי, לאחסן במאגר מידע, לפרסם, להציג בפומבי, או להפיץ בכל אמצעי, את החומר המוצג באתר זה, כולו או חלקו, בלא קבלת הסכמתה המפורשת מראש ובכתב של הרשות הלאומית להסמכת מעבדות.

הרשות הלאומית להסמכת מעבדות

Israel Laboratory Accreditation Authority

רח' כנרת קרית שדה התעופה, ת.ד. 89, לוד

נמל תעופה 7015002

טל' 03-9702727

פקס 03-9702413

דוא"ל : israc@israc.gov.il

www.israc.gov.il

Procedure Updates:

Section	Date	The Change
General	Dec 14th, 2020	Periodical review of the GLP manual including update of the Normative References.
3.2.5	Feb 4th, 2021	Improvement initiative No. 1932 following internal audit 223: Risk based approach for the monitoring program.
3.4.3		Improvement initiative No. 1932 following internal audit 223: Options for conducting studies to be included in the request for recognition of new test facility.
3.10.2.2		Improvement initiative No. 1932 following internal audit 223: A special inspection is subject to ISRAC General Manager decision.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

Table of Contents

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

1.0 GENERAL

This Manual describes the structure and procedure of the Israel National Good Laboratory Practice (GLP) Monitoring Unit within the Israel Laboratory Accreditation Authority (ISRAC) i.e. Israel National Good Laboratory Practice Monitoring Authority (IL-GLP-MA).

The Manual complies with the following the Organization for Economic Co-operation and Development (OECD) documents:

"Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice", *Environment Monograph No. 110*, OECD/GD (95)66, 1995

and "Guidance for the Conduct of Laboratory Inspections and Study Audits" *Environment Monograph No. 111*, OECD/GD (95)67 1995.

This Manual is part of ISRAC's documented Quality System.

1.1 Introduction

Compliance with the principles of GLP is a regulatory requirement for test facilities that undertake health and environmental safety studies, and some other testing, that will be submitted to regulatory authorities for the purpose of risk assessment.

Governments and industry are concerned about the quality of non-clinical health and environmental safety studies upon which hazard assessments are based. As a consequence, OECD member countries have established criteria for the performance of these studies.

This GLP Manual describes the policies and procedures for IL-GLP-MA operation.

***Note** 1: Where a variation is found between the requirements of this GLP Manual and ISRAC's general Quality Manual (document number 1-432000) or other procedures of ISRAC, the GLP manual instructions are to be followed.*

1.1.1 GLP is a managerial concept covering the organizational process and conditions under which laboratory studies are planned, performed, monitored, recorded, archived and reported. GLP principles are required to be followed by test facilities, carrying out studies to be submitted to national authorities for the purposes of assessment of chemicals and other uses relating to the protection of man and the environment.

1.1.2 The internationally accepted principles of GLP were developed by the OECD. The application of these Principles by Israel should help to promote the development of quality test data and to form the basis for international acceptance of data generated by Israeli test facilities. Thus, duplicative testing can be avoided, thereby saving time and resources. In addition, the application of

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

GLP Principles is meant to avoid the creation of technical barriers to trade, and thus encouraging the participation of Israeli manufactures in the global market.

1.2 Israel National GLP Monitoring Unit

The Israel National GLP Monitoring Unit (IL-GLP), forms part of ISRAC.
IL-GLP is responsible for the monitoring test facilities' compliance with GLP. IL-GLP operates in accordance with the OECD environment monographs number 110 and 111 (also designated as documents number 2 and 3 of the *OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring*).
IL-GLP deals with all enquiries on GLP from Israel and overseas regulatory authorities, and monitoring authorities. It also acts as a contact point and provides information and guidance to industry, test facilities, sponsors, and the public on any aspect of GLP. To this end, the GLP MA may publish occasionally guidance on the interpretation or application of GLP principles, in particular situations or circumstances.

1.3 Definition of Terms

1.3.1 The definitions of terms in documents number 1, 2 and 3 of the OECD series on Principles of Good Laboratory Practice and Compliance Monitoring are applicable to this document. Some of these definitions are quoted below:

1.3.1.1 Good Laboratory Practice (GLP)

A quality system concerned with the organizational process and the conditions, under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

1.3.1.2 GLP Compliance Monitoring

The periodic inspection of test facilities, and/or auditing of studies, for the purpose of verifying adherence to the GLP Principles.

1.3.1.3 Test Facility

The persons, premises and operational unit(s) that are necessary for conducting the non-clinical health and environmental safety study. For multi-site studies, those which are conducted at more than one site, the test facility comprises the site at which the Study Director is located and all individual test sites, which individually or collectively can be considered to be test facilities.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

1.3.1.4 **Test Facility Inspection**

An on-site examination, of the test facility's procedures and practices to assess the degree of compliance with GLP Principles. During inspections, the management structure and operational procedures of the Test Facility are examined, key technical personnel are interviewed, and the quality and integrity of data generated by the facility is assessed and reported.

1.3.1.5 **Study Audit**

A comparison of raw data and associated records with the interim or final report in order to determine whether the raw data have been accurately reported, to determine whether testing was carried out in accordance with the study plan and Standard Operating Procedures, to obtain additional information not provided in the report, and to establish whether practices were employed in the development of data that would impair their validity.

1.3.1.6 **Inspector**

A person who performs the test facility inspections and study audits on behalf of the IL-GLP.

1.3.1.7 **GLP Compliance Status**

The level of adherence of a test facility to the GLP Principles as assessed by IL-GLP.

1.3.2 **ADDITIONAL DEFINITIONS**

1.3.2.1 **The Law**: National Laboratory Accreditation Authority Law, 1997, approved by the Knesset on April 2nd, 1997.

1.3.2.2 **Receiving Authority**: The unit within the Regulatory Authority which is responsible for all administrative actions to permit the sale of chemicals and substances on the market.

1.4 Normative References

1.4.1 Council decision [C(97)186/final].

1.4.2 OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring:

1.4.2.1 Number 1: The OECD Principles of Good Laboratory Practice, ENV/MC/CHEM (98)17, Environment Directorate; Organization for Economic Co-operation and Development, Paris 1998.

1.4.2.2 Number 2: Guidance for GLP compliance Monitoring Authorities: Guidance for Compliance Monitoring Procedures for Good Laboratory Practice, Environment Monograph No. 110, OECD/GD (95)66, Environment Directorate; Organization for Economic Co-operation and Development, Paris 1995.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

1.4.2.3 Number 3: Guidance for GLP compliance Monitoring Authorities: Guidance for The Conduct of Laboratory Inspections and Study Audits.

1.4.2.4 Number 4: GLP Consensus Document: Quality Assurance and GLP, Environment Monograph No. 48, OECD/GD (92)35, Environment Directorate; Organization for Economic Co-operation and Development, Paris 1992.

1.4.2.5 Number 5: GLP Consensus Document: Compliance of Laboratory Suppliers with GLP Principles, Environment Monograph No. 49, OECD/GD (92)36, Environment Directorate; Organization for Economic Co-operation and Development, Paris 1992.

1.4.2.6 Number 6: GLP Consensus Document: The Application of the GLP Principles to Field Testing Studies, Environment Monograph No. 50, OECD/GD (92)37, Environment Directorate; Organization for Economic Co-operation and Development, Paris 1992.

1.4.2.7 Number 7: GLP Consensus Document: The Application of the GLP Principles to Short-Term Studies, Environment Monograph No. 73, OECD/GD (93)104, Environment Directorate; Organization for Economic Co-operation and Development, Paris 1993 008882.

1.4.2.8 Number 8: GLP Consensus Document: The Role and Responsibilities of the Study Director in GLP Studies, Environment Monograph No. 74, OECD/GD (93)105, Environment Directorate; Organization for Economic Co-operation and Development, Paris 1993 008883.

1.4.2.9 Number 9: Guidance for the Preparation of GLP Inspection Reports (1995), Environment Monograph No. 115.

1.4.2.10 Number 11: The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP (1998). ENV/MC/CHEM (98)16.

1.4.2.11 Number 12: Requesting and Carrying our Inspections and Study Audits in Another Country. ENV/JM/MONO (2000)3.

1.4.2.12 Number 13: The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies. ENV/JM/MONO (2002)9.

1.4.2.13 Number 14: The Application of the Principles of GLP to in vitro Studies. ENV/JM/MONO (2004) 26.

1.4.2.14 Number 15: Establishment and control of Archives that operate in compliance with the principles of GLP.

1.4.2.15 Number 16: Guidance on the GLP Requirements for Peer Review of Histopathology.

1.4.2.16 Number 17: Application of GLP Principles to Computerised Systems.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

1.4.2.17 Number 19: Management, Characterization and use of Test Items

1.4.2.18 Number 21: OECD Position Paper Regarding Possible Influence of Sponsors on Conclusions of GLP Studies

1.4.3 CFR Title 21 Chapter 1- Food and Drug Administration, Department of Health and Human Services, Part 58: Good Laboratory Practice for non-clinical laboratory studies.

1.4.4 EPA Good Laboratory Practice Standards- Federal Insecticide, Fungicide and Rodenticide Act 40CFR, part 160.

1.4.5 EPA Good Laboratory Practice Standards-Toxic Substances Control Act 40 CFR, part 792.

1.4.6 ISO/IEC 17011: Conformity assessment – General requirements for accreditation bodies accrediting conformity assessments bodies.

1.4.7 ISO/IEC 17025: General requirements for the competence of testing and calibration laboratories.

1.4.8 ISO 15189: Medical laboratories – Requirements for quality and competence.

1.4.9 ISRAC's documents:

1.4.9.1 Procedure number 1-432000: Quality manual.

1.4.9.2 Procedure number 1-611051: Introduction to ISRAC and to the recognition process of test facility working according to GLP principles.

1.4.9.3 Procedure number 2-421003: Confidentiality.

1.4.9.4 Procedure number 2-432007: Dealing with complaints.

1.4.9.5 Procedure number 2-520001: Choosing, training and certification of assessors.

1.4.9.6 Procedure number 2-650001: Measures to be taken for suspension, termination, reduction, voluntary withdrawal of accreditation/GLP recognition.

1.4.9.7 Procedure number 2-651002: Procedure for hearing.

1.4.9.8 Procedure number A-621001: Financial arrangement for the process of accreditation and recognition.

1.4.9.9 Procedure number 2-623001: Planning and Performing an Assessment.

1.4.9.10 Procedure number 1-000023: Definitions used in ISRAC's documents.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

2.0 THE ISRAEL NATIONAL GLP MONITORING UNIT WITHIN ISRAC

2.1 Background

2.1.1 The Israel Laboratory Accreditation Authority (ISRAC) was established by the Israeli Government, authorized by law since 1997 and operates as an independent non-structural governmental body as a none profit public organization. ISRAC is provided with Israel government fund in order to ensure its independence.

2.1.2 The organization of ISRAC is determined by the Law and decisions of the Council. The organizational structure of ISRAC includes the Council, and the executive body headed by the General Manager of ISRAC, see organization chart in 2.2.1

2.1.3 ISRAC's scope of activities is determined by the council (abiding by the law). All the activities regarding the accreditation of the testing, calibration and inspection laboratories are performed in compliance with ISO/IEC 17011.

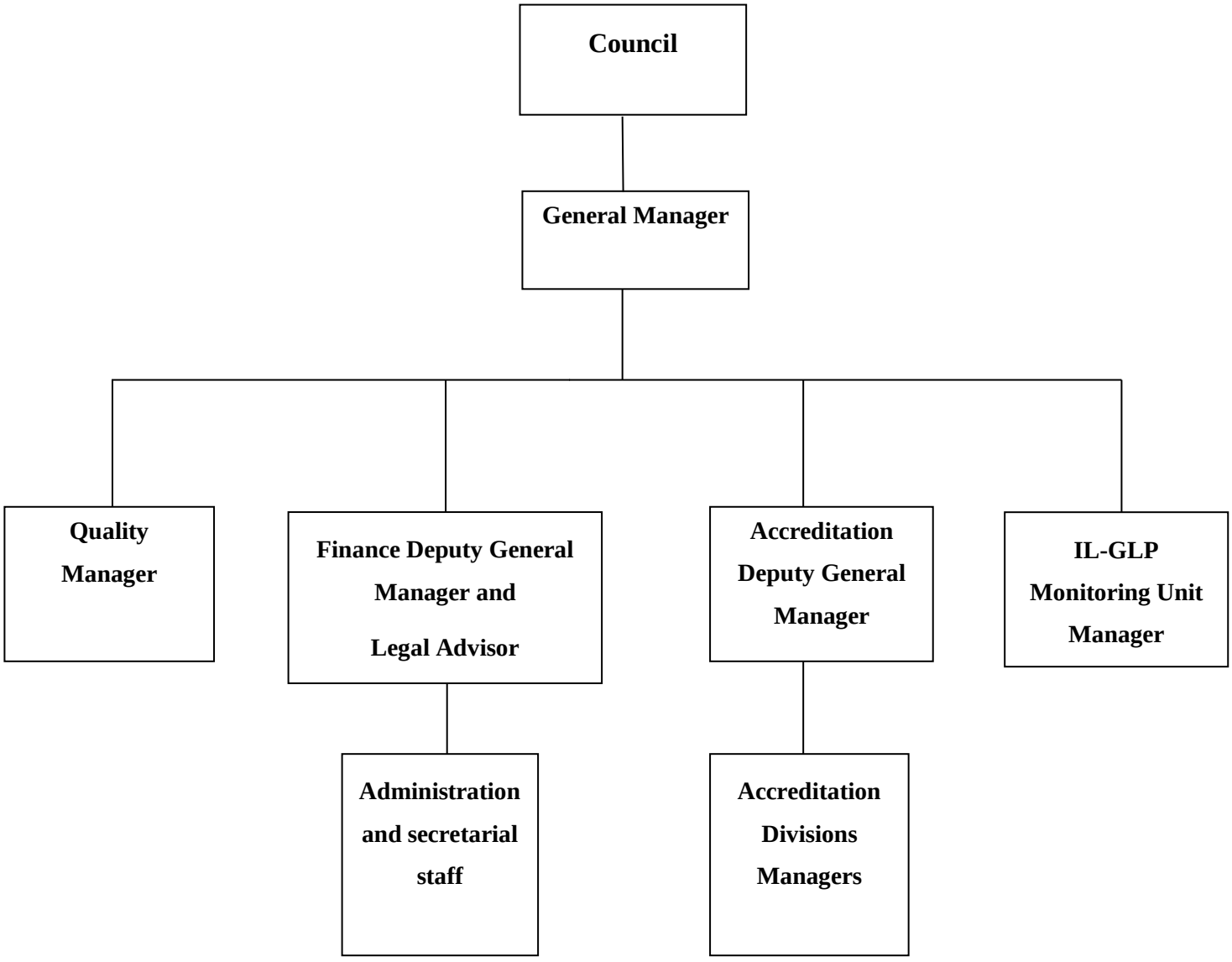
2.1.4 The Minister of Economy and Industry extended the scope of activities of ISRAC to cover the GLP activity. Based on this decision ISRAC General Manager authorized the establishment of a GLP Monitoring Program, which complies with the relevant OECD documents (see document number 1-611051: Introduction and preliminary information about testing and research facilities working according to OECD-GLP principles).

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

2.2 Organization

2.2.1 Organizational Chart of ISRAC including IL-GLP:



העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

2.2.2 **STRUCTURE OF IL-GLP**

2.2.2.1 The IL-GLP is responsible for the implementation of the National GLP Compliance Program within Israel.

The head of the IL-GLP reports directly to the General Manager of ISRAC for approval of decisions. The Head of IL-GLP is responsible for Israeli GLP-Compliance Monitoring Program and acts as the main contact person.

2.2.2.2 The inspectors for GLP are ISRAC's assessors. The number of inspectors is determined by the volume of work anticipated. The inspectors, when performing their GLP services, act in accordance to the procedure described in this manual.

2.2.2.3 In addition, where it is suspected that a criminal offence may have been committed, the IL-GLP may need to refer the matter to the appropriate Ministry for legal actions.

2.2.2.4 The IL-GLP employs experts under contract in specific scientific fields whenever necessary to assist the GLP experts.

2.3 Personnel and Training

2.3.1 The inspectors are scientifically and academically qualified all have minimum of three years of university education, with experience in some of the disciplines relevant to the scope of the GLP Compliance Monitoring Program. They have knowledge of the principles of GLP and with the requirements and standards necessary to comply with those principles.

2.3.2 The IL-GLP ensures that:

2.3.2.1 At all-time the number of inspectors is adequate; see procedure number 2-623001.

2.3.2.2 Inspectors are adequately qualified and trained; see procedure number 2-520001.

2.3.2.3 When experts are required, they are introduced to the fundamentals of principles of laboratory inspection and study audit.

2.3.2.4 Inspectors and experts have no financial or any other interest in the test facilities inspected, the studies audited or the organizations sponsoring such studies.

2.3.3 IL-GLP encourages ISRAC staff consultations, including joint training activities where necessary, with other OECD-GLP complying authorities in order to promote international harmonization in the interpretation and application of GLP Principles, and in the monitoring of compliance with such principles, in Israel.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

2.4 Confidentiality

2.4.1 Inspectors and any other persons who gain access to information related to GLP compliance monitoring are bound to maintain confidentiality of the information obtained from the GLP activity (see document number 2-421003).

2.4.2 IL-GLP ensures that, unless all commercially sensitive and confidential information has been excised, reports of Test Facility Inspections and Study Audits are made available only to Monitoring Regulatory Authorities and, where appropriate, to the test facilities inspected or concerned with Study Audits and/or to study sponsors.

2.4.3 IL GLP will follow ISRAC law requirements and will provide information by demand of the Court, of the Attorney General, or for purposes of lawful investigation.

2.4.4 There are, however, certain categories of information which are not considered confidential and may be released by the IL-GLP. These are:

2.4.4.1 On ISRAC web site there is a list of testing facilities which are recognized by ISRAC to comply with OECD GLP. The list includes the number, name, contact detail, etc. of the testing facility.

2.4.4.2 Annual update on visits made in the various research facilities over the past year (based on a template provided by the OECD Organization) will be provided to OECD secretariat. This information will be saved in the OECD data base and would be open to representatives of OECD member countries.

2.4.4.3 IL-GLP will inform OECD secretariat on non-compliant studies. The report will be in accordance with OECD template. This information will be saved in the OECD data base and would be open to representatives of OECD member countries, in file I:\9. 3\קשרים\1. קשרים_GLP/year.

2.4.4.4 The IL-GLP may also need, in the performances of its legal duties, to disclose confidential information to monitoring or regulatory authorities of parties which Israel signed relevant agreements; reports of test facility inspections and study audits, information on non-compliant studies or non-compliant testing facilities.

2.4.4.5 IL-GLP will provide Israeli regulators with data on international non-compliant testing facilities, or on non-compliant studies upon requests.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

3.0 THE ISRAEL GLP COMPLIANCE MONITORING PROGRAM

3.1 Scope of Program

3.1.1 The IL-GLP conducts Test Facility Inspections to determine the degree of conformity of Test Facilities and studies with GLP Principles and to determine the integrity of data to assure that resulting data are of adequate quality for assessment and decision-making by national Regulatory Authorities.

3.1.2 Test facilities will be included in the GLP compliance monitoring program at the request of the facility after initial inspection demonstrating compliance with OECD-GLP requirements.

3.1.3 IL-GLP will join the GLP monitoring program testing facilities that performs a non-clinical experiment or set of experiments:

3.1.3.1 In which an item is examined under laboratory conditions or in the environment in order to obtain data on its properties or its safety (or both) with respect to human health, animal health or the environment;

3.1.3.2 The results of which are, or are intended, for submission to the appropriate regulatory authorities; and compliance with the principles of good laboratory practice is required in respect of that experiment or set of experiments by the appropriate regulatory authorities.

3.1.4 The range of test facilities monitored by the GLP Monitoring Authority covers the following substances and types of studies (areas of expertise):

3.1.4.1 <u>Substances</u>

a. Cosmetics;

b. Industrial chemicals;

c. Pharmaceuticals/ medicinal products;

d. Food additives;

e. Animal feed additives;

f. Pesticides;

3.1.4.2 <u>Type of studies</u>

1. Physical-chemical testing;

2. Toxicity studies;

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

3. Mutagenicity studies;
4. Environmental toxicity studies on aquatic and terrestrial organisms;
5. Studies on behavior in water, soil and air; bioaccumulation;
6. Residue studies;
7. Studies on effects on mesocosms and natural ecosystems;
8. Analytical and/or clinical chemistry testing.

9 Others

3.1.5 IL GLP requires the testing facilities to maintain their competence of study conduct. ISRAC recommendation is that a test facility will perform at least three GLP compliant studies per two years. In cases where low number of GLP studies is expected, test facility shall maintain a written plan of competence maintenance. Testing facility should be able to justify the technical arguments that have led to the plan of competence maintenance.

3.1.6 IL-GLP includes in the test facility inspection, the compliance with health and safety regulations, waste management, use of animals and safety legislation at the test facility premises. If irregularities are found, they will be reported in ISRAC's report.

Note 2*: The issue remains primarily the responsibility of the relevant governmental authority, meaning that inspection reports, whether or not including remarks concerning safety of workers, do not reflect IL-GLP approval of the safety and workers' health status in the inspected test facility.*

3.2 Monitoring program schedule

3.2.1 Periodic Inspections of Test Facilities i.e. general inspection of test facility joining the GLP Compliance Monitoring Program will normally be performed every 2 years.

3.2.2 If serious deficiencies are identified during a routine facility inspection, additional directed inspection or study audit may be necessary to ensure that the test facility continues to operate in accordance with the principles of GLP.

3.2.3 IL-GLP-MA may perform additional inspections at its consideration, for example when a severe complaint on the testing facility arrived at ISRAC (see procedure number 2-432007) or at the request of a Regulatory Authority.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

3.2.4 IL-GLP-MA will consider performance of additional test facility inspection, upon notification on significant changes from the test facility. The inspection purpose will be to assess whether GLP compliance has been affected by the changes.

3.2.5 The monitoring program activities detailed above are scheduled according to a risk based approach.

3.3 Entry to the test facility

Inspectors will not normally enter test facilities or attempt to gain access to data held by a test facility without the expressed permission of the test facility management and where appropriate, the sponsors of the study. In the case that access is refused, the IL-GLP will consider it lack of cooperation and will act to withdraw the recognition of compliance with OECD GLP from the test facility.

3.4 Request to Join the IL-GLP Compliance Monitoring Program

3.4.1 Test facilities seeking to join the Program may be a private research test facility, part of industrial plant, governmental test facility or academic test facilities. The test facility should submit an application to the head of the IL-GLP to join the Program.

3.4.2 A letter of request to join the GLP program can be found as form number T1-200000-01 and is available on the ISRAC website: www.israc.gov.il

3.4.3 The minimum requirement for GLP recognition is a presentation of at least three completed full studies, performed in a reasonable period of time (within 2 years). The studies included in the request for recognition of new test facility may be conducted according to two options:

3.4.3.1 To conduct GLP studies with a formal OECD GLP compliance claim by the Study Director, with a sponsor willing to take the 'risk'; or

3.4.3.2 To conduct GLP studies 'in-house' (with/without a sponsor, with a formal GLP claim of the Study Director). Such an in-house study could be a study for which no GLP was originally intended, a mock study (for example a series of sample analyses), etc.

The responsibility for a recall of any non-compliant study lays on the test facility.

3.4.4 In addition, the test facility shall submit the following documents to ISRAC:

3.4.4.1 Description of facility including structural charts and labeling of the areas clearly defined zones GLP.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

3.4.4.2 Organizational chart and job description, relating to at least: GLP facility management; GLP quality assurance; Study director/s; Archive manager.

3.4.4.3 CVs of the officials listed in the paragraph above.

3.4.4.4 Standard Operating Procedures list (comprehensive and updated) including version number.

3.4.4.5 A copy of the procedures that describe the following:
Handling of test item (transport, receive, storage), equipment (maintenance and calibration), computer systems (validation, operation and maintenance), management of records (encoding studies, collection of raw data, including the use of computerized systems), writing a protocol, writing a report, and quality assurance (planning and scheduling and performing audits, and test facility quality assurance).

3.4.4.6 A GLP studies updated list. The list will include at least three studies, and at least one study in every field of expertise.

Note 3: *Fields of expertise are managed by ISRAC using Forms T1-000016-01, T1-000016-03*

3.4.4.7 A Copy of at least one research (protocol and report) in each field of expertise.

3.4.4.8 A filled table indicating the areas of recognition sought

3.4.4.9 A signed request should be sent to ISRAC (form number T1-200000-01).

3.5 Request to extend the recognition.

3.5.1.1 When an organization seeks to expand the areas of recognition: domain expertise or materials tested, it must submit a request for extension.

3.5.1.2 A letter of request to be submitted to GLP program can be found as a form number T1-200000-13 and is available on ISRAC website www.israc.gov.il

3.6 Notification on change

Each test facility entering the GLP program is required to sign up a surveillance agreement, which renew periodically, see form number T1-200000-09.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

If significant changes in the Test Facility are made, such as in the management, QA staff, the personnel, the infrastructure of the Test Facility, the Test Facility has the obligation to notify the IL-GLP. The obligation is grounded in surveillance agreement between ISRAC and the testing facility.

3.7 Inspection and study audit

3.7.1.1 In general, the inspection is planned and performed according to form number T1-200000-07: Combined Checklist for GLP.

3.7.1.2 Each inspector carries ISRAC's identification card and can be called upon to introduce it during inspections and study audits, See form number T1-200000-19.

3.7.1.3 Whenever a test facility has to be inspected for the first time a pre-inspection visit is optional to be carried out. The pre-inspection will be performed as detailed in the pre-inspection plan, see form number T1-200000-04 and to the checklist, see form number T1-200000-05.

3.7.1.4 Prior to conducting a test facility inspection or study audit, Inspectors will review any existing information on the test facility, including previous inspection reports, the lay out of the facility, organization charts, study reports, protocols and curricula vitae (CVs) of key person, etc. This is to have an indication on the type, size and layout of the facility; the range of studies, the management structure. Inspectors will note in particular, any deficiencies recorded at previous test facility inspections and/or study audits.

3.7.2 A notification of the inspection date will be sent by IL-GLP, at least 2-3 weeks prior to the visit, using form number T2-623001-05. The team will usually consist of 2 people (inspector/s and expert/s). The duration of the inspection is 2-5 days according to the size of the test facility and the number of studies to be audited. For GLP inspection program, see form number T1-200000-12.

3.7.3 The inspection begins with an opening meeting. The purpose of the opening meeting is to inform the management and staff of the test facility of the reason for the inspection or study audit that is about to take place, and to identify the test facilities areas, study/studies selected for audit, documents and personnel likely to be involved.

3.7.4 Test Facility inspections will generally include, inter alia, Study Audits, which review ongoing or completed studies. Specific Study Audits may also be requested by Regulatory Authorities and can be conducted independently of Test Facility inspection.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

3.7.5 The wide variety of test facilities and diversity of study type means that inspectors will inevitably have to use their own judgment to assess the extent of compliance with the principles of GLP. Inspectors will nevertheless strive for a consistent approach in evaluating whether an adequate level of GLP compliance has been achieved.

3.7.6 During test facility inspections and study audits inspectors will have discussions with staff engaged in regulatory studies on any GLP points as they arise. A final meeting with management and relevant test facility personnel will normally be held in order that they may be informed of the outcome of the inspection or study audit. At this meeting a summary of the inspector's findings will be presented using form number T2-623001-25 and consent shall be documented by the facility representative's signature on the form. Mention may also need to be made of work that the inspector was unable to observe.

3.8 Inspection and study audit reports

3.8.1 A full written report of the inspector's findings will be provided to test facility management after completion of an inspection or audit (within fourteen (14) working days). This report will indicate the nature of any deviations from the GLP principles or other deficiencies found at the time of inspection or audit. These may be deviations or deficiencies that are not sufficiently serious to affect the validity of studies emanating from the test facility, or they could be serious deviations or deficiencies that may, in the view of the inspector, affect the validity or integrity of studies emanating from the test facility. The report will be written in accordance with IL GLP template, using form number T1-200000-12.

3.8.2 Where an inspection or study Audit has been conducted at the request of a Regulatory Authority, a full report of the findings should be prepared and sent via the relevant (National) GLP Monitoring Authority Regulatory Authority concerned.

3.9 Responding to inspection and study audit report

3.9.1 As soon as possible, and in any case no more than twenty (20) working days, a response to the inspection or audit report should be forwarded by test facility management to IL GLP. This response should detail any action taken, or being taken (including due date), to rectify the GLP deviations or deficiencies reported by the inspector. Corrective actions should include reference demonstrating performance, and systematic view.

3.9.2 IL GLP will consider whether, the proposed remedial actions are appropriate to correct the deviations or deficiencies identified by the inspector.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

3.9.3 The testing facility will be informed, in writing, whether or not the proposed remedial actions are acceptable to the IL GLP.

3.9.4 When the IL GLP is satisfied that all deviations or deficiencies identified during the inspection have been corrected, the inspectors shall fill form number T1-200000-11: Summary for discussion of inspection and add it to the inspection file.

3.9.5 ISRAC general manager will review the testing facility GLP inspection file and will report its status in a letter to the testing facility. A GLP compliance statement will be issued according to procedure number 2-660001.

3.9.6 Sometimes more than one round of respond is necessary. Round three and above of corrective action response will be extra charged based on inputs (see procedure number A-621001).

3.9.7 When the testing facility is delayed in providing satisfactory correction to the findings, beyond the recognition expiry date, IL GLP will consider:

3.9.6.1 Grant Administrative Extension to the testing facility. The Administrative Extension will be at most six months and will provide the testing facility with time to address the deviations. In this period the testing facility is still in IL GLP program, but will not be granted with renewed GLP compliance statement.

3.9.7.2 To initiate withdrawal process, according to procedure number 2-650001.

3.9.8 If a serious deviation from the GLP Principles does not receive a suitable response within a reasonable time frame IL GLP will consider withdrawal of recognition to GLP compliance, following procedure number 2-650001.

3.10 Voluntary withdrawal from OECD GLP recognition program

3.10.1 If an organization chooses to voluntarily withdraw from ISRAC's OECD-GLP monitoring program, it will submit a request that will include the following documents:

- List of studies performed since last inspection.
- Organization policy regarding the archive (paper and samples).
- A declaration stating that the organization will stop using ISRAC symbol immediately.
- The wording of the message that will notify the organization's customers of termination of activities related to performance of studies meeting OECD GLP principles.

3.10.2 The organization wishes to withdraw from ISRAC's OECD-GLP monitoring program may choose one of the following two options:

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

3.10.2.1 The organization shall be withdrawn from the program immediately upon receipt of the request as per procedure number 2-650001.

3.10.2.2 The organization will maintain its recognition until expiration date. An inspection may be held in the organization upon request submission, subject to ISRAC General Manager decision. Such an inspection shall represent the activities/sites included in the recognition.

3.11 Compliance statements

3.11.1 Following a satisfactory inspection, the IL GLP will normally issue a GLP compliance statement. This states the name and address of the test facility, and an indication of the areas of expertise of that test facility, see procedure number 2-660001.

Note 4: *Some regulatory authorities require the testing facility to append a statement to the test report certifying that the testing facility has implemented GLP principles and was operating in compliance with those principles when the study was conducted.*

Note 5: *In any case, ISRAC is not responsible for the results of a study.*

3.11.2 If a serious deviation from the GLP Principles is identified IL-GLP will consider:

3.11.2.1 Not to grant recognition to GLP compliance.

3.11.2.2 Withdrawing the recognition of GLP compliance, according to procedure number 2-650001.

(Action through the courts will be taken, where warranted by circumstances and where legal/ administrative procedures so permit).

3.11.3 When a testing facility asks to get off the OECD GLP monitoring program it has two options:

3.11.3.1 To be removed from the program immediately upon receipt of the request message. The request will include the following documents: a. list of studies until closure of the program, b. a policy regarding the future of the archived documents and samples, c. a statement that the Organization will stop using the ISRAC logo, d. the announcement of stopping providing the services of studies according to OECD GLP

3.11.3.2 To stay in the program until the recognition expiring date depending on being inspected by ISRAC. This inspection will be of up to one full day for the sake of closure.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

3.12 Procedure for the Hearing and Appeal Committee

3.12.1 Problems or differences of opinion, between inspectors and Test Facility management, arising from an Inspection or a Study Audit will normally be resolved during the course of a Test Facility inspection or study, usually at the Exit Meeting.

3.12.2 However, if agreement is not reached the Test Facility management may appeal in writing to IL GLP, specifying the exact point of disagreement, properly substantiated by adequate evidence: representation against the inspection's findings observed and communicated by the inspector. Such representation must be addressed, in writing, and will be treated by IL-GLP according to procedure number 2-651002.

3.13 Publication on ISRAC web site

ISRAC publishes on its web site the following:

3.13.1 List of testing facilities entitled to the statement of GLP.

3.13.2 Indication of testing facilities under Administrative Extension

3.13.3 List of testing facilities that their statement of GLP compliance was withdrawn

4.0 INTERNATIONAL ACCEPTANCE OF INSPECTION RESULTS

4.1 The acceptability of a study is decided by the particular Regulatory Authority and not by the IL-GLP. However, following the OECD decision on the mutual acceptance of data and the agreement made between the state of Israel and the European Committee, a regulatory authority of an OECD member country will accept a study on GLP grounds where a facility inspection and/or study audit has been conducted and the facility and/or study has been found to be in compliance with GLP principles.

4.2 Israel Monitoring Authority prepares a statement of GLP compliance to test facilities which are in compliance with GLP principles see procedure number 2-660001. This statement of GLP compliance may be used by the management of the Test Facility.

5.0 INTERNATIONAL RELATIONS

IL GLP is a full member in the OECD working group on Good Laboratory Practice.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021

IL GLP will send to the OECD secretariat an annual report describing the status of all monitored testing facilities which is filled in I:\9. קשרים\3. קשרים\1_GLP.

6.0 RECOVERY OF COSTS

6.1 The operating cost of the IL-GLP is recovered by the Test Facilities participating in the Israel GLP Compliance Program. Each test facility pays for the time investment of inspectors, throughout the inspections and the study audits.

6.2 Part of the Israel Laboratory Accreditation Authority's budget is covered according to paragraph 27 of The Law (section 1.3.2.1. of this document).

6.3 For details see procedure A-621001.

7.0 APPENDICES

7.1 Form number T1-200000-01: Request to join GLP.

7.2 Form number T1-200000-04: Standard Form Pre-Inspection Program GLP.

7.3 Form number T1-200000-05: Checklist Pre-inspection GLP.

7.4 Form number T1-200000-07: Combined Checklist for GLP.

7.5 Form number T1-200000-08: A checklist to GLP inspection file

7.6 Form number T1-200000-09: Surveillance Agreement

7.7 Form number T1-200000-11: Summary for discussion of inspection

7.8 Form number T1-200000-12: Template of GLP inspection program and report

7.9 Form number T1-200000-13: Request for extension of GLP scope

7.10 Form number T1-200000-15: Notification to the organization of an on-site assessment for organization's approval.

7.11 Form number T1-200000-16: Accompanying letter to the surveillance letter.

7.12 Form number T1-200000-19: GLP Inspector's Identification Card.

העותקים המאושרים היחידים של מסמך זה הם אלה הנמצאים על מחשב ISRAC ועותק המקור השמור ב-QA. כל שאר העותקים אינם מבוקרים והם בתוקף ליום בו הודפסו בלבד. הודפס ב-8 בפברואר 2021

The authorized copies of this document are those on ISRAC computer network and the master copy held by the QA. All other copies are uncontrolled and are only valid on the date printed. Printed on February 8, 2021