



April 30, 2010

Notice

Our file number: 10-109087-604

Health Canada is pleased to announce the release of the finalized ***Guidance Document Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice.***

Good Laboratory Practice (GLP) covers the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, conducted, monitored, recorded, archived and reported. It is intended to promote the quality and validity of test data and improve the international acceptance of data generated in adherence to its principles.

This guidance applies to all sponsors who submit non-clinical study data from a Clinical Trial Application (CTA), CTA Amendment (CTA-A), Drug Identification Number (DIN) Application and applications to support a post-DIN change, New Drug Submission (NDS), Abbreviated New Drug Submission (ANDS) and submissions to support a post-Notice of Compliance (Post-NOC) change, that is, Supplement to an NDS (SNDS), Supplement to an ANDS (SANDS), and Notifiable Change (NC). Non-clinical studies include all *in vitro* and *in vivo* testing, not involving human subjects, performed to determine the safety of human drugs.

Health Canada and the Standards Council of Canada (SCC) have signed a Memorandum of Understanding allowing SCC to act as the monitoring authority for GLP compliance of test facilities within Canada. Health Canada expects that studies submitted in support of pharmaceutical (including disinfectants), radiopharmaceutical or biologic drugs have been conducted in accordance with the Principles of GLP and hence compliant effective immediately. A one-year transition period, commencing on the date of posting, is granted to test facilities in Canada thereby allowing sufficient time for SCC recognition.

The final guidance document addresses comments received as a result of the August 27, 2009 to October 26, 2009 consultation on the draft Guidance. Comments related to various issues including, applicability of the document, requirement for inspection, acceptance of study data, and role and workload of the SCC. Health Canada considered all stakeholder comments in the finalization of this guidance document and has developed a Questions and Answers document, as a companion piece, to expand on some of the questions identified through the consultation. A table of comments from industry stakeholders in response to the draft GLP Guidance is available upon request.

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Questions related to this guidance document should be directed to:

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GUIDANCE DOCUMENT

Non-Clinical Laboratory Study Data

Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice

Published by authority of the
Minister of Health

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Health Products and Food Branch

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>The Health Products and Food Branch's (HPFB) mandate is to take an integrated approach to managing the health-related risks and benefits of health products and food by:</p> <ul style="list-style-type: none"> • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
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Également disponible en français sous le titre : Ligne directrice : Données d'études non cliniques en laboratoire à l'appui des demandes et des présentations de drogues : respect des bonnes pratiques de laboratoire

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada's mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant programme area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1.0 INTRODUCTION

The Health Products and Food Branch (HPFB) is meeting Canada's international obligations as a member country of the Organisation for Economic Co-operation and Development (OECD) [1989 OECD Council Decision-Recommendation C(89)87(Final)] with respect to Good Laboratory Practice (GLP) standards for pharmaceuticals, biologics and radiopharmaceuticals, and has recognized the Standards Council of Canada (SCC) as Canada's GLP Monitoring Authority.

1.1 Policy Objective

To inform sponsors and affected stakeholders that non-clinical data included in drug product applications and submissions provided to the Therapeutic Products Directorate (TPD) and the Biologics and Genetic Therapies Directorate (BGTD) should be accompanied by evidence that the studies and facilities adhere to the OECD *Principles of Good Laboratory Practice* (GLP) [ENV/MC/CHEM(98)17, and subsequent revisions]. This evidence should be provided by a GLP monitoring authority recognized by the OECD.

1.2 Policy Statements

- 1) A GLP compliance statement consistent with the OECD Principles of GLP should be provided when study data from a non-clinical study are included in a Clinical Trial Application (CTA), CTA Amendment (CTA-A), Drug Identification Number (DIN) Application and applications to support a post-DIN change, New Drug Submission (NDS), Abbreviated New Drug Submission (ANDS) and submissions to support a post-Notice of Compliance (Post-NOC) change, that is (i.e.), Supplement to an NDS (SNDS), Supplement to an ANDS (SANDS), and Notifiable Change (NC).
- 2) When adequate / relevant safety data cannot be obtained from clinical studies, the quality of the non-clinical safety data may be considered crucial and thus expected to be obtained from well-designed studies conducted under the GLP framework. Any study not conducted in accordance with GLP should be appropriately justified.
- 3) Study data generated in a facility that is not shown to have employed GLP Principles will not be considered sufficiently credible for regulatory decision making. Data that cannot be shown to be sufficiently reliable will only be considered as supplementary information rather than primary evidence for decision making.

4) Evidence that the facility was assessed and found to be compliant with GLP, including details of the study types for which the facility is GLP-compliant, should be provided by a GLP monitoring authority that has been recognized by the OECD. In the absence of such evidence, alternatives may be considered acceptable when the standard used to assess the facility's compliance is deemed to be equivalent to the OECD, such as that of the United States Food and Drug Administration. Study-specific evidence may be requested upon evaluation.

5) The OECD recommends the manner in which all documentation, electronic records, samples of tests, reference items and specimens should be kept in accordance with the OECD Principles of GLP. Further, Health Canada recommends that sponsors store all documentation, study plan, raw data, and final report of each study in support of an approved drug product for a minimum of 10 years (from the market notification date) and a longer period when required by the *Food and Drug Regulations*. Archive conditions should protect the contents from untimely deterioration.

1.3 Scope and Application

This Guidance document applies to all non-clinical data relating to pharmaceutical (including disinfectants), radiopharmaceutical or biologic drugs for human use which are included in the following applications and submissions:

1. CTAs and CTA-As filed and reviewed in accordance with Division 5 of Part C of the *Food and Drug Regulations* (subsections C.05.005 and C.05.006);
2. DIN Applications and DIN applications seeking post-DIN changes filed and reviewed in accordance with Division 1 of Part C of the *Food and Drug Regulations* (including subsections C.01.014.1 and C.01.014.4); and
3. NDSs/ANDSs and submissions to support a post-NOC change, i.e., SNDSs, SANDSs filed and reviewed in accordance with Division 8 of Part C of the *Food and Drug Regulations* (subsections C.08.002, C.08.002.1, C.08.003 and C.08.004); and NCs to new drugs that have received an NOC pursuant to Section C.08.004 of the *Food and Drug Regulations*.

This Guidance document does not apply to non-clinical data provided or reviewed in applications and submissions relating to veterinary drugs, natural health products, medical devices, food additives or cosmetics.

Examples of studies requiring GLP compliance are included as Appendix A. This list is not exhaustive and is subject to change. Generally, at a minimum, all the pivotal or core battery toxicity studies conducted to support drug development should be performed

under GLP conditions. On a case-by-case basis, certain non-clinical studies may not need to adhere to GLP conditions, depending on the importance of such studies and whether any claims are made based on these studies. For example, primary pharmacodynamic studies intended to investigate the mode of action and/or the effects of a substance in relation to its desired therapeutic target are generally conducted during the early stages of development and are not generally required to adhere to GLP. Sponsors are advised to consult the International Conference on Harmonisation (ICH) guidelines to determine which studies would be considered pivotal or core battery, and therefore, determine which studies should be performed under GLP conditions.

1.4 Definitions and Acronyms

Biologic – a drug listed in Schedule D to the *Food and Drugs Act* that is in dosage form, or a drug that is a bulk process intermediate that can be used in the preparation of a drug listed in Schedule D to the *Act*.

Disinfectant – an antimicrobial agent capable of destroying pathogenic and potentially pathogenic microorganisms on environmental surfaces and inanimate objects.

Facility – for the purpose of this guidance, a facility is defined as any establishment that performs non-clinical safety testing of substances in support of the development of drugs for human use.

Good Laboratory Practice – the organizational process and the conditions under which laboratory studies are planned, performed, monitored, recorded, archived and reported.

Good Laboratory Practice Compliance Statement – a declaration issued by the management of the test facilities by which the study was carried out in accordance with OECD GLP Principles.

Good Laboratory Practice (GLP) Monitoring Authority – a body established with responsibility for monitoring the good laboratory practice compliance of facilities and for discharging other such functions related to good laboratory practice.

Non-clinical laboratory study – All *in vitro* and *in vivo* testing, not involving human subjects, performed to determine the safety of human drugs.

Pharmaceutical - a drug other than a drug listed in Schedule C or D to the *Food and Drugs Act*, as defined within Division 1A of the *Food and Drug Regulations*.

Radiopharmaceutical – a drug listed in Schedule C of the *Food and Drugs Act* that is in dosage form, or a drug that is a bulk process intermediate that can be used in the preparation of a drug listed in Schedule C to the *Act* that is of biological origin.

Sponsor - an entity which commissions, supports and/or submits a non-clinical health and environmental safety study.

Acronyms

ANDS	Abbreviated New Drug Submission
BGTD	Biologics and Genetic Therapies Directorate
CTA	Clinical Trial Application
CTA-A	Clinical Trial Application Amendment
DIN	Drug Identification Number
GLP	Good Laboratory Practice
GLPMA	Good Laboratory Practice Monitoring Authority
HPFB	Health Products and Food Branch
MAD	Mutual Acceptance of Data
NOC	Notice of Compliance
NDS	New Drug Submission
OECD	Organisation for Economic Co-operation and Development
Post-NOC	Post-Notice of Compliance
SANDS	Supplement to an Abbreviated New Drug Submission
SNDS	Supplement to a New Drug Submission
SCC	Standards Council of Canada
TPD	Therapeutic Products Directorate

1.5 Background

The Therapeutic Products Directorate (TPD) and the Biologics and Genetic Therapies Directorate (BGTD) regulate pharmaceutical, radiopharmaceutical and biologic drugs to ensure that these products available to Canadians meet the standards for safety, efficacy and quality and that the benefits of these products outweigh their risks.

Good Laboratory Practice (GLP) refers to the organizational process and the conditions under which non-clinical studies are planned, performed, monitored, recorded, archived and reported. Application of GLP Principles helps to assure sponsors and regulatory authorities of the quality, reliability, and integrity of test data generated from non-clinical studies. Following GLP will provide greater assurance that the data obtained from

non-clinical studies is reliable. The use of reliable data is an integral part of the regulatory system for authorization of pharmaceutical, radiopharmaceutical and biologic drugs in Canada.

Providing efficient and effective regulatory oversight over the life-cycle of a therapeutic product requires that international best practices are used in all stages of the development. Compliance with GLP, Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) are consistent with this concept.

As a member country of the Organisation for Economic Co-operation and Development (OECD), Canada will use the OECD *Principles of Good Laboratory Practice* as the basis for ensuring high quality and reliable test data. Canada has formally implemented GLP and monitors compliance with OECD GLP Principles.

The Principles of GLP are intended to promote quality and validity of test data and form the basis for Mutual Acceptance of Data (MAD). MAD was established under the OECD Council Act in 1981. *It states that data generated in an OECD member state in accordance with OECD Test Guidelines and Principles of GLP will be accepted in other member countries for assessment purposes and other uses relating to the protection of health and the environment.*

2.0 GUIDANCE FOR IMPLEMENTATION

2.1 Good Laboratory Practice Standards

- The OECD Principles of Good Laboratory Practice [ENV/MC/CHEM(98)17, and subsequent revisions] is recognized as the GLP standard by HPFB. This document is available on the OECD website in both French and English ([http://www.olis.oecd.org/olis/1998doc.nsf/LinkTo/NT00000C5A/\\$FILE/01E88455.PDF](http://www.olis.oecd.org/olis/1998doc.nsf/LinkTo/NT00000C5A/$FILE/01E88455.PDF)).

2.2 Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice Monitoring Authority in Canada

Under the 1989 OECD Council Decision-Recommendation [C(89)87(Final)], OECD member countries are required to designate a GLP compliance monitoring authority and to establish procedures for monitoring compliance with GLP based upon facility inspections and audits. Health Canada has recognized the Standards Council of Canada (SCC) as an acceptable GLP Monitoring Authority (GLPMA) for Canadian facilities that generate non-clinical test data in support of the authorization of human drugs.

The SCC is an OECD-approved compliance monitoring authority that can recognize GLP compliance by issuing formal documentation in the form of a certificate to successful facilities that supports the validity of their study GLP compliance statements and the acceptability of these studies in OECD member countries.

The SCC carries out its GLP monitoring functions consistent with the procedures outlined in the OECD document, *Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice* [OCDE/GD(95)66, or subsequent revisions]. The SCC functions on a full cost recovery basis between facilities and the SCC according to the Council's current published fee structure.

To apply for recognition of GLP compliance and for more details on the SCC GLP compliance program, sponsors should contact the SCC. Refer to the contact information in section 4.0 of this guidance.

The SCC GLP monitoring authority is periodically evaluated by an OECD Mutual Joint Visit (MJV) peer review team. The MJVs include a site visit to the GLP monitoring authority by a team of observers from GLP monitoring authorities in other OECD Member countries, with the objective of providing assurance about the manner in which inspections and study audits are carried out, and for the mutual acceptance of test data. Monitoring authorities have key requirements including maintaining a team of trained inspectors, having published program documents and maintaining records of inspected facilities. They also report annually to each other, the OECD and the European Commission on all activities. Any change in the compliance status of a facility is reported immediately to other Member countries and the regulatory authorities.

3.0 EFFECTIVE DATE

Non-clinical study data submitted in support of pharmaceutical, radiopharmaceutical or biologic drugs should have been conducted in accordance with GLP Principles and hence GLP compliant effective immediately. Health Canada recognizes that it may take time for facilities in Canada to be assessed by the SCC GLPMA. Therefore, in order to allow for a sufficient implementation period, facilities will be expected to have been assessed and found to be compliant with GLP by the SCC within one-year from posting of this document on the Health Canada website.

4.0 CONTACT INFORMATION

GLP Coordinator
Standards Council of Canada
200-270 Albert Street
Ottawa, Ontario
K1P 6N7
Canada
Fax: (613) 569-7808
Email: info@scc.ca
Website: www.scc.ca

Questions related to this guidance document should be directed to:

Bureau of Policy, Science and International Programs
Therapeutic Products Directorate
Health Products and Food Branch
Health Canada
1600 Scott Street
Holland Cross, Tower B
2nd Floor, Address Locator 3102C1
Ottawa, Ontario
K1A 0K9
Fax: 613-941-1812
Email: Policy_Bureau_Enquiries@hc-sc.gc.ca

5.0 REFERENCES

The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring are available in French and English on the Organization for Economic Co-operation and Development website (www.OECD.org). Facilities should refer to the most up-to-date versions of these documents.

5.1 Standards Council of Canada (<http://www.scc.ca/en/publications/criteria/labs.shtml>)

- Application for Recognition of GLP Compliance
- Fee Schedule for the Good Laboratory Practice Program Specialty Area
- SCC Monitoring Authority Requirements for the Recognition of GLP Compliant Facilities

The Standards Council of Canada Publications webpage is located at:
<http://www.scc.ca/en/edocs>

APPENDICES

Appendix A: Examples of Studies and the requirement for Good Laboratory Practice Compliance

Bioanalysis in support of Human Bioequivalence	No. Should be conducted under GCP.
Safety pharmacology and pharmacodynamic studies	Yes/No*
Primary pharmacodynamic studies during the discovery phase of pharmaceutical development	No
Pivotal or core battery toxicity studies including repeated-dose, pharmaco/toxicokinetics, reproductive, developmental, local tolerance, photosafety, immunotoxicity, etc., as applicable	Yes
Carcinogenicity studies	Yes
Genotoxicity studies	Yes
Physical-chemical testing including dissolution studies, stability studies and studies on impurities and degradation products	Yes, if conducted solely under a non-clinical study. Other standards may apply (i.e. GCP, GMP) if testing is done to support the marketing authorization of a drug.
Data that cannot be obtained in clinical studies for ethical reasons	Yes

*Studies that are considered to be core battery or pivotal as per the ICH guidelines, Health Canada guidelines, or other international guidelines should be conducted under GLP conditions. Certain non-clinical studies may not need to adhere to GLP depending on the importance of the studies and whether any claims are made based on such studies.

Appendix B: Review Bureaux/Centre Responsibilities

Biologics and Genetic Therapies Directorate (BGTD)

Centre for Biologics Evaluation (CBE): CBE is responsible for the regulation of biologics, including but not limited to blood and blood products, viral and bacterial vaccines, cells, tissues, organs and xenografts. Key functions include the evaluation of submissions provided in support of product quality, safety, and effectiveness, development of laboratory standards and methods, pre-approval on-site evaluations in support of submission review and managing the lot-release program for biologics.

Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB): CERB is responsible for the regulation of biologics and radiopharmaceuticals, including but not limited to, gene therapies and somatic cell therapies, hormones, monoclonal antibodies, enzymes, allergenic extracts and cytokines. Key functions include the evaluation of submissions provided in support of product quality, safety, and effectiveness, development of laboratory standards and methods, pre-approval on-site evaluations in support of submission review and managing the lot-release program for biologics.

For inquiries relating to BGTD submissions:

Director General's Office
Office of Regulatory Affairs
200 Tunney's Pasture Driveway, Address Locator 0701A
Ottawa, Ontario
K1A 0K9
Phone: 613-957-1722
Fax: 613-941-0364
Email: BGTD_RAD_Enquiries@hc-sc.gc.ca

Therapeutic Products Directorate (TPD)

The Bureau of Metabolism, Oncology and Reproductive Sciences (BMORS) is comprised of the Reproduction and Urology Division, Oncology Division, and Metabolic and Musculoskeletal Drugs Division. Responsibilities include, but are not limited to, the clinical, pre-clinical and labelling review of drug submissions indicated for use in/as: hormone replacement, contraceptives, menopause, erectile dysfunction, oncology (includes hormone based therapies), diabetes, obesity, osteoporosis and musculoskeletal anti-inflammatories.

Regulatory Project Management Division, servicing BMORS
Health Canada
Finance Building Number 2
Tunney's Pasture, Address Locator 0202D2
Ottawa, Ontario
K1A 1B9
Fax: (613) 941-1365

The Bureau of Gastroenterology, Infection and Viral Diseases (BGIVD) is comprised of the Division of Anti-Infective Drugs, Disinfectants Unit, Gastroenterology Division, Acquired Immune Deficiency Syndrome (AIDS) and Viral Diseases Division, and the Non-Prescription Drug Evaluation Division. Responsibilities include, but are not limited to, the clinical, pre-clinical and labelling review of drug submissions indicated for use in/as: anthelmintics, anti-fungals, antibacterials, antibiotics, sterile diluents, antiherpetics, AIDS, influenza, cytomegalovirus, hepatitis B and C, antidiarrheals, antispasmodics, antiulcers, colitis therapy, digestive aids, ophthalmics for macular degeneration and glaucoma, contrast agents and antidotes/poison treatments. The Bureau's responsibilities include the evaluation of pre-market applications and the management of all issues related to nonprescription drugs, including DIN applications for products subject to Category IV Monographs and to Labelling Standards.

Regulatory Project Management Division, servicing BGIVD
Health Canada
Finance Building Number 2
Tunney's Pasture, Address Locator 0202B1
Ottawa, Ontario
K1A 1B9
Fax: (613) 941-1183

The Bureau of Cardiology, Allergy and Neurological Sciences (BCANS) contains the Cardio-Renal Division, Allergy and Respiratory Drugs Division, and Central Nervous System Division. Responsibilities include, but are not limited to, the clinical, pre-clinical, and labelling review of drug submissions indicated for use in/as: neurology, anaesthesiology, pain management, psychiatry, obesity, substance related disorders, hypertension, vasodilators, myocardial ischemia, stroke, diuretics, antithrombotics, anticoagulants, antiplatelets, plasma expanders, dialysis, immunosuppressants, allergy, asthma and cough and cold.

Regulatory Project Management Division, servicing BCANS
Health Canada
Finance Building Number 2
Tunney's Pasture, Address Locator 0202A1
Ottawa, Ontario
K1A 1B9
Fax: (613) 941-1668

The Bureau of Pharmaceutical Sciences (BPS) is responsible for the chemistry and manufacturing review as well as the evaluation of clinical comparative bioavailability data, including but not limited to bioequivalence studies for all submission types of all therapeutic classes of pharmaceutical products. Responsibilities also include the assessment of pharmaceutical product information and labelling of generic product submissions, and DIN applications for prescription drug products. The Bureau also performs highly specialized research activities in the area of analytical testing and dissolution.

Regulatory Project Management Division, servicing BPS
Health Canada
Finance Building Number 2
Tunney's Pasture, Address Locator 0201D
Ottawa, Ontario
K1A 1B9
Fax: (613) 957-3989

The Office of Clinical Trials is responsible for managing and evaluating information related to clinical trial applications for drug products used in Phase I, II, or III clinical trials. This includes but is not limited to receiving and reviewing Clinical Trial Applications, serious unexpected adverse drug reactions, and providing guidance to all relevant stakeholders.

Office of Clinical Trials
Health Canada
Holland Cross, Tower B
5th Floor, Address Locator 3105A
1600 Scott Street
Ottawa, Ontario
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