

Questions and Answers

(Guidance Document Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice)

APPLICABILITY ISSUES

Q1: Does a prescription or nonprescription Drug Identification Number (DIN) application require non-clinical laboratory study data? Will Health Canada exempt nonprescription products from GLP requirements?

A: For both prescription DIN applications and nonprescription DIN applications (e.g. labelling standards, monograph or outside monograph applications) filed and reviewed in accordance with Division 1 of Part C of the *Food and Drug Regulations*, it is possible that non-clinical data will form part of the submission package (e.g. in vitro data for photostable sunscreens) and there are also occasions where non-clinical study data has subsequently been requested/required to support the safety and efficacy of the drug product.

Exemptions from GLP requirements will not be granted for nonprescription products filed and reviewed in accordance with either Division 1 or Division 8 of Part C of the *Food and Drug Regulations*.

Q2: Will Notifiable Change (NC) submissions be included in the list of applications subject to this Guidance?

A: Yes. It is possible, though uncommon, for non-clinical data to be submitted with an NC (i.e. Level II 90 days or 120 days). For example, manufacturers could have explored possible mechanisms behind an adverse event, or tried to characterize something further via animal data.

Q3: Will bioanalysis in support of human bioequivalence studies be required to adhere to GLP requirements and necessitate GLP recognition?

A: No. These types of studies are not covered by Organisation for Economic Co-operation and Development (OECD) GLP. Bioanalytical studies in support of human bioequivalence data are to comply with Good Clinical Practices (GCP) requirements as outlined in Division 5 of the *Food and Drug Regulations* and the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practices E6(R1).

Q4: The guidance on Bioequivalence (Report A) indicates the expectations for the bioanalytical work to be conducted under GLPs. Has Health Canada changed its position?

A: Guideline A was drafted in 1992 prior to the adoption of ICH GCP. In addition, the Guidance is in the process of being revised and reference to GLP will be omitted.

Q5: Do the organizational process and conditions surrounding test item characterization in a Quality Control environment need to conform with GLP?

A: No. These types of testing fall under Good Manufacturing Practice (GMP).

Q6: Will Health Canada expect that safety and efficacy data from non-clinical studies adhere to GLP?

A: The Guidance Document on Good Laboratory Practices applies to non-clinical safety data. Our definition of non-clinical data is consistent with OECD GLP Principles as it applies to all in vitro and in vivo testing, not involving human subjects, performed to determine the safety of human drugs. However, Health Canada allows for flexibility i.e. the Principles of GLP apply to data that cannot be obtained in clinical studies for ethical reasons.

Q7: Could Health Canada expand the scope of the guidance to include reference to certain medical and combination products such as autoinjectors?

A: No. Currently, there are no Canadian regulations that are specific to combination products. Nonetheless, products must meet the requirements of the applicable set of regulation depending on the designated principal mechanism of action. For products that are classified as medical devices, adherence to GLP would not be required as medical devices currently fall outside the scope of the guidance. Compulsory monitoring of GLP for medical devices will be implemented as capacities and priorities permit.

Q8: Could Health Canada provide further explanation on how materials intended as disinfectants fall within the common use of the word "drug"?

A: Disinfectants are classified as drugs or pest control products according to their claim and intended use. Please refer to the Health Canada Guidance Document on Disinfectant Drugs.

Q9: Will Health Canada exempt from GLP requirements products with extensive global post-marketing safety data available as safety and efficacy is already proven by human data?

A: Health Canada allows for flexibility on a case-by-case basis.

Q10: Could Health Canada expand the scope of the guidance to include reference to efficacy data gathered under an *Animal Efficacy Rule*?

A: The Principles of GLP apply to data that cannot be obtained in clinical studies for ethical reasons.

Q11: Will Health Canada provide a rationale for not applying the guidance to non-clinical data in submissions relating to veterinary drugs, natural health products, medical devices, food additives or cosmetics?

A: Health Canada's initial efforts are to support the immediate international acceptance of non-clinical safety data generated in Canada for pharmaceuticals, radiopharmaceuticals and biologics. GLP implementation in this industry sector is very well studied, supported and standardized both by industry and our regulatory counterparts internationally. This effort is very resource intensive for both industry and the GLP monitoring authority, but is now an essential legal prerequisite for Canada's continued participation in global clinical trials. Health Canada recognizes Canada's continuing obligation to the OECD to establish compulsory monitoring of GLP for food additives, feed additives, veterinary drugs and medical devices, and fully intends to establish these requirements as capacities and priorities permit. Health Canada will base these subsequent guidances on the lessons learned from the current implementation.

In the case of cosmetics, although the OECD GLP requirements list this area, there are currently no regulated requirements for pre-market safety data (i.e.: premarket approval) under the Canadian *Food and Drugs Act and Regulations*, and therefore these data cannot currently be requested by Health Products and Food Branch in the context of pre or post market approval. In addition, natural health products are completely exempt from the context of OECD GLP.

Q12: What are Health Canada's expectations with regards to Clinical Trial Applications (CTAs) given that the non-clinical data that may be submitted are part of the "Investigation Brochure"?

A: The Investigation Brochure (IB) includes only a summary of the non-clinical (and clinical, if available) data, however, sponsors should indicate within the IB whether the data from the pivotal non-clinical studies were obtained under GLP conditions.

The expectation of Health Canada pursuant to the GLP Guidance is that, at a minimum, sponsors confirm within the IB that all of the pivotal non-clinical studies (for example [e.g.], repeated-dose toxicity studies, safety pharmacology studies, genotoxicity studies, reproductive toxicology studies, etc.) conducted in accordance with the applicable ICH guidelines to support the clinical trial in question, were carried out in compliance with GLP. Sponsors can confirm this by incorporating a statement within each of the sections that summarize each of the pivotal non-clinical studies to indicate that the studies were conducted under GLP, or a statement could be added at the beginning of the IB, such as following the table of contents, indicating that all the

pivotal non-clinical studies have been carried out in compliance with GLP, with a cross-reference to each of the applicable studies.

Since the sponsor has to already certify within Appendix 3 of the Health Canada Form 3011 that all of the information and material submitted within, or referenced by, a CTA "are complete and accurate and are not false or misleading", the sponsor's statement(s) within the IB confirming that the pivotal non-clinical studies were carried out under GLP conditions, would be considered sufficient at the time of CTA submission. Should Health Canada request the actual toxicology study report, then the report itself should be accompanied by evidence that the study was carried out under GLP conditions, if applicable.

Q13: Could the GLP requirements for clinical trials involving marketed products be waived?

A: Generally GLP requirements could be waived for marketed drugs except in circumstances where a new pivotal non-clinical study would be required to support a clinical trial with the marketed drug (e.g., juvenile animal studies, new repeat dose toxicity studies, etc.).

GLP RECOGNITION ISSUES

Q14: Will a facility outside of Canada generating nonclinical study data in support of a Canadian submission require OECD recognition?

A: Yes. At the time of submission, evidence declaring that the test facility was assessed and found to be GLP compliant by a GLP monitoring authority recognized by the OECD should be included in the submission/application. 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 (FDA).

Q15: Could Health Canada provide clarification regarding potential acceptability of compliance outside of OECD oversight?

A: Health Canada evaluators can obtain information through the Standards Council of Canada (SCC) about the compliance history of an overseas facility if enough data was gathered on that facility. The SCC can ask other Monitoring Authorities if they have ever assessed the facility in question in the country of interest. The decision to treat the data as primary or supplementary ultimately rests with Health Canada.

Q16: Is the Guidance intended to require GLP recognition for Canadian sites only, or for any site providing non-clinical data in support of a submission to Health Canada?

A: Health Canada will require GLP recognition for both domestic and foreign sites. For Canadian sites, Health Canada expects to see proof of inspection by the Standards Council of Canada (SCC) in the form of the certificate which it issues specifying the Areas of GLP Expertise. For foreign sites, Health Canada will expect to see evidence declaring that the facility was assessed and found to be GLP compliant by an OECD-approved GLP Monitoring Authority.

Q17: Could a facility located in a country that has no Monitoring Authority go to the SCC for verification of their inspection reports/study reports before submitting to Health Canada?

A: No. As a Monitoring Authority, the SCC would not review or give an opinion on a study prior to its submission to Health Canada.

Q18: Would the SCC inspect a facility/site located overseas if it was located in a country that does not have a GLP compliance Monitoring Authority adhering to the Mutual Acceptance of Data (MAD)?

A: Yes. If serious concerns are raised by Health Canada evaluators, the SCC could be asked to conduct a study audit or an inspection of an overseas facility.

Q19: Could Health Canada provide a list of the Monitoring Authorities (MA) recognized by the OECD?

A: There is no list of MAs recognized by the OECD but there are individual lists for each country. Each monitoring authority has to report their annual activity to the OECD GLP secretariat and the other MAs. This information is available on the GLP Working Group's protected site and can be produced by the SCC as required. Each MA is expected to send the information to their respective regulatory authorities. Sponsors should contact the Bureau of Policy, Science and International Programs of Health Canada.

Q20: Will the United States FDA accept GLP recognition by the Canadian Monitoring Authority when data is submitted by a Canadian sponsor to the FDA and Health Canada, as is often the case?

A: Yes. The Mutual Acceptance of Data (MAD) directive states that data generated in a facility recognized by the national GLP compliance monitoring authority must be accepted for purposes of assessment by OECD members countries and non-member countries which are adherent to the

MAD Decision (1981). Canada and the US are signatories to the OECD Council Act Decisions on MAD, which means that Canada and the US are to mutually accept non-clinical GLP studies.

Q21: It is unclear whether the GLP certificate should be included as an integrated part of each study report or whether the dossier should contain a section including a series of GLP certificates for all of the laboratories used to perform the activities included in the dossier.

A: Each study report, when applicable, should include a declaration issued by the management of the test facilities by which the study was carried out in accordance with OECD GLP Principles. Any evidence declaring that the facility was assessed and found to be GLP compliant should be included in the current Good Manufacturing Practices / Establishment License (GMP/EL) information section – CTD Module 1.2.5 Compliance and Site Information.

ACCEPTANCE OF STUDY DATA

Q22: Will Health Canada waive the GLP requirements for studies conducted between 1981 and 1989 (when adherence to GLPs was not monitored in a regulated manner)?

A: Non-clinical data submitted in support of pharmaceutical, radiopharmaceutical or biologic drugs should have been conducted following quality processes and systems to ensure adequate data integrity. Sponsors should state how the data was collected and what inspections were performed, if any, to verify the data. The decision to treat the data as primary or supplementary ultimately rests with Health Canada.

Q23: How will Health Canada handle studies that are ongoing, started or completed before the implementation date?

A: Health Canada will not retrospectively require GLP recognition for facilities conducting non-clinical studies. Nonetheless, although the facility conducting the studies may not have been inspected for GLP compliance, it is expected that the studies be conducted under the principles of GLP (same quality processes). Proof of quality of the study will need to be provided and will be assessed on a case-by-case basis.

Q24: Could Health Canada define “evidence” and “comparable evidence”

A: Evidence, in the form of a letter or certificate declaring that the facility was assessed and found to be compliant with GLP by an OECD-approved GLP monitoring authority should be provided to the Regulator. Alternatives may be considered acceptable when the standard used to assess the facility's compliance is deemed to be equivalent to the OECD therefore comparable, such as that of the United States FDA. Documentation should include details of the study types

for which the facility is GLP-compliant and inspection dates. In instances where documentation cannot be provided, Health Canada evaluators may ask the SCC to provide the compliance history for the facility.

Q25: Given that the adherence to OECD principles is certified in writing by the testing facility management, is this sufficient if indicated in the submission?

A: No. The study's GLP compliance statement should be supported and validated by an OECD-approved compliance monitoring authority.

STANDARDS COUNCIL OF CANADA (SCC) TOPICS

Q26: How will the OECD monitor the SCC's GLP compliance monitoring activities?

A: The SCC's 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 regulatory authorities.

Q27: How can studies become GLP compliant before an authority inspection has taken place and before a GLP certificate is issued by the SCC? What happens if a certificate cannot be issued due to severe nonconformities?

A: Health Canada expects that the non-clinical study data submitted in support of pharmaceutical, radiopharmaceutical or biologic drugs comply with GLP principles at the time of submission. Given the wide international acceptance of the OECD standard by both industry and regulatory authorities, Health Canada already receives a great number of studies conducted in accordance with GLP requirements. The majority of test facilities are currently using quality processes and systems to ensure adequate data integrity. This is supported by a declaration issued by the management of the test facilities stating that the study was carried out in accordance with OECD GLP Principles.

Health Canada recognizes that it may take time for test 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 of the posting of the Guidance to Health Canada's website. The implementation date is

dependent on the publication date. A one-year transition period will allow sponsors sufficient time to obtain SCC recognition. Health Canada can not reject a study due to nonconformities but data may be deemed to be secondary.

Q28: In section 3.0/272 of the guidance document, the required timeframe for GLP recognition is not specified. Will Health Canada take into account the time required for planning and to schedule an inspection? Can data be submitted conditionally, pending certification, in the event of a substantial delay?

A: The SCC has the necessary resources to address each application within a timely manner, and has already begun processing requests for SCC inspections from sponsors. A one-year transition period is considered to be sufficient time to allow sponsors to obtain SCC recognition. Extenuating circumstances resulting in delays will be dealt with on a case-by-case basis.

Q29: Do the fees charged by SCC present a potential conflict of interest given that they benefit financially by granting and maintaining compliance recognition?

A: There is no conflict of interest. Fees charged by SCC are for cost recovery purposes, they are not dependent on the outcome (i.e. success or failure to become or remain recognized as a compliant facility) of the activities conducted. Once an application is received and once a visit is conducted, the full applicable fees are charged for the activities performed. The success of the application does not have a bearing on these fees. As long as a facility remains recognized by SCC, fees are charged for the ongoing activities to maintain that recognition.

SCC's review and approval practices are based on the examination of objective evidence provided in the inspection reports and are independently balloted by individuals with no direct interest in the finances of the SCC. Supporting evidence for recognition decisions is examined by the representatives of the Office of the Auditor General as part of their audits. The SCC's Conformity Assessment Branch also provides an impartiality report to its Advisory Council on Conformity Assessment (ACCA) at each ACCA Meeting.

Q30: Is the plan to audit 'anyone' contributing to a GLP study?

A: Yes, if a sponsor requests an audit as part of their application. If a 3rd party asks the SCC to conduct an inspection, this is also possible according to the SCC policy.

Q31: What is the typical cost for a SCC GLP recognition audit?

A: Costs are dependant on scope and size of the team required. (Cost = Type of Audit + Travel). A cost estimate, detailing expected maintenance of the recognition, is provided to the applicant

once the completed application has been received. A fee schedule for the GLP program is available from the SCC website.

Q32: If the SCC recognizes GLP compliance and then a problem is discovered at the facility, is the SCC liable for the company's compliance?

A: No, the SCC is not liable for the company's compliance. GLP recognition demonstrates compliance with required guidelines, it does not unconditionally guarantee the quality of the work being done.

Q33: What happens if the final report goes to the regulatory authority (RA) for evaluation and is clearly not compliant? Does the RA contact the SCC to verify the data they are receiving if there is doubt of the GLP compliance? Does Health Canada train their evaluators on what to look for with respect to GLP compliance?

A: Evaluators are thoroughly trained to identify GLP compliance issues. If issues were found in a final report, sponsors may be asked to provide further evidence, and if evidence were not satisfactory, evaluators may ask the SCC to provide compliance history for the facility. Part of the Memorandum of Understanding between the SCC and Health Canada is to maintain open communication. The details of specific inspections will be readily available to Health Canada from SCC.

Q34: What kind of timelines are there between inspection and receiving the GLP recognition?

A: A decision is usually made within 2 weeks of the final report being issued. However, the timelines are dependant on both the company and the SCC. The faster the company responds to the findings, the faster the process can be completed.

OTHER ISSUES

Q35: Could Health Canada provide a rationale for the 10 year retention period?

A: Health Canada's recommendation with respect to records retention is harmonized with international requirements which vary from 2 to 15 years. It is felt that the clinical experience gathered with a product that has been on the market for a period of approximately 10 years is sufficient to cover for uncertainties with regard to the non-clinical safety database. This record retention period is appropriate to support facility inspections and study audits as well.

Q36: Will Health Canada issue a regulatory directive as is the case for pest control products where the Pest Management Regulatory Agency has issued a regulatory directive concerning Good laboratory Practice?

A: Health Canada is planning to proceed with mandatory GLP requirements as part of the modernization of the *Food and Drugs Act* and the subsequent amendments of its regulations.

Q37: Why are only a few OECD referenced documents appearing in the references?

A: Instead of listing all available OECD documents in the Health Canada's Guidance Document we have provided under references a link/ address to the OECD website which provides access to OECD GLP Guidelines.

Q38: Any claim of GLP compliance made by a study director or principal investigator in the United Kingdom for work conducted by a Canadian facility might constitute a "False Instrument" (see Regulation 12.- of The Good Laboratory Practice Regulations) if the GLP compliance status of the Canadian facility has not been officially verified by the responsible Canadian Government Agency." Could Health Canada clarify the situation so that the requirements of Canada and other OECD countries coincide?

A: In August 2009, the Medicines and Healthcare products Regulatory Agency (MHRA) made an announcement recognizing the compliance monitoring programme in Canada. Again, OECD countries are signatories to the OECD Council Act Decisions on the Mutual Acceptance of Data (MAD), which means that regulatory authorities in countries adhering to the MAD [e.g. Canada, USA, UK, Netherlands, Germany, etc.] are to mutually accept non-clinical GLP studies from each other.

Q39: Has the OECD/MHRA reviewed Canada's proposed monitoring program and agrees that it satisfies their concerns?

A: OECD has reviewed the policy guidance and indicated that it met the requirements of the mutual acceptance of data agreement.