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Health Canada Santé Canada

GUIDE TO THE DRUGS DIRECTORATE LABORATORY ACTIVITIES QUALITY ASSURANCE PROGRAM

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INTRODUCTION

National and international developments over the past few years in the field of good laboratory practice (GLP) have led the Drugs Directorate (DD) to re-examine all its laboratory activities.

The policy of Health Protection Branch (HPB) is that all laboratory work be conducted in the spirit of GLP, despite the fact that the term "good laboratory practice" is usually applied only to non-clinical, routine toxicological studies, and, as such, that its application directly affects only a small portion of current DD laboratory work.

The purpose of this guide is to provide an outline for ensuring the high quality of all aspects of laboratory activities within DD, thereby preserving the integrity of the laboratory science being conducted. The guide will also simplify certification procedures should any other DD unit at some future time become subject to GLP.

Laboratory work incorporates many elements, which are presented in this guide in the following order:

- **Data** that have been recorded in a laboratory either on an instrument or by a person should be handled in a reliable manner (Section 1).

- The laboratory's **working environment** should take into consideration safety, comfort, and freedom from contaminants (Section 2).

- **Instruments should be properly installed, maintained, and operated**, so that test results produced in DD laboratories are of the highest integrity (Section 3).

- **Analytical methods** should be validated, documented, and modified in a consistent manner, so that the results produced are accurate (Section 4).

- **Glassware** used in laboratories should be of a specific grade and type, according to the analytical method employed. All laboratory glassware must be cleaned and calibrated according to specific standards (Section 5).

- **Reagents and reagent solutions** must be of high quality. All reagents or reagent solutions are specific to the types of analyses in which they are employed (Section 6).

- **Media** for analytical tests must meet prescribed quality standards and be properly stored to ensure continuing quality (Section 7).

- **Reference standards** must also meet quality standards and must be acquired, stored, and verified for use in standard laboratory procedures (Section 8).

- **Test samples** must be received, recorded, handled, and stored according to standardized procedures (Section 9).

- Work must be monitored on a routine basis using **quality assurance** audits and inspections (Section 10).

- The **résumés and training files** of laboratory personnel must be recorded and updated on a routine basis (Section 11).

- The use of **computers and electronic data** storage methods must meet prescribed standards, including security, and routine backup and archiving of data (Section 12).

- All **files and test results** must be archived in a routine manner, considering the available facilities, the personnel, the type of material being archived, and the required storage duration (Section 13).

References appearing throughout the text are listed following Section 13. The references are, in turn, followed by a **glossary of acronyms and initialisms** used in the Drugs Directorate's laboratory activities.

Finally, **Appendix A** provides additional information about the Drugs Directorate staff involved in the presentation of this guide.

1. RECORDING, HANDLING, AND VALIDATING DATA

When a quality assurance (QA) system for validating scientific data is in place, experimental results are accurately and permanently recorded in a meaningful, accessible, and reliable manner.

All data may be recorded in either official language.

1.1 Security Classification Levels

The level of security accorded to data varies according to the particular organization. The following levels of classification are suggested:

- **Fully confidential data.** Test results for prosecutions and for important proprietary information.
- **Confidential data.** Routine assay results obtained during the evaluation of commercial products.
- **Research data.** Test results that may be required to satisfy public scrutiny of HPB research and methods of validation.
- **Other data.** Exploratory studies and non-confidential analytical assays.

1.2 Books, Logs, Laboratory Notebooks, and Records

In the daily routine of a laboratory, certain data concerning instruments, analytical tests and samples, reagents, quality assurance, glassware, media, reference standards, and personnel must be gathered and recorded. This data is recorded in one or more books, logs, laboratory notebooks, or files. These records can include:

a. Performance and maintenance log book (for an instrument)

b. User log book (for an instrument)

c. Laboratory notebook

d. Sampling methods manual (sample log)

e. Reagent and reagent solutions log

f. Reference standards log

g. QA file

h. Personnel training file

i. Computer and electronic data file

j. Archive log

Whatever the records are called, they should meet the minimal acceptable procedures for laboratory notebooks as described in Section 1.3 (next).

1.3 Minimum Acceptable Procedures for Laboratory Notebooks

Format

All data pertaining to an analysis must be permanently recorded in a laboratory notebook. The laboratory notebook can be either:

a. a bound notebook of duplicate pages numbered consecutively. This is the preferred method for recording information within the laboratory. Wherever possible, for ease of reference by other staff members, reporting should follow a standardized format.

b. an operator-bound notebook in which pre-printed or photocopied work-sheets are bound in book form and the pages are numbered consecutively. This is a compromise between loose sheets and a bound notebook, this method offers standardization of format and is advantageous in recording repetitive analyses.

Laboratory notebooks must be well labelled and must contain a table of contents. The table of contents identifies samples, analyses, projects, and so on, and their location within the notebook.

Storage and Distribution

Blank notebooks should be issued, and completed notebooks stored, by a central source. The authority level of the source may vary depending on the organization.

The source should establish a master file and record the following information about each notebook:

a. Storage location of the notebook

b. Number assigned to the notebook

c. Notebook type (if more than one type of notebook is used)

d. Date of issue

e. Name of person to whom issued

f. Date of return and signature

g. Subject (e.g., project title, assay title)

Ink/Corrections

All notebook entries must be made in permanent ink. Entries made in pencil or erasable ink are unacceptable.

The only form of correction permitted is the drawing of a single line through the erroneous entry. This cancellation must not obscure the nature of the error. A cancellation must be initialled and dated by the individual making it. If needed, a brief explanation for the cancellation should be made in the margin.

Entries

As previously stated (see "Storage and Distribution," above), data pertaining to an analysis must be permanently recorded in the laboratory notebook. Details to be included are:

a. identification of the sample,

b. sample preparation procedure,

c. methodologies employed,

d. rough notes,

e. raw data (e.g., weighings, burette readings, dilutions),

f. comments,

g. identification of reference standard,

h. calculations, and

i. validation results.

In most cases, it is impractical to handwrite all data concerning an analysis in the laboratory notebook. It is more feasible to consider the laboratory notebook to be a directory in which the location of all data associated with an analysis can be found. This concept offers the analyst the freedom to refer to project files (e.g., chromatogram file, photographic file, printouts from computer programs or data stations, instrument log books) that may be considered to be extensions of the laboratory notebook.

Both the laboratory notebook and its extensions must adhere to specific guidelines for the entry of data:

a. Proper scientific notation must be used, and analytical data must be reported to the correct number of significant figures.

b. Under no circumstances should data be recorded on scraps of paper. Such scraps are easily lost and difficult to identify.

c. All entries in the laboratory notebook either must be completed test results or must unequivocally identify the extension in which the completed test results may be found. The reverse must also hold true. That is, all information found in the extensions of the laboratory notebook must be unequivocally identified and cross-referenced to the appropriate laboratory notebook, including the page number where reference to the extension was made. All material within the extension must be properly and permanently identified.

d. Data that pertain to an analysis - such as chromatograms, instrument readout tapes, calculator tapes, and so on - may be glued, taped, or stapled into the laboratory notebook. Such items should be properly and permanently identified.

Validation of Test Results

The signatures and initials of the personnel responsible for analyses must be kept on file for future reference.

Test result entries must be dated and initialled by the person making the entries. Such validation can occur at the end of each entry or each page, or at intervals throughout the laboratory notebook and any extensions. The frequency is determined by the person approving the test results.

A review of the test results must occur at regular intervals. The date of the review and the initials of the person approving the results are required. In situations where test results are stored electronically, hard copies must be made at regular intervals and must be signed and approved as described above.

If, at any time, information has been removed from the laboratory notebook or extensions, an explanation must be provided. The date and the initials both of the supervisor and of the individual that removed the information must accompany the explanation.

2. THE WORKING ENVIRONMENT

Any QA program dealing with the working environment should consider safety. Employee safety is mandated under Part IV of the Canada Labour Code, which states: "*Every employer shall ensure that the safety and health at work of every person employed by him is protected.*"

This section sets out certain minimum acceptable procedures that are intended to help the responsible authorities to ensure that all laboratories are safe, comfortable, and contaminant-free. It does not attempt to list all of the mandated precautions and safety measures that may be required. More detailed information concerning these and other specific procedures and guidelines may be obtained by consulting the references [3], [4], [5], listed at the end of this guide.

2.1 The Laboratory Environment

General

All laboratories must have adequate electrical power, proper lighting, sufficient working space, and regularly cleaned surroundings and work stations, as well as provision for special conditions as required (e.g., subdued lighting, instrument rooms).

Air Ventilation

All laboratories must have proper ventilation. Where necessary, laboratories should be equipped with laminar flow hoods and fume hoods. Written instructions for the safe use of these hoods should be provided.

Cleanliness of Labs

In accordance with Part IV of the Canada Labour Code, all laboratories must be free (to a no-effect level) of contaminants that might interfere with analysis or might lead to illness or occupational injury in the workplace.

Sanitation of Labs

Each laboratory must have a sanitation program with a set of written instructions outlining the procedures to be used, the personnel responsible, the areas and equipment to be cleaned, and the materials to be used to maintain clean, sanitary, and orderly premises. It is desirable that each laboratory have as much control as possible over cleaning procedures within the laboratory by lab staff and maintenance personnel.

2.2 Environmental Hygiene and Health

Hygiene

Each analyst bears responsibility for adhering to good personal hygiene practices. Each laboratory should also have a personal hygiene program designed to protect the employees and to forestall the contamination of test and control substances and of test systems.

Eating/Drinking/Smoking

Eating, drinking, smoking, and other unhygienic practices that could result in illness or injury to employees are prohibited in working areas.

Health

Personnel should have no health or medical condition likely to have an adverse effect on the project. Personnel whose health or medical condition might compromise the quality of the project should be excluded from operations.

2.3 Clothing

Appropriate work clothes should be worn. Clothes should be changed as often as necessary to provide protection to the employee and to prevent microbiological, radiological, chemical, or other contamination of test systems and of test and control substances.

2.4 Security

Laboratory access must be restricted to authorized personnel in order to protect the integrity of the projects and to guard against breaches of safety.

2.5 Evacuation Procedures

Evacuation procedures must be established by the Building Safety Committee in collaboration with Facilities Management. A set of written instructions must be prepared, outlining the procedures to be followed for the orderly and safe evacuation of the area, with due consideration for maintaining the integrity of samples and studies (e.g., narcotics to be secured).

2.6 Monitoring

Each laboratory must maintain a relevant environmental monitoring program with a set of written instructions concerning air, surfaces, and the presence of rodents and insects within the laboratory.

All laboratories must have a self-inspection program that is performed at least once each year. As a check on the effectiveness of, and as a complement to, this internal inspection program, each laboratory should be inspected by an independent inspector at least once each year.

3. POLICY ON INSTRUMENTS AND EQUIPMENT USED IN THE DRUGS DIRECTORATE

The policy on instruments and equipment establishes quality-control criteria for the operation, maintenance, performance, checking, and repair of all instruments used in the Drugs Directorate. The purpose of the policy on instruments and equipment is to ensure the integrity of test results produced in DD laboratories, as the instruments and equipment used have a direct influence on the quality of results.

Instruments and equipment must be handled and maintained so that the accuracy required to ensure quality results is achieved. The slow deterioration of electrical, mechanical, and optical components is often difficult to detect, particularly in cases where the instrument or piece of equipment is used for comparing the response of a known standard to that of a sample, thereby masking changes in the instrument or piece of equipment itself. Obtaining an apparently satisfactory reading does not necessarily mean that the instrument or piece of equipment is functioning properly. Therefore, performance criteria for each instrument or piece of equipment must be available and must be incorporated into its written performance check schedule (PCS). In certain cases, establishing a service contract may be the most cost-effective way of ensuring reliable performance.

The system established to ensure that all necessary maintenance, checks, and repairs are carried out must also ensure that a permanent historical record of each instrument and piece of equipment is maintained.

3.1 Definitions

For the purpose of DD instrument and equipment policy, the following definitions apply:

- **"Instrument"** is a measuring device (e.g., spectrophotometer).
- **"Equipment"** is devices used to collect, prepare, and store samples and other materials (e.g., ultracentrifuge).
- **"Custodian"** is the specific individual that is responsible for a particular instrument or piece of equipment.

3.2 Installation

New instruments and equipment must be installed and calibrated by the manufacturer's representative, who gives all results to the custodian. The custodian must then insert the results into the performance and maintenance log book.

3.3 Performance Checks

The custodian performs scheduled maintenance checks, including the calibration of new instruments and equipment or of those that are suspected to be operating improperly. (Method-related checks or method-related operation are the responsibility of the individual operator, who is not necessarily the custodian.)

The custodian documents specific performance checks and maintenance performed on each instrument or piece of equipment.

3.4 Maintenance

The custodian performs, or arranges for, routine maintenance as indicated in the documentation for each instrument or piece of equipment.

The custodian keeps a written record for the instrument or piece of equipment. This record is the performance and maintenance log book. The specific format of the log book is left to the discretion of the custodian, but the minimum information to be included is:

a. a description of the instrument or piece of equipment, including the make, model, serial number, and asset number.

b. the date of purchase and the cost of the instrument or piece of equipment.

c. a description of malfunctions and repairs - specifically, the nature and date of the malfunction, the nature and date of the repairs, the parts replaced, the downtime, and the name of the person performing the service. Any instrument, piece of equipment, or part thereof, replaced in the course of an analytical study must be calibrated according to the initial specification of the standard operating procedure (SOP) for the instrument, or piece of equipment.

d. the date of routine maintenance and the person carrying it out.

e. a description of performance checks, specifying the identity of the analytical standard, the test method, raw data, calculations, test result, operator, and date of analysis.

3.5 Operation

At the discretion of the custodian, a user log book may also be kept for each instrument or piece of equipment.

Users must immediately report all malfunctions to the custodian, who must mark the instrument or piece of equipment "OUT OF ORDER" whenever a malfunction occurs.

It is strongly recommended that, whenever possible, susceptible instruments or equipment be kept in a separate room, free from laboratory fumes and dust.

4. HOW TO SELECT ANALYTICAL METHODS

Analytical methods must be selected with a view to the purpose to which the method is to be put. At DD, analytical methods are used for one of two purposes:

a. to support DD's regulatory function, either directly or indirectly - methods used by the Drug Identification Division (DID) to analyse illicit drugs and by the Pharmaceutical Chemistry Division (PCD) to evaluate drug raw materials and formulations.

b. to carry out research projects that have a potential for regulatory impact.

4.1 Criteria for Selecting a Method

The analytical method chosen must be consistent with the level of analyte being measured and be appropriate for the particular substrate or matrix containing the analyte.

In general, the prudent laboratory supervisor will choose analytical methods that are documented in the literature, provided that such methods are consistent with the above considerations. The independent development of an analytical method can be a costly proposition if properly performed and, if not properly performed, can lead to problems and frustration in later applications. A prudent lab supervisor will resist the temptation simply to devise a method based on his or her knowledge of chemistry (immediately putting it into practice after a couple of samples have been run), or the temptation to abstract a method from the general literature.

Standard Method

Usually, the best analytical methods are those produced by organizations that have thoroughly investigated and tested each method in numerous laboratories before designating it as a standard. The laboratory that uses standard methods is less vulnerable to criticism concerning its use of proper methods. Sources of standard methods include:

a. Schedule B publications of the *Food and Drugs Act*, including the *United States Pharmacopoeia (USP)*, the *British Pharmacopoeia (BP)*, and the *European Pharmacopoeia (EP)*;

b. the American Society for Testing and Materials (ASTM);

c. the Association of Official Analytical Chemists (AOAC); and

d. the Cosmetics, Toiletries and Fragrances Association (CTFA).

New Methods

The periodic literature about analytical methods is extensive. Besides the general purpose journals (e.g., *Analytical Chemistry, Analytica Chimica Acta, Journal of the AOAC*), there are many specialized journals (e.g., those dealing in food chemistry, pharmaceuticals, paper, plastics) that publish occasional articles containing or featuring analytical methods. Patent literature and in-house literature, especially that from instrument manufacturers, are also fruitful sources of analytical methods.

4.2 Validating New Methods

Excepting standard or official analytical methods, any new method or major modification of an existing method that is being considered for use in routine testing of large numbers of samples should be subjected to selection criteria particular to that laboratory. The purpose of the selection criteria is

a. to demonstrate that the method is appropriate for the analysis of the substrate to which it will be applied, and

b. to obtain information on the precision and accuracy inherent in the method.

Standard or official analytical methods may be tested to establish their range and limitations (e.g., to verify that a method for chromatographic impurities responds to specific compounds).

The selection criteria used in establishing a new method can vary in their degree of rigor and reliability. The following list can be used as a reminder. It is in ascending order of preference:

a. Selection criteria established by the laboratory that developed the method.

b. Selection criteria established by one or more laboratories outside of the laboratory that developed the method.

c. Selection criteria arising from a collaborative study.

An analytical method need be approved only once, unless evidence that questions the validity of the method appears. Testing at a higher reliability level is not considered repetitive (e.g., participating in a collaborative study after having approved the method in your own laboratory).

Approval of a method is applicable only to the method as written. Any modification or any application (e.g., types of sample, range of use) not covered by the selection criteria results in a new method that must be validated.

Minimum Acceptable Procedures for a New Method

All non-official methods must be tested and approved.

A working definition of "official analytical methods" is those methods documented in public legal documents (e.g., those used in enforcing the *Food and Drugs Act and Regulations*), and giving an indication of use. "Official analytical methods" include DO methods and compendial methods, but not "acceptable" methods.

"Approval" is either a collaborative study or a systematic check of the method by the user-laboratory. If properly performed, the approval need not be repeated.

All method approval must be documented in written reports, containing the following sections:

a. Introduction

b. Background

c. Objective

d. Statistical analysis

e. Discussion

f. List of recommendations.

The report should also contain a copy of the method, a description of the approved testing procedure, and a description of the materials used for approved testing (type, source, and preparation).

Attributes to Note When Evaluating a New Method

During the approval process, consideration should be given to the following attributes of an analytical method. The significance of each attribute will vary depending on the reason for the analysis.

a. **Reliability**

"Reliability" summarizes the performance of the analytical method, taking into consideration the quality requirements for the test results. Thus, while a method may be reliable for one use, it may not be reliable for another.

b. **Applicability**

"Applicability" indicates the limitations of the method as well as the type of commodity, formulation, or substance that can be analysed using the method.

c. **Specificity**

"Specificity" is the degree to which the method's response to the substance being sought is unique. Specificity is tied to applicability in the matter of interferences. In other words, if a method can be used to identify several substances, but is used in situations where only one of those substances is present, then the method becomes highly specific within the limitations of the method.

d. **Detectability**

"Detectability" is defined as the minimum amount or concentration of test material that provides a measurable response. In some cases, the substance of interest is present in amounts that do not require delectability at low levels, while, in other cases, the level of delectability is very important. In chemical analysis, it is often the test blank that determines the limit of detection. Note that both the absolute size and the variability of the test blank are important.

e. **Sensitivity**

"Sensitivity" is defined as the amount of response per unit of the substance being measured, that is, the slope of the calibration curve. The slope of the calibration curve is frequently mistaken for the detection limit.

If the calibration curve is a straight line, the sensitivity is constant over the range. If the slope is steep, the method is highly sensitive, that is, a small change in the substance concentration results in a large change in the measured response. If the slope is shallow, the method has low sensitivity, that is, a large change in the substance concentration results in a small change in the measured response.

f. **Accuracy**

"Accuracy" defines the degree of correlation with the true value. Analytical methods can have a positive bias (yielding high results), a negative bias (yielding low results), but not both. They can also exhibit no bias.

Many methods in use are accurate by definition. When a regulation or specification includes the method of analysis to be used in determining compliance with the regulation or specification, then the bias of the method is zero by definition. In these cases, strict adherence to the method in every detail is essential.

g. **Precision**

"Precision" defines the amount of variation in the test results. Measures of precision are often incorrectly used to refer to accuracy. Care should be taken to distinguish between these terms. Standard deviation or coefficient of variation are the usual numerical measures of precision.

The overall precision of a method is affected by differences

- **between laboratories**. The variation encountered when the same method is used in different laboratories is usually the largest component of variation.

- **between analysts**. This is the variation encountered when different analysts in the same laboratory use the same method.

- **within analysts**. This is the variation encountered by an analyst between analyses performed on the same day, or between analyses performed on different days, using the same method.

When comparing analytical methods, it is important to know which components of precision are being discussed. Valid comparisons can be made only in terms of the same components.

h. **Cost**

Other attributes of analytical methods are of practical importance even though they are not directly related to quality. These attributes can be summarized under "cost of analysis." The following cost components should be considered:

i. Time required to complete an analysis

ii. Material input required (e.g., instruments, reagents)

iii. Expertise (i.e., the degree of skill and training required)

Techniques for Approval of a New Method

Once the attributes of a new method have been evaluated (determining the attributes that are the most significant in the circumstances), the procedure for approving the method should be carefully planned. This planning should occur before any work is undertaken and should maximize both the information obtained and its usefulness, as well as minimize the work required.

A method must be thoroughly checked by the originator and must meet the stated selection criteria before it is sent for approval by another laboratory or collaborative study.

Approval of a Method by the Originating Laboratory

Initial approval steps, evaluation of ruggedness, and method comparison are discussed by Youden and Steiner.[1] Aspects of special importance are:

- **Recovery studies**. Ideally, approval of the method, including recovery studies on spiked samples, should be performed in accordance with statistically sound experimental designs. Also, a statistician should be consulted before any work is undertaken. However, in practice, it may be necessary to operate at a lower level of sophistication. Results from recovery studies must be interpreted cautiously, owing to the difficulty in obtaining uniform distribution of analyte in the test material, especially if the test material is a solid.

- **Authentic samples**. Authenticated samples are used to approve methods for identifying drugs. Materials that have had their identity authenticated by supplier certification or by structure elucidation through spectroscopic or physical and chemical measurements of unique properties (e.g., MS, IR, NMR, mixed melting point) can be used as authentic samples in the approval of drug identity methods.

Approval of a Method by One or More Laboratories

Participating laboratories should be given a copy of the test procedure and representative samples of known composition to analyses. There should be no discussion of the test procedure between the originator and the laboratories approving the method.

Collaborative Studies

In the case of collaborative studies, the procedure proposed by Youden and Steiner[1] for approving a method should be followed.

4.3 Authorizing New Methods

Division Chiefs should authorize approved new methods for use and should have the new methods added to the methods manual.

4.4 Documenting New Methods

All analytical methods that are used for standard, repetitive testing in the laboratory should be written in a methods manual, and the written method should correspond exactly to the method as it is actually used in the laboratory. Laboratory supervisors should monitor operations closely to be certain that deviations from the written methods do not occur. If deviations from the approved method represent an improvement, and if it is established that the deviation does not have a deleterious effect on quality of data, then the method should be rewritten.

The written method must be clear and unambiguous. An experienced analyst, unfamiliar with the method, should be able to use it with no instruction from the supervisor. The written method should provide information sufficient for the analyst to interpret the results obtained. No analyst should use a method whose scientific basis is unclear.

Format for Writing a New Method

All written analytical methods should follow the format set out below. The written method should be clear and concise, and each part should contain the information described below.

- **Title**

  The title should be brief and should contain the name of both analyte and substrate (e.g., *Determination of 1,4-Dioxane in Cosmetic Products*). If more than one analytical method exists for a given analyte/substrate combination, the name may include a designation of the specific measurement method (e.g., *Spectrophotometric Method for Determination of Colour in Wastewater*). Occasionally, use of the method will depend on the level of the analyte present; this fact should be noted in the title (e.g., *Determination of Low-Level Phenol in Wastewater*).

- **Date authorized**

  The date that the method was authorized for use by the Division Chief must be noted.

- **Numbering**

  See Section 4.7 for the numbering method.

- **Style**

  Analytical methods should be written using the imperative mood. Use short sentences, and avoid convoluted phrases.

- **References**

  Include references to the literature on which the method is based or to in-house documentation of the approval studies (which are to be maintained in a special file).

- **Abbreviations**

  An abbreviation should be defined the first time it is used.

- **Scope**

  The scope should show the range of analyte concentrations for which the analytical method is useful. It should also show the type and nature of the matrix to which the method can be applied, and an estimate of the time required for a single analysis. Interfering substances should be indicated, enabling the analyst to decide quickly whether the method is suitable for the task at hand.

! Basic principles

Describe the chemical, physical, or biological principles on which the method is based. Unusual chemical reactions should be detailed, separation processes outlined briefly, and the effect of interfering substances described. Methods used to eliminate interference should also be described.

! Apparatus and reagents

Describe instruments and unusual apparatus that are required. Common laboratory equipment (e.g., pH meters and analytical balances) need not be listed unless special capabilities - such as the need to measure 0.001 pH units, or the capability to weigh to the micro or semi-micro level - are required. Similarly, common glassware need not be listed, but specialized pieces (e.g., a Soxhlet extractor) should be mentioned.

Reagents should be fully described, including chemical name and purity. A description of the method of preparation should be included for those reagents that must be prepared prior to analysis. Where stability may be a problem, the shelf-life of the reagent should be given.

! Safety precautions

Any safety precautions peculiar to the analysis should be described. These might include:

a. necessity for working in a hood,

b. steps to avoid hazardous reactions such as explosions,

c. need for special safety devices or clothing, and

d. special precautions to dispose of hazardous waste.

The reasons for the indicated safety precautions should be given so that the analyst may more readily assess the degree of hazard represented.

! Procedure

List the instructions in a strict time sequence, exactly as the test is run. There is nothing more frustrating than suddenly to reach an instruction such as: *Add 20 mL of a 1:10 dilution of a 50:50 mixture of reagents A and B, which have previously*

been mixed and filtered. This instruction causes the analyst to turn his or her attention from the sequence of operations in the procedure to mix two reagents, filter the mixture, and dilute 1:10 before continuing the main sequence of the procedure.

Be specific. Don't say *neutralize with HCI*, when what you mean is *add 0.1 M HCl dropwise to a pH of 7.0 ± 0.2*. On the other hand, it is not necessary to detail common laboratory operations (e.g., weighing or titrating).

Indicate critical steps in the analysis, and the consequences if care is not taken during these steps.

! Calculation

Give the equations necessary to calculate the results of the analysis, including the units of all variables and the units of derived results. If the equations are not straightforward, indicate how they were derived.

! Statistics

Summarize all information available on the precision and accuracy of the method. Refer, if necessary, to the source of the method and to any validation studies that were run in the laboratory.

! Quality assurance

Indicate the reference samples that are available, and the frequency with which they should be analysed.

! Comments

Add any special comments or remarks that may promote understanding of the method or interpretation of the results.

4.5 Modification of Analytical Methods

In the course of normal operations, minor modifications to a method are often found to be desirable (e.g., a change in sample size or a slightly different pH).

All such modifications should be subject to validation. If the modification is truly minor and judged by the supervisor to be unlikely to affect results, validation could simply consist of running several samples by the modified and unmodified methods, with comparison of results. On the other hand, major modifications that might be suspected of affecting results should have a full validation study.

Any modification, major or minor, if adopted as part of the method, must be documented, becoming part of the written method. The documentation can consist of an addendum to the written method, with notes in the procedure referring the reader to the addendum. The addendum should clearly indicate the form of the modification, the test results or a reference to an approved study that may be documented elsewhere, and the date on which the modification was adopted as part of the authorized method.

4.6 Manuals

Methods and their selection criteria should be appropriately archived, and readily available to all personnel. Bulky manuals requiring laborious updating should be avoided.

4.7 Numbering of New Methods

Methods are to be identified by Bureau and Division of origin, using a designation, such as:

a. "BDR/PCD" (Bureau of Drug Research/Pharmaceutical Chemistry Division),

b. followed by a number representing the date on which the method was authorized by the Division Chief, written in the style "year, month, day."

Each revised method is to receive a new number and is to list the number of the method that it supercedes. Methods that have been superceded are to be so marked in the computer files.

5. HANDLING GLASSWARE

Glassware used in a laboratory is an integral part of the analytical method. Therefore, the grade of the glassware, the type of volumetric glassware, the specifications for volumetric glassware, and the cleaning and handling of glassware must all be taken into account.

5.1 Minimum Acceptable Procedures

The minimum acceptable procedures for handling laboratory glassware are:

a. Class A volumetric glassware must be used for volumetric analysis.

b. Proper technique must be used in handling volumetric glassware. "Proper technique" includes making related measurements of solutions at constant (room) temperature.

c. General cleaning procedures must ensure that glassware used in analytical testing is free from contamination.

d. Volumetric glassware must be absolutely clean, to ensure that the film of liquid never breaks at any point.

e. Special cleaning requirements must be met.

f. Special purpose glassware must be used when specified (e.g., light-resistant glassware for vitamin analysis).

g. Chipped, cracked, or etched glassware must not be used.

5.2 Grades of Glassware

Laboratory glassware serves three major functions:

a. storage and transfer,

b. measurement of volumes, and

c. confinement of reactions.

For the purposes of the discussions in this section, "glassware" includes containers made from porcelain and plastic.

There are many grades of glassware from which to choose. Some possess specific properties, for example,

a. resistance to thermal shock (Vycor brand),

b. alkali resistance (Corning brand),

c. light resistance (Ray-Sorb or Low-Actinic brands), and

d. super strength (Corex brand).

Soft glass containers are usually relatively soluble and therefore are not recommended for general laboratory use. The mainstay of the modern analytical laboratory is a highly resistant borosilicate glass (Kimax or Pyrex brand). The use of containers and other apparatus made of teflon, polyethylene, polystyrene, and polypropylene has increased markedly in recent years. In many cases - such as in microbiology laboratories - sterile disposable materials should be used.

5.3 Types of Volumetric Glassware

Accurately calibrated glassware for precise measurement of volume has become known, by common usage, as volumetric glassware. This glassware group includes volumetric flasks, volumetric pipettes, and accurately calibrated burettes. Less accurate types of glassware, including graduated cylinders and measuring pipettes, are used in the analytical laboratory when exact volumes are not necessary.

5.4 Handling Volumetric Glassware

The precision of volumetric work depends, in part, upon the accuracy with which volumes of solutions can be measured. There are certain sources of error that must be carefully considered when working with precise volumes.

- **!** The **volumetric apparatus must be read correctly**; that is, the bottom of the meniscus should be tangential to the calibration mark.

- **!** Another source of error is **change in temperature**, which results in changes in the actual capacity of glass apparatus and in the volume of the solutions.

The capacity of an ordinary glass flask of 1000 mL volume increases 0.025 mL per degree rise in temperature, but if the flask is made of borosilicate glass, the increase is much less. One litre of water or of most 0.1 N solutions increases in volume by approximately 0.20 mL per degree rise in temperature. Thus, solutions must be measured at the temperature at which the glass apparatus was calibrated. This temperature, which is indicated on all volumetric glassware, is usually 20°C. The temperature in most laboratories is usually higher than 20°C; but this discrepancy is inconsequential, provided the laboratory temperature is relatively constant.

! There may also be **errors of calibration** of the apparatus; such apparatus should be recalibrated or replaced.

Volumetric glassware is calibrated to contain or to deliver a definite volume of liquid. The calibration is indicated on the apparatus, together with the letters TC (to contain) or TD (to deliver). (Volumetric flasks are calibrated to contain a given volume.)

Volumetric pipettes are calibrated to deliver a fixed volume. The usual capacities are 1 through 100 mL, although micro-pipettes are also available. It is most important to remember that the liquid remaining in the tip of a volumetric pipette is not removed. In the case of measuring and serological pipettes, the small amount of liquid remaining in the tip is to be blown out and added to the volume. Such pipettes are marked by a frosted band near the top.

The general rules regarding the handling of a burette are:

a. Do not attempt to dry a burette that has been cleaned for use; simply rinse it two or three times with a small volume of the solution with which it is to be filled.

b. Do not allow alkaline solutions to stand in a burette; the glass will be attacked, and the stopcock, unless made of Teflon, will tend to freeze.

c. A 50 mL burette should not be emptied faster than 0.5 mL per second, because too much liquid adheres to the walls. As the solution drains down, the meniscus gradually rises, giving a high false reading.

d. Generally, the titrant volume used should be between 30 percent and 100 percent of the total burette volume. Where there is less than 10 mL of titrant to be measured, a 10 mL micro-burette should be used.

Glass apparatus for delivering liquids must be absolutely clean; the film of liquid should never break at any point. If careful attention is not paid to this fact, the required amount of solution will not be delivered. Various cleaning agents and their use are described in Section 5.6 and 5.7 of this guide.

Table A

NBS Specifications for Volumetric Glassware

Volumetric Flasks

	Designated volume (mL)						
	10	**25**	**50**	**100**	**250**	**500**	**1000**
Limit of error, mL	0.02	0.03	0.05	0.08	0.12	0.15	0.30
Limit of error, %	0.20	0.12	0.10	0.08	0.05	0.03	0.03

Volumetric Pipettes

	Designated volume (mL)						
	1	**2**	**5**	**10**	**25**	**50**	**100**
Limit of error, mL	0.006	0.006	0.01	0.02	0.03	0.05	0.08
Limit of error, %	0.60	0.30	0.20	0.20	0.12	0.10	0.08

Burettes

	Designated volume (mL)		
	10 ("micro" type)	**25**	**50**
Subdivisions, mL	0.02	0.10	0.10
Limit of error, mL	0.02	0.03	0.05

5.5 Specifications for Volumetric Glassware

Circular 602 of the National Bureau of Standards, "Testing of Glass Volumetric Apparatus," describes the Federal specifications for volumetric glassware. The National Bureau of Standards (NBS) specifications are listed in Table A.

When the NBS accepts stock quantities of volumetric glassware apparatus from manufacturers or dealers for certification, it is no longer permitted to return this glass apparatus to the manufacturer for future sale to consumers. Consequently, glass manufacturers have stopped listing NBS-certified glassware. Instead, volumetric glassware that meets the Federal Specifications is designated "Class A," and all such glassware is permanently marked with a large "A." This glassware includes the usual burettes, volumetric flasks, and volumetric pipettes.

Class A glassware need not be recalibrated before use. However, if a particular piece of glassware must, for some reason, be calibrated, directions for calibration can be found in texts on quantitative analysis of glassware.

5.6 Cleaning of Glass and Porcelain

The method used to clean glass and porcelain should be adapted both to the substances that are to be removed and to the determination to be performed. Generally, glassware is washed in automatic dishwashers using water and low residue detergents (e.g., Jet Clean from Fisher, CDC from Diversey Canada Ltd.). Afterward, each vessel is rinsed with small, successive amounts of purified water. Substances that are more difficult to remove may require the use of an organic solvent, a dichromate cleaning solution, nitric acid, or aqua regia (25% v/v conc. HNO_3 in conc. HCl). In all cases, it is good practice to rinse a vessel with tap water, or with a suitable organic solvent followed by water, as soon as possible after use. Material that is allowed to dry on glassware is much more difficult to remove.

Volumetric glassware, especially burettes, may be thoroughly cleaned using a burette brush and a mixture of 30 g sodium hydroxide, 4 g sodium hexametaphosphate (trade name: Calgon), and 8 g trisodium phosphate, dissolved in 1 L water. In some cases, a gram or two of sodium lauryl sulphate or another surfactant will improve action.

Dichromate solution (chromic acid) is a powerful cleaning agent; however, owing to its destructive effects on clothing and laboratory furniture, it should only be used when required. Chromic acid solution may be prepared in the laboratory by adding 1 L of concentrated sulphuric acid slowly, while stirring, to 35 mL saturated sodium dichromate solution. To use, allow the dichromate solution to stand for approximately 15 minutes in the vessel that is being cleaned.

(The solution may then be returned to a storage bottle.) EXTREME CARE MUST BE TAKEN WHEN USING DICHROMATE SOLUTION FOR CLEANING. If any of the solution is spilled, it must be cleaned up immediately. When the acid becomes dilute, it is no longer effective as a cleaner. Following the chromic acid wash, the vessels should be rinsed thoroughly with tap water, then with successive, small portions of purified water.

Fuming nitric acid acts more rapidly than chromic acid, but is disagreeable to handle. A mixture of concentrated sulphuric acid and fuming nitric acid is even more efficient but is also hazardous to use.

A persistent greasy layer or spot may be removed with acetone or by allowing a warm solution of sodium hydroxide - about 1 g per 50 mL of water - to stand in the vessel for 10 to 15 minutes. Rinse with water, with dilute hydrochloric acid, and with water again. Alcoholic potassium hydroxide is also effective for removing grease.

A non-corrosive cleaning agent that can be used for normal organic wastes on glass porcelain is Decon 75 Concentrate from BDH (catalogue code 56019). This cleaner was originally developed for removing radioactive materials but works well on all material that is not baked on.

5.7 Cleaning and Handling of Special Purpose Glassware

Absorption cells used in spectrophotometers should be kept scrupulously clean-free of scratches, fingerprints, smudges, and evaporated film residues. For removal of organic residues, the cells may be cleaned with detergent solutions. They should not be soaked for prolonged periods in caustic solutions, as etching may result. Organic solvents may be used to rinse cells in which organic materials have been used. Nitric acid rinses are permissible, but dichromate solutions are not recommended owing to the light-absorbing properties of dichromate on glass.

The preferred practice is to use alcohol or acetone to rinse and dry cells before they are stored. Matched cells should be checked for equivalence by placing portions of the same solution in both cells and by taking several readings of the transmittance (%T) or optical density (OD). If a cell is mismatched, it should be discarded or reserved for rough work.

For certain determinations, especially those involving trace metals, the glassware should, in addition to normal washing, be rinsed with a 1:1 nitric acid and water solution. Follow with thorough rinses using first tap water and then successive portions of purified water. As many as 12 to 15 rinses may be required, especially if chromium is the trace metal being determined. The nitric acid rinse is especially important if lead is the trace metal being determined.

Glassware to be used for phosphate determinations must not be washed with detergents containing phosphates. Further, the glassware must be thoroughly rinsed with tap water and purified water. For ammonia and Kjeldahl nitrogen determinations, the glassware must be rinsed with ammonia-free water.

Glassware to be used in the preparation of microbiological media must be cleaned in a way that eliminates all bacteriostatic and bactericidal material.

Glassware that has been contaminated with radioisotopes can be cleaned using chemicals that are especially formulated for this purpose, such as Contrad-70 (Canlab) or Dekasol (ICN). The resulting solutions of radioisotopes should be discarded according to the guidelines put forward by the Atomic Energy Control Board (AECB) of Canada.

6. REAGENTS AND REAGENT SOLUTIONS USED IN ANALYTICAL METHODS

This section describes the grades of reagent or reagent solutions used in DD laboratories. All reagents or reagent solutions must be high quality and used for a specific analytical method. Water used in analytical methods is considered to be a reagent solution and must be purified to meet specialized requirements.

6.1 Minimum Acceptable Laboratory Procedures with Respect to Reagents

The following are the minimal acceptable procedures for handling laboratory reagents.

a. Reagents must be analytical reagent grade unless otherwise specified.

b. Reagents must be matched against specifications of quality required by the method, by regulation, or by good laboratory practice in certain types of analysis.

c. Upon receipt, all reagents must be properly labelled with the following information: date received, expiry date (if applicable), and date opened. Reagent solutions must be similarly dated when prepared. The initials of the operator should also be added.

d. Each laboratory must have suitable equipment to produce, store, and test all types of water used in that laboratory.

e. All units must have a general supply of ACS Reagent Grade* or College of American Pathologist (CAP) Type III† water. The water must also meet specific large-use requirements (e.g., *USP*). These requirements must be adequately maintained and monitored.

f. Reagent-grade water can be further purified to meet the specialized requirements of each unit. For example:

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* Reagent-grade water that meets standards published by the American Chemical Society. ACS specifications are: specific conductance at 25°C, not more than 2.0×10^{-5} ohm^{-1} cm^{-1} cm-1; silicate (as $Si0_2$), not more than 0.01 ppm.; and heavy metals (as Pb), not more than 0.01 ppm.

† CAP specifications are: specific conductance, 10 μS/cm (microhmos/cm); specific resistance, 0.1 MΩ-cm; and 1.0 silicate (mg/L).

i. use in particulate or foreign matter analysis requires extra filtration.

ii. use in microbiological analysis requires water that is of high microbial quality and that meets suitability tests for the absence of bactericidal and inhibitory compounds.

iii. use in metals analysis requires purity with respect to metals.

g. Each laboratory must designate one person to develop and to carry out a written monitoring and maintenance program that assures the quality of purified water. The program must take into account the type of raw water available, the volume of water used, and the types of tests performed in the laboratory by each unit.

h. A record must be kept of quality checks performed.

6.2 Reagent Quality

Some confusion exists among chemists about the definition of the terms *analytical reagent grade, reagent grade,* and *ACS analytical reagent grade*. A review of the literature and of chemical supply catalogues indicates that the three terms are synonymous. Hereafter, in this document, the term *analytical reagent (AR) grade* will be used. The term "AR" is intended to indicate that the chemicals and solvents conform to the current specifications of the Committee on Analytical Reagents of the American Chemical Society.

Chemical reagents, solvents, and gases are available in a variety of grades of purity, ranging from technical grade to various ultra pure grades. The grade required in analytical chemistry varies with the type of analysis. The parameter being measured and the sensitivity and specificity of the detection system are important factors in determining the grade of the reagents required. For many analyses (e.g., most inorganic analyses) AR grade is satisfactory. Other analyses (e.g., trace organic) frequently require special ultra pure reagents and solvents. For methods in which the grade of reagents is not specified, it is intended that AR grade be used. Reagents of a lesser grade than that specified by the method should not be used. The labels on the container should be checked, verifying that the grade of the reagents meets the needs of the particular method.

It is important to note that problems with reagents often arise after they have been received in the laboratory. As soon as a container is opened, the possibility of contamination is present. Bottles that are not tightly resealed expose their contents to the air, with the possibility

for loss or pickup of moisture, for absorption of carbon dioxide, or for absorption of contaminating vapours, if present. Also, material could be removed with a contaminated spatula, especially by untrained technicians, who often do not understand the extreme care needed to prevent contamination.

6.3 Reagent Solutions

Reagent solutions prepared in the laboratory should be labelled with the date of preparation, the concentration of active ingredients, and an expiration date. Even solutions that are known to be stable should be given with an expiration date beyond which they are not to be used. No reagent solution more than six months old should be used in an analytical laboratory.

One practice that is prevalent in many laboratories, and that should be vigorously discouraged, is pouring unused portions of solutions back into reagent bottles. The rationale for this behaviour is the conservation of costly reagents and of preparation time; however, the offsetting possibility for contamination should be obvious.

Every laboratory should have a reagent preparation notebook, which is kept in a suitable location. When a reagent solution is prepared, the person responsible for the preparation should record in the notebook the date, the ingredient weights and volumes actually used, and his or her signature. This information is of inestimable assistance in tracing possible sources of error in an analysis.

6.4 Reagents for Metals Analyses

It is recommended that reagents and solvents be of spectrophotometric quality, although AR grade is sometimes satisfactory. Analytical reagent grade acids should be distilled in borosilicate glass. Alternatively, special ultra pure acids may be used.

In general, fuel and oxidant gases used for atomic absorption can be of commercial grade. Air supplied by an ordinary laboratory compressor is quite satisfactory, if adequate pressure is maintained and if necessary precautions are taken to filter oil, water, and possible trace metals from the line.

6.5 Reagents for Organic Residue Analyses

The minimum grade of reagents and solvents used in organic analysis is AR grade. Owing to the great sensitivity (to nanogram and subnanogram quantities) of gas chromatography (GC), much greater purity is frequently required.

The specificity of some GC detectors requires that reagents and solvents be free of certain classes of compounds. For example, analyses by electron capture require that reagents and solvents be free of electronegative materials that would interfere with the determination of specific compounds in the sample. Similarly, a flame photometric detector requires that reagents and solvents be free from sulphur and phosphorus interference.

Pesticide-quality solvents are available from several sources. These are often satisfactory for many organic GC determinations. The labels on the container should be checked to verify that the grade of the reagents meets the needs of the particular method.

The quality of gases required in GC determinations varies with the type of detector. In general, compressed gases are a pre-purified dry grade. The use of molecular sieves, carrier-gas filters, and drying tubes are required on combustion gases and are also recommended for use on all other gases.

6.6 Reagents for Drug Analyses

All reagents should be of AR grade unless otherwise specified. Where AR reagents are not available, or if the required grade differs for some reason, compendial specifications for reagents of acceptable quality are provided and should be used. Where no specification exists and a method requires the use of a suitable grade, the intent is that a suitable commercially available grade shall be used.

Unless otherwise directed, the analyst should use the general test methods provided by the compendia (if any) to examine the reagents and to determine their compliance with specifications.

In the Drug Identification Service, the chloroform used for extractions of particularly small amounts of material (e.g., LSD) should be of distilled-in-glass quality.

6.7 Specifications for Purified Water

Purified water must be used in the laboratory for:

a. dilution,

b. preparation of media and reagents, and

c. final rinsing of glassware.

Water purity has been defined in many different ways, but a generally accepted definition states that high-purity water is water that has been distilled and/or deionized to have a specific resistance of 500,000 ohms (2.0 μS (microhmos) conductance) or greater (ACS Specification for reagent grade water). This definition is satisfactory as a base; but, for other requirements, the breakdown by the ASTM (shown in Table B) has been suggested to express degrees of purity. Analysts must assure that the grade meets the requirements of their analysis.

Table B

ASTM Specifications for Reagent Grade Water

	Category			
	Type I	**Type II**	**Type III**	**Type IV**
Total matter, max. mg/L	0.1	0.1	1.0	1.0
Electrical cond. max. μS/cm (microhmos/cm) at 25°C (77°F)	0.6*	1.0	1.0	5.0
Electrical resist. min. MΩ-cm at 25°C (77°F)	16.66	1.0	1.0	0.20
pH at 25°C (77°F)	6.8-7.2	6.6-7.2	6.5-7.5	5.0-8.0
Min. colour retention of potassium permanganate, time in minutes	60	60	10	10
* NOTE: Theoretically pure water has a conductance of 0.055 μS (micromhos)				

- **Type I** grade reagent water is to be prepared by the distillation of feed water having a maximum conductance of 20 μS/cm (microhmos/cm) at 25°C (77°F), followed by polishing with a mixed bed of ion-exchange materials and a 0.22 μm membrane filter. Type I water is to be used where maximum accuracy and precision are indicated.

- **Type II** grade reagent water is to be prepared by distillation, using a still designed to produce a distillate having a conductance of less than 1.01 μS/cm (microhmos/cm) at 25°C (77°F). Type II water should be sterile and pyrogen free as produced and generally may be used whenever freedom from organic or biological contaminants is desirable. If there is a requirement for sterile water, Type II water must be bottled and heated to 120°C for 20 minutes. This procedure is most easily carried out by autoclaving at 130 kPa (15 psi) for the necessary period. Type II water should be pyrogen-free, but must be tested to conform with the requirements of the *USP XVIII*, if proof is required.

- **Type III** grade reagent water is to be prepared by distillation, ion exchange, or reverse osmosis, followed by polishing with a 0.45 μm membrane filter. Type III water is recommended for general laboratory testing.

- **Type IV** grade reagent water is to be prepared by distillation, ion exchange, reverse osmosis, or electrodialysis. Type IV water is to be used in procedures requiring large amounts of water of moderate purity, particularly for preparing synthetic test solutions.

ACS reagent grade water should easily pass other specific specifications such as *USP* for purified water; but each laboratory should check that their supply does, in fact, meet these requirements.

For microbiological analysis, only distilled water or demineralized water that has been tested and found free of traces of dissolved metals and of bactericidal and inhibitory compounds may be used for the preparation of culture media and reagents. Bactericidal compounds should be measured by an appropriate biological test procedure. Residual chlorine or chloramines may be found in distilled water prepared from chlorinated water supplies. The presence of these compounds should always be ruled out or verified by a suitable quantitative procedure such as a starch-iodide titration. If chlorine compounds are found in the distilled water, they should be neutralized by addition of the equivalent amount of sodium thiosulphate or sodium sulphite. The water should then be redistilled, eliminating these compounds from the distilled water used in the preparation of dilution waters.

All laboratories performing particulate or foreign matter analysis must have equipment for filtering water through a membrane filter (0.22 or 0.45 μm).

In summary, ordinary distilled water is quite adequate for many analyses. Certain situations may require the use of double-distilled, or even triple-distilled water. Redistillation from an alkaline permanganate solution can be used to obtain water with a low organic

background. When determining trace organics by solvent extraction and gas chromatography, distilled water with sufficiently low background may be extremely difficult to obtain. In this case, pre-extraction of the water with the solvent used in the respective analysis may be helpful in eliminating undesirable peaks in the blank.

6.8 Water Purification Systems

Water used in an analytical laboratory should be produced in a properly designed metal still that is periodically cleaned to remove solids. The distilled water must be monitored routinely for quality and stored in either glass or polyethylene containers in the laboratory.

	Concentration (μg/L) of Element							
	Zn	**B**	**Fe**	**Mn**	**Al**	**Cu**	**Ni**	**Pb**
All-glass still	1	12	1	1	4	5	1	2
Metal still	9	13	2	1	5	11	2	26

Figure 1: Comparison of Distillates from Glass and Metal Stills

Design of Still

Properly designed metal stills from reputable manufacturers offer a convenient and reliable source of distilled water (ACS reagent grade, Type IV, or better). These stills are usually constructed of copper, brass, and bronze. All surfaces that contact the distillate should be heavily coated with pure tin to prevent metallic contamination. The metal storage tank should be of sturdy construction and should have a tight-fitting cover and a filter in the air vent to remove airborne dust, gases, and fumes. For metal analyses, an all-glass distillation unit may be preferable to a metal still. All-glass distillation units are usually smaller, with a limited capacity compared to metal stills. Distillates from an all-glass still and from a metal still were analysed spectrographically for certain trace metal contaminants and the comparative results are shown in Figure 1.

Cleaning of Still

All stills require periodic cleaning to remove solid deposits. Feedwater that is hard or has a high content of dissolved solids promotes scale formation in the evaporator; the frequency of

cleaning therefore depends on the quality of the feedwater.

The boiler of an all-glass still should be drained daily and refilled with clean water. Scale build-up is easily detected. The boiler and condenser coils should be cleaned at frequent intervals.

Metal stills usually incorporate a constant bleeder device that, to some extent, retards scale formation. Nevertheless, these units should still be dismantled and cleaned at regular intervals. Cleaning should always follow the manufacturer's instructions. Pre-treatment of the incoming feedwater often improves the performance of the still and raises the quality of the distillate. If trace concentrations of ions are a major concern, the distillate may be passed through a mixed-bed ion exchanger.

Measuring Water Quality

Specific conductance is a rapid and simple measurement for determining the inorganic quality of distilled water. Frequent checks should be made to determine that optimum performance is being maintained. A purity meter installed between the still and the storage reservoir will monitor the conductance of the distillate, in terms of the mg/L of sodium chloride. If the reading on the meter begins to rise above the pre-set limit of conductance, effective action should be taken to eliminate the source of contamination.

Organic quality is more difficult to monitor, but the total organic carbon determination is a simple and rapid test for organic contaminants.

A piping system for delivering distilled water to the area of use within the laboratory is a convenient and desirable feature. If a piping system is used, special care should be taken that the quality of the water is not degraded between the still and the point of use. Piping may be fabricated of thin, tin-lined brass, stainless steel, plastic, or chemically resistant glass, depending on the quality of the water desired and on available funds. Tin is best but very expensive. As a compromise, plastic pipe, or glass pipe with teflon O-rings at all connecting joints is satisfactory for most purposes. Glass pipe has an obvious advantage when freedom from trace amounts of organic materials is important.

Storage of Distilled Water

Where there is no piped-in supply, distilled water will probably be transported to the laboratory and stored in large polyethylene or glass bottles. If stored in glass, distilled water will gradually leach the more soluble materials from the glass, causing an increase in dissolved solids. Therefore, only borosilicate-free glass containers should be used. Polyethylene bottles contain organic plasticizers, and traces of these materials may leach from the container walls. Plasticizers

are of little consequence, except in some organic analyses. The rubber stoppers often used in storage containers contain leachable materials, including significant quantities of zinc. This is usually no problem, as the water is not in direct contact with the stopper. However, the analyst should be aware of the potential for contamination, especially when the supply is not replenished owing to infrequent use.

The delivery tube may consist of a piece of glass tubing that extends almost to the bottom of the bottle and is bent downward above the bottle neck with a three to four foot piece of flexible tubing. Teflon is preferable to latex rubber for the latter, because it is less leachable. However, a short piece of latex tubing may be required at the outlet for better control of the pinchcock. The vent tube in the stopper should be protected against the entry of dust.

7. MEDIA PREPARATION FOR ANALYTICAL METHODS

Detailed procedures must be in place in a DD laboratory to handle, to store, and to assure the quality of any media that are either commercially prepared or prepared on site.

7.1 Minimum Acceptable Procedures

The minimum acceptable procedures for media preparation are:

a. Each microbiology laboratory must have purchasing standards for commercially prepared media and instructions for the media's storage.

b. Standard procedures must exist for the preparation, handling, and storage of each medium.

c. A program must be established to determine sterility and growth-promoting qualities of prepared media.

d. A program must exist for the decontamination and disposal of media.

7.2 Quality Assurance

While the quality of the media required for large and small laboratories is essentially the same, the practical methods of achieving quality assurance may differ.

In a small laboratory, media and equipment preparation is usually performed by the analysts, in the course of the analysis. It is therefore possible to quality assure media by including an adequate number of positive and negative controls while using the media for analytical purposes. If quality failure or non-sterility is detected in the controls, the analytical work must be repeated after the faulty medium has been replaced. Because only one determination must be repeated, and because the time delay and amount of work involved is generally going to be small, this may be the best approach to media quality assurance in the small laboratory.

In a large microbiology laboratory, the approach described above may not be economical. Many technicians could perform many analyses before quality failures become apparent. Therefore, in a large microbiology laboratory, where media and equipment are processed by special sections, it is essential that prepared media be pre-tested for sterility, pH, appearance, ability to promote growth, and so on, before they are used for analytical work.

In most laboratories, a combination of these two approaches will usually be in use.

Before release, the sterility of prepared media must be determined according to the following criteria:

a. An adequate number of sterility controls must be included during analytical tests (see individual standard operation procedures (SOPs) where applicable). Tests may have to be repeated if controls are found to be non-sterile.

b. All units of a sterilized batch of medium should be incubated before use and examined for visible evidence of growth. This method can cause some problems with liquid media, especially diluents, as at least 106 microorganisms/mL are required to produce visible sediment or cloudiness. Blood agar must be tested in this manner. Media produced by boiling or dispensed aseptically may also be tested in this manner.

c. Media processed with biological indicators generally may be released as soon as all biological indicators have been incubated and are shown to be sterile. (See the appropriate SOP.)

d. Media without biological indicators should be tested for sterility as described in the appropriate SOP.

7.3 Handling

When media are received from a manufacturer, records should be kept of the batch code, expiry date, date of receipt, and quantity. If any medium purchased from a manufacturer is found to be defective, it should be quarantined immediately. Furthermore, steps should be taken to inform the manufacturer and have the media replaced.

If media are produced by a central supply unit within the laboratory, then standard media request forms should be used. These forms should indicate:

a. type of media required,

b. size and type of container,

c. volume per unit after sterilization, and

d. number of containers of media required.

Individual media bottles must be clearly identified as having been sterilized by heat and pressure. Chemical indicators can be used in the individual bottles for the purpose of identifying them as sterilized.

7.4 Storage of Media

During storage, precautions should be taken against contamination of the media by closure leakage, air pump effect, or vapour pump action.

8. REFERENCE STANDARDS FOR ANALYTICAL TESTING

A reference standard may be regarded as a model of the essential properties that assure a level of excellence:

- **Standard of identity**. Qualitative criteria ensuring that the proper substance is present.
- **Standard of purity**. Expressed numerically as maximum tolerances for designated impurities, or as the absence of an impurity.
- **Standard of potency**. Expressed quantitatively as the required concentration of a substance.

8.1 Specifications

A reference standard must be used in all determinations that require a comparison to a chemical substance.

Whenever a reference standard is specified in an analytical method or by the pharmacopoeial standards, then the specified standard must be used. (USP and NF reference standards must be those appearing on the current list of lot numbers.)

If the limits set in any individual test are based upon the behaviour of the appropriate reference standard, then only that reference standard can be relied upon implicitly for regulatory purposes. Any other reference substance may give rise to indeterminate errors and would negate the analysis for legal purposes, unless that substance has been shown to react exactly as the reference standard when used under the conditions of the test procedure.

8.2 Storage, Handling, and Labelling

The manufacturer's procedures for storage, handling, and labelling are designed to ensure the integrity of reference standards and, when specified on the label, must be followed. When such procedures are not specified, formal written procedures for storage, handling, and labelling must be developed by each laboratory.

All reference standards should be stored under lock and key. Reference standards should be arranged so that only one bottle or vial is used at a time. Each container's label should bear the proper chemical name, the pharmacopeial standard (if applicable), and the lot number. Reference standards requiring special storage conditions should have those conditions prominently marked on the label.

Each reference standard or group of reference standards should be under the direct control of a designated staff member. The responsibilities of this staff member should include replacement of standards as they are consumed, disposal of expired or outdated reference standards, reporting of defective standards to the appropriate authority or designate, and provision of adequate storage conditions and security control for each reference standard.

A signature should be required when a reference standard is removed from central custody. The standard should be maintained in good condition at all times and should be returned to custody as soon as it is no longer required. Even the empty bottle or vial should be returned so that a new quantity may be ordered, if required.

8.3 Records

The records kept for each reference standard should include:

a. identity,

b. activity and purity (if applicable),

c. date received,

d. lot number,

e. original source (e.g., manufacturer's name, HPB research laboratories),

f. storage and handling procedures, and

g. procedure for assuring quality, with test results or certification.

8.4 Quality

Reference standards not meeting quality criteria set for that standard must be removed from use, and the situation must be reported to the appropriate authority.

8.5 Shipping

Where necessary, reference standards must be shipped according to the legal requirements for the shipment of official samples so that the continuity, identity, and integrity of the reference standard cannot be questioned.

8.6 Standard Solutions

Volumetric titrated solutions (e.g., 0.103 N NaOH) and stock and working reference standard solutions (e.g., diluted reference standards, stock cultures) should be prepared by a qualified person.

The following information should be inscribed on the label of the flask or bottle:

a. the identity of the ingredients,

b. the concentration to the correct number of significant figures,

c. the expiry date (if appropriate),

d. the name or initials of the person preparing the solution, and

e. the preparation date.

Unused portions of a reference standard solution should be kept in closed containers under the conditions necessary to maintain its stability. All the weighings and the processes used in making a reference standard solution should be recorded in a laboratory book so that the authenticity of the solution can be verified.

Generally, any reference standard solution that has not been recently standardized should be restandardized, especially if it is to be used in the analysis of a violative sample. The length of time between standardizations is judged by experience and depends on the situation.

Reference standard solutions should be standardized against a primary reference standard, not against each other. Nevertheless, it is a good practice to analyse a new reference standard solution together with the previous one to see if there is any deviation.

8.7 Acquisition and Source

The chief sources of drug reference standards are pharmacopeial organizations. Pharmacopeial reference standards are certified for suitability.

Other reference substances are not certified, nor are they usually accompanied by a certificate of analysis. Even when they are accompanied by a certificate, the certificate data normally are not guaranteed. When a reference substance is not certified and no tests are specified by the manufacturer, each laboratory must develop and perform tests on the substance in order to assure that it is suitable for the tests and assays for which it is intended.

8.8 Verification of Reference Standards

The purity profile required for a reference standard depends upon that standard's use as well as on the precision of the method of test analysis. A higher purity profile is required for quantitative purposes than for identification purposes. Purity of at least compendial grade is desirable for determining the potency of the active ingredient in a drug formulation. To evaluate a purity profile, the analyst must rely on results obtained by applying several techniques appropriate to the situation (e.g., *USP* standard requirements for raw materials).

8.9 Antibiotic Reference Standards

In microbiology, the antibiotic reference standards used are *USP*, *BP*, or equivalent. A record must be kept of the relevant information concerning reference standards (see Section 8.3, "Records"). Where appropriate, antibiotic reference standards should include the following additional information:

a. date of issue and expiry,

b. narrative information concerning certification and recertification history, and the compendial test for which the antibiotic may be used,

c. references for methods that must be used to recertify, and

d. other relevant information.

8.10 Microbiological Reference Strains

Specific reference strains are required for the performance of compendial antibiotic dosage tests. Currently, each laboratory that needs such strains orders them from England (NCTC strains) or the United States (ATCC strains). Reference strains are also required for quality control (e.g., negative and positive controls).

A record must be kept of the relevant information concerning reference standards (see Section 8.3, "Records"). The following additional information should be considered for inclusion in records concerning microbiological reference strains:

a. reference number.

b. storage condition and expected duration of vitality.

c. method, medium, and temperature recommended for reconstitution.

d. narrative information regarding specific compendial tests for which the strain is suitable, and other relevant information - such as hazards that the strain might cause, the need to inoculate analysts, and so on.

e. certificate of purity and identity. This certificate should give, relevant to the last purification of the strain, date, method, and analyst's name. In addition, the records should list the most important biochemical and serological characteristics of the strain, as well as the date when these characteristics were last confirmed and the identification of the person that confirmed them.

If contaminated reference strains are received, notify the culture supplier in writing and use the following statement: "The culture (identification) sent to (laboratory) was contaminated AS RECEIVED. The following method was used to purify the culture (detail) . . ."

9. HANDLING AND RECEIVING SAMPLES

The stability of samples under storage conditions, test conditions, and in transit should be established.

It is of prime importance to use written procedures for sampling and to collect these procedures in a sampling/methods manual. The manual should be kept in the laboratory, where it will be available to all personnel involved in obtaining samples. Only current sampling methods should appear in the manual. A historical file of current and obsolete methods may be kept in the Quality Assurance Director's files or in archives.

It is the laboratory supervisor's responsibility to ensure that personnel involved in obtaining samples are thoroughly instructed in the techniques to be used and are aware of the need for a sampling/methods manual. If sampling takes place at a remote location, a copy of the manual may be kept in the vehicle used to transport personnel and equipment to that location.

9.1 Receipt and Recording of Samples

Samples for laboratory analysis should arrive in good condition, be recorded in a samples log, and be labelled before they are processed. Storage and disposal of samples are also discussed in this section.

Labelling of Samples

As soon as the sample is taken or received, a label should be prepared and attached to the sample container.

Various techniques for labelling are used, depending on the circumstances under which the sample is taken. For example, the sample containers may be numbered, and a logsheet showing the sample numbers may be completed with the information pertinent to each sample as it is taken. In other cases, the label may be attached to the container prior to sampling, and the information entered at the time the sample is taken. The important principle is that the information be entered when the sample is taken, and not before or after. If a sample container consists of two or more parts (e.g., container and lid), all parts should be clearly identified to prevent cross contamination.

The minimum information required on a sample label should be the laboratory's designated code (see "Recording," below).

Receipt

Immediately upon receipt of a sample, the analyst should verify the sample's condition and should check the sample and its accompanying requisition for testing.

Recording

Samples received for laboratory analysis should immediately be recorded in a sample log book.

Samples should be logged into the laboratory system on the day they are received.

Each sample should be given an unambiguous laboratory code (e.g., BDR/ PCD-0001), even if it has already been assigned a sample number by the sampler or the client.

The sample log should contain the following information:

a. date of receipt;

b. laboratory code for the sample;

c. source;

d. sample description (e.g., name, client's number); and

e. other information essential to the project or activity (e.g., sampler's name, nature of the matrix, analyses requested and methods to be used, sample storage location, special storage conditions).

All correspondence associated with the sample should be filed according to the established procedure.

If a computerized log-in system is used, then a data backup on an auxiliary disk must be kept, and a hardcopy printout should be made at least once each working day.

9.2 Processing Samples

Each type of sample should have its own written sampling procedure. Written sampling procedures are particularly important for biological samples, radioactive samples, and samples of controlled or illegal substances.

The sampling procedure must preclude contamination, deterioration, or mix-ups, and must conform to current safety practices.

9.3 Handling Samples

In sections where the accountability of samples is important (e.g., illicit drugs, expensive materials), procedures should be designed to ensure that:

a. samples are distributed in a manner that precludes the possibility of contamination, deterioration, or damage;

b. samples are identified throughout the distribution process;

c. the receipt, distribution, and reconciliation of each sample is recorded;

d. the date and quantity of each sample is recorded; and

e. the name of the employee distributing, receiving, or returning each sample is recorded.

Identification of the samples must be maintained throughout the entire handling process.

9.4 Storing Samples

Samples in storage must also be labelled with the laboratory's designated code.

A log book of stored samples should also be maintained. The log book should include:

a. the code,

b. the expiry date,

c. the actual date of storage or disposal, and

d. the initials or names of the persons responsible for the sample and for its storage or disposal.

Storage conditions should be identified, including safety instructions, stability of sample, and other relevant information.

Storage containers should be designed with the following requirements in mind:

a. adequate size;

b. safety;

c. stability of sample; and

d. security.

9.5 Characterizing Certain Samples

It should be established whether the samples have to be characterized. In some cases, the purpose of receiving the samples is to characterize them: thus characterization is part of the analysis.

Samples that are to serve as reference compounds, or that are to be tested by new methods, should be characterized both immediately upon receipt and prior to undertaking the study in which they will be used.

9.6 Disposing of Samples

Disposal of samples should be carried out with caution. All safety procedures and security recommendations specific to the sample being disposed of should be followed.

Special care should be taken with any sample that has an expiry date. Expired samples should be disposed of.

The general recommendations described above apply to all samples being disposed of, including:

a. powders, solids, and liquids;

b. solutions (halogenated wastes, non-halogenated wastes);

c. biological hazards;

d. radioactive wastes; and

e. hazardous wastes (carcinogens, mutagens, etc.).

10. INSPECTION AND REPORTING OF QA DEFICIENCIES

A quality assurance (QA) inspection program is intended to ascertain that studies are being properly conducted and to assure that test results are of adequate quality. This guide recommends that QA laboratory inspections and study audits be conducted as a part of an overall GLP compliance program. The inspections and audits should result in reports that describe the degree of adherence to GLP.

A period of a month or two should be allowed to put a new QA program into effect. The QA Director should be available during this time for consultation and discussion about any problems that may arise.

After sufficient time has elapsed, the QA Director should conduct a full audit of the laboratories to assess compliance with the standard operating procedures (SOPs). A full report should be prepared, reporting to management the degree of compliance and problems that were uncovered, if any.

With a QA program in place, the QA Director can confine his or her attention to monitoring the system and collecting data that can be used to respond to problems involving the quality of the laboratory's test results.

10.1 QA Audits

To ensure compliance, the QA Director should periodically audit the inspection program. Two audit methods are:

a. In conjunction with the Laboratory Supervisor, conduct a comprehensive audit that includes a checklist covering all applicable SOPs.

b. On a random basis, audit each laboratory on one aspect of the QA program, preferably discussing with lab personnel the extent to which they are complying with the aspect under audit.

Ideally, both methods should be used. The full audit can be undertaken on an annual basis, or more frequently during the first six months. The random audit can be conducted more often, as time permits.

No. ____

Bureau _____

Division _____

Section _____

Location _____

Part I (to be filled out by QA Director)

Date _____

Nature of QA irregularity _____

_____

_____

Signed _____

Part II (to be filled out by Laboratory Supervisor)

Steps taken to investigate irregularity _____

_____

Explanation of probable cause of irregularity _____

_____

Steps taken to prevent future occurrence _____

_____

Name of analyst who performed work _____

Signed _____

Name _____

Date _____

Figure 2: Quality Assurance Irregularity Report

The inspection is to determine the extent to which the laboratories are in compliance with standards. The audit of selected studies is to determine whether:

a. the testing was performed according to the specified methodology;

b. reported irregularities (if any) may have affected the reliability of the test results; and

c. the test reports fully and accurately reflect the test procedures and results.

10.2 Monitoring QA Data

The QA Director should become the collector and the focus of all data generated in support of the QA program. This data should include the results of all audits, all correspondence related to quality assurance and accreditation, authorization of new methods, and so on. The QA Director should also keep comprehensive files of all information related to quality assurance.

10.3 Reporting QA Problems

Because the QA Director receives authority from, and is responsible to, management, it is the Director's duty to report to a superior any problems or irregularities detected in the QA system, especially as the ultimate responsibility for the quality of test results rests with management. A mechanism should be established for reporting quality assurance irregularities to management. One method might be to use the form illustrated in Figure 2. The term "irregularity" is used in place of "deficiency" because many reported incidents may be of a minor nature not requiring immediate attention from management.

The top half of the form is completed by the QA Director, who describes the irregularity as he or she perceives it. Photocopies or other evidence may be attached to support the case. The form is then given to the Laboratory Supervisor. Completing the second half of the form, the Laboratory Supervisor must investigate the problem, determine a probable cause, and describe the efforts made to eliminate the problem. The form is then returned to the QA Director, who circulates it to management. Managers initial the form, indicating that they have received and read it. The QA Director then files the form and follows up to see that the problem has been corrected.

The mechanism described above forces the Laboratory Supervisor to take action, ensures that management has been informed, and documents both facts.

A statement of compliance, Figure 3, is issued when the lab is found to be operating in compliance with the principles of GLP.

A general inspection for compliance with the principles of Good Laboratory Practice was carried out at:

Bureau _____

Division _____

Section _____

Location _____

on

Date (s) _____

as part of the GLP compliance program.

The laboratory was found to be operating in compliance with the principles of Good Laboratory Practice.

Date _____

Signed _____

Name _____

Appointment _____

Figure 3: Good Laboratory Practice Statement of Compliance

10.4 Training of QA Auditors

HPB staff, inspectors, or investigators that carry out QA inspections and that audit selected laboratory studies must have relevant education and experience in the appropriate field, as well as training in laboratory inspections.

10.5 Scheduling and Frequency of Inspections

The scheduling and frequency of QA inspections should be based on one of the following criteria:

a. Random inspections once each year for any particular laboratory, and more frequently during the first six months.

b. Requests from appropriate departments or agencies to carry out a GLP inspection of a particular laboratory or an audit of a particular study. A comprehensive inspection could be combined with an audit of a particular study. Although the QA Director would be available for consultation, the inspection should be performed by a representative of the external department or agency to prevent the mixing of external and internal audit functions.

c. Follow-up to a comprehensive inspection whose findings showed significant deviations from GLP or significant/major discrepancies between the QA report and original test results data or the actual records of a laboratory study.

10.6 Inspection Standard

The standard to be used is the Canadian standard for GLP in non-clinical laboratory studies. Official policies and interpretations by the HPB on this subject are working documents that are also applicable to conducting QA inspections and audits. When evaluating laboratories, the Canadian standard supersedes other standards or regulations but does not negate the requirement to adhere to the other standards or regulations.

10.7 Preparation for Inspection/Audit

Prior to an inspection, existing information about the laboratories should be reviewed. Such information would include previous inspection reports, the layout of the laboratory, study reports and protocols, and, in particular, irregularities from previous inspections (if any). The

final report and the protocol of the study selected for audit should also be reviewed beforehand. To ensure that the required personnel will be in attendance and that relevant records are available, the laboratory to be inspected should be notified in advance of the scheduled visit.

10.8 Inspection Procedure

The inspector should request to see relevant documents or other information required to complete the inspection - for example, study plans, standard operating procedures, or study reports. The powers granted to the GLP Auditors should be defined.

The inspection should cover the following specific items:

a. facilities,

b. apparatus, material, and reagents,

c. test systems,

d. test and reference substances,

e. standard operating procedures,

f. performance of the study,

g. reporting of study results, and

h. storing and retaining of records and material.

Facilities

Purpose: Determine whether the facilities are of adequate size and design to allow studies to be conducted in accordance with the principles of GLP.

Tasks: Check

a. that the size and design of the laboratory is appropriate to the types of studies conducted therein.

b. for environmental control and monitoring procedures in important areas, such as animal rooms, areas for storing test substances, and laboratory areas.

c. the current cleanliness of the facilities.

d. that separation is maintained in rooms or areas where functions requiring separation are performed.

e. the effectiveness of pest control procedures.

Apparatus, Material, and Reagents

Purpose: Determine whether the laboratory has suitably located apparatus in sufficient quantity and of capacity adequate to meet the requirements of the tests conducted. Check that materials and reagents are properly labelled, used, and stored.

Tasks: Check

a. the general condition and cleanliness of apparatus.

b. documentation concerning apparatus operation, maintenance, standardization, and calibration.

c. that materials and reagents are properly labelled, used, and stored.

Test Systems

Purpose: Determine whether test systems (animal, plant, microbial, cellular, subcellular, chemical, physical) are adequately accommodated and controlled.

Tasks: Check,

a. for physical/chemical test systems

    i. that such systems are in accordance with biological test systems.

    ii. that reference substances are used.

b. for biological test systems,

    i. that the test system exists as specified in the study plan.

    ii. that procedures are in place for receiving, handling, housing, and examining the test systems.

iii. that adequate provision has been made for evaluating the health of animal and plant test systems and for isolating them, if necessary.

iv. that written records are kept of examination, quarantine, morbidity, mortality, and diagnosis and treatment of animal and plant test systems.

v. that the test systems are adequately identified (i.e., animals properly tagged).

vi. that the environment exists as specified in the study plan or SOPs (i.e., housing, temperature, humidity, and light/dark cycles).

vii. that provisions for the appropriate disposal of the test system have been made.

Test and Reference Substances

Purpose: Determine whether the procedures designed to ensure that the identity and quantity of test and reference substances used in test systems accord with the study plan.

Tasks: Check

a. that procedures exist for receiving, handling, sampling, and storing test and reference substances.

b. that, where applicable, procedures exist for determining the identity, purity, homogeneity, and stability of test and reference substances and for preventing their contamination.

c. that, where applicable, procedures exist for determining the homogeneity and stability of mixtures containing test or reference substances.

d. that test and reference substances are property labelled, and that, where applicable, records are kept of their composition, characterization, concentration, homogeneity, and stability.

e. that mixtures containing test or reference substances are properly labelled, and that, where applicable, records are kept of their homogeneity and stability.

f. that samples from each batch of test substance have been taken for analytical purposes and that their integrity (chemical stability, purity) has been maintained throughout the study.

Standard Operating Procedures

Purpose: Determine whether the laboratory has written SOPs that are related to the tests being conducted.

Tasks: Check

a. that each laboratory unit has immediately available the relevant written sops.

b. SOPs are available for, but not necessarily limited to, the following activities:

i. receiving, identifying, labelling, handling, sampling, and storing test and reference substances.

ii. maintaining, cleaning, and calibrating measuring apparatus and environmental control equipment.

iii. preparing reagents.

iv. recordkeeping, reporting, and record storage and retrieval.

v. preparation and environmental control of areas containing test systems.

vi. receipt, transfer, location, characterization, identification, and care of test systems.

vii. handling of test systems before, during, and at the end of a study.

viii. handling and disposal of test systems.

ix. use of pest control and cleaning agents.

x. the operation of the Quality Assurance Program.

c. that changes to SOPs are authorized and dated.

Performance of the Study

Purpose: Determine whether study plans and amendments to them are generated and approved in accordance with the principles of GLP.

Tasks: Check

a. that written study plans exist and that amendments (if any) are approved.

b. that raw data is recorded, signed, and dated.

c. that changes in the raw data (if any) are made in accordance with the principles of GLP.

d. that the measurements, observations, and examinations accord with the study plan and the SOPs.

e. that audits have been carried out to ensure that the results presented in the final report of the study correctly reflect the raw data.

f. that unforeseen events are recorded in the data and mentioned in the final report.

Reporting of Study Results

Purpose: Determine if a final report has been prepared in accordance with the principles of GLP.

Tasks: Check

a. that, when a final report is available, it is signed and dated by responsible personnel.

b. that amendments are made by the responsible personnel.

c. that the final report contains the required information.

d. that a quality assurance statement is included in the final report, and that it is signed and dated by the responsible personnel.

e. that the final report lists the location of all samples, specimens, and raw data.

Storing and Retaining Records and Material

Purpose: Determine whether provision is made for storing and retaining records and materials.

Tasks: Check

a. that archives exist for the storage of study plans, raw data, final reports, samples, and specimens.

b. that a procedure exists for retrieving archived materials.

c. that a procedure exists to limit access to authorized personnel.

d. that records and test materials are retained for the required period of time.

10.9 Completion of an Inspection Visit

An inspection visit ends with a consultation between the inspector and lab representatives to discuss the inspection findings.

10.10 Inspection Report

The results of the QA inspection visit are to be documented in a written report that covers all aspects of the inspector's investigations. The final QA inspection report has two parts (Figures 2 and 3, and the checklist described in Section 10.8, above) and includes changes (if any) agreed to at the meeting after the QA inspection. A copy of the findings and conclusions of the QA inspection is sent to the laboratory for review and comment.

10.11 Appeal Mechanism

After receipt of the final report, a laboratory may request to dispute or appeal part or all of the report. This request is granted if it is received within 15 working days of the final report. The QA Director may be requested to authorize additional time. The request to dispute or appeal must be made in writing, and disputed points must be specifically noted in the letter. If the appeal cannot be resolved by letter, appropriate arrangements for a meeting are to be made.

11. CURRICULA VITAE AND PERSONNEL TRAINING RECORDS

This chapter defines the procedures to be followed with regard to keeping personnel training records and *curricula vitae* (c.v.) for all laboratory staff.

11.1 Curriculum Vitae

A résumé (*curriculum vitae*) must contain the following information:

a. name,

b. work status/position,

c. education/qualifications,

d. subjects taken to achieve highest qualification (e.g., subject of thesis or degree; subjects passed in last year at school),

e. subjects studied since highest qualification attained (e.g., computer courses) and certifications,

f. GLP training,

g. work experience (e.g., place, work performed), and

h. list of publications and presentations.

The date that the c.v. was prepared (year/month/day) must be shown at the top right-hand corner of the document.

Each *curriculum vitae* or résumé is to be updated as necessary, or annually. The revised copy to be submitted to the Division Chief for inclusion in the DD employee files. The employee is responsible for ensuring that his or her c.v. is appropriately updated.

11.2 Personnel Training Records

If an employee attends training courses or seminars applicable to his or her work, such attendance should be recorded in memoranda to the Division Chief for inclusion in the employee's personnel file.

12. COMPUTERS AND ELECTRONIC DATA

Computers can be divided into four categories according to their size and computing power: super computers, mainframes, minicomputers, and microcomputers. Generally, only computers in the last two categories are found in laboratories. Minicomputers usually serve as central departmental computers, while microcomputers are found either as stand-alone workstations or attached to minicomputers through various communication lines (e.g., Ethernet, RS-232C). Microcomputers can also be attached to various laboratory instruments, where they are dedicated to instrument control, data collection, and data reduction.

The physical component of a computer system is called the "hardware." Computer hardware should be selected based on the tasks that the system will be expected to perform (the "application") and the availability of appropriate programs ("software"). The software that allows the computer to perform application processing and to manage the various storage, display, printing, and plotting devices is called an "operating system." Operating systems range in complexity, from single-user, single-task environments (e.g., DOS), to multi-user, multi-tasking environments, (e.g., UNIX).

Software for application processing is often available "off the shelf." Sometimes, however, no application software currently on the market responds to a laboratory's particular needs; in this case, a customized application program might be created. Both off-the-shelf and custom-developed software must be accompanied by documentation explaining exactly how to operate the program. The life cycle of an electronic data processing (EDP) system and current concepts of quality assurance are detailed in *Computerized Data Systems for Nonclinical Safety Assessment*, published in September 1988, by the Drug Information Association, P.O. Box 3190, Maple Glen, PA 19002, USA.

Computerized data must be given special attention in the matter of backups, security, and data archives.

12.1 Computer Backups

Regular backups are highly recommended as a means of avoiding the loss of valuable (sometimes unique) data. Backups are usually made using a long-term magnetic storage medium, such as diskette, tape, or an alternate hard disk (either removable or fixed).

Backups should be performed routinely each day or after new information has been entered into the computer. A backup can include all the information currently stored in the computer, or it can be "incremental," backing up only data that has been added or modified since

the last backup. A historical series of backups should be retained, so that, if the data becomes corrupted and the errors are not immediately noticed, a new backup of the corrupted data does not displace an older backup containing good data.

At least one copy of the most recent backup should be stored in a remote location, to be available in case of fire or other physical damage to the regular installation. The label attached to the backup must clearly state the software used for the backup, all necessary retrieval parameters, and the date and time of the backup.

Ideally, computer backups should be performed daily. Each day's backup should be kept for one week. At the end of the week, a full daily backup should be performed and kept as the weekly backup. The weekly backups should be kept for a month. The last full daily backup of the month is retained as a monthly backup. Monthly backups should be kept for one year. A copy of each monthly backup should also be archived.

12.2 Security of Computers

The proliferation of microcomputers throughout the DD has caused computer security to become a major concern to all. Computer security involves the overall protection of hardware, software, and computer data from unauthorized or accidental modification, or disclosure.

a. Original diskettes should be stored in a secure location, other than at the workstation. Duplicates should be used for day-to-day operation.

b. Software diskettes should not be stored in the associated manuals.

c. Important files are not to be stored on hard disks. They are to be backed up or stored on "properly identified" diskettes and secured.

d. Diskettes should be secured during silent hours and whenever an individual is absent from his or her workstation for a lengthy period of time.

e. Power bars or surge protectors should be used to protect computers against static electricity, electrical surges or spikes, and "line noise."

f. Personal software is not to be used except for evaluation and demonstration. Required software should be purchased to minimize problems with computer viruses.

Microcomputer security problems arise from the user's ability to copy, store, and process information in an unsecured environment. For a laboratory working under regulatory requirements, security mechanisms must be in place to protect the information collected and manipulated by any computer system, including microcomputers. If a microcomputer is used to collect and manipulate information within a distributed system in which the microcomputer data is eventually uploaded to a larger central computer system, then security is normally built into the larger, multi-user operating system of the central system.

12.3 Archiving Electronic Data

An archive is intended to provide a secure area for long-term storage (with the capability for retrieval) of original computer data. While backups are used to recover information lost due to system failure or disaster, computer data archives serve to insure that information can be traced to verify its integrity. The GLP requirements for computer data collection and storage are no different from those for manually recorded information. In other words, the information must be able to be reviewed for accuracy, validity, and integrity. An electronic data archive should have a proper environment and procedures for controlled access. The physical security of the electronic data archive should be assured by an authorized archivist.

All material entered into the archive must be identified by project number or file name, and an attached index must state the contents of that material. The archivist is to check the material against the index for accessibility, accuracy, and completeness.

13. ARCHIVING INFORMATION

The object of an archive is to preserve information; therefore, it is of the utmost importance that all precautions be taken to ensure the integrity of the material being archived. In the context of scientific research, archived material may present a wide range of physical characteristics, from paper records of chromatograms, to magnetic tape containing electronic data, to tissue. Significant financial outlay may initially be required if suitable storage is to be provided.

13.1 Physical Facilities

It is recommended that the archive be kept in one or more well-ventilated rooms, without appreciable variations in temperature, humidity, and luminosity. Prolonged contact with ultraviolet radiation accelerates the deterioration of paper products. If large quantities of paper are to be archived, the archive rooms should be devoid of large windows situated on exterior walls.

An archive room should be equipped with shelves for storing material, a desk for the sole use of the archivist, and a desk for use of the staff admitted into the archive for consultation. Self-locking doors (with adequate provision for safety) should be installed, and the doors should be kept closed (and locked) regardless of whether staff members are working in the archive.

In the Branch, certain staff, facilities, and procedures are available to provide assistance on the best ways to store material in an archive room.

Within each Bureau, a common area for archives is thought to be advantageous. However, to expedite retrieval, each division should be given its own section within the common archive.

13.2 Personnel

To ensure efficient management of the archives, an archivist should be appointed. The responsibilities of the archivist include management of the physical facilities as well as control over the material placed in the archive. Owing to the sensitive nature of certain archived materials, the appointee will require a security clearance.

13.3 Standardization of Archived Material

To maximize the usefulness of the archives and to ensure that material can be easily retrieved, standards for archived material must be set. Standards should address: the format of the original material, the storage media, the storage containers, the storage environment, and the computer hardware/software that stores and retrieves the material.

Format of Original Material (Text, Computer Data, Tissues) for Archiving

Standard forms should be used for stored information concerning SOPs, protocols, documents, tissue indexes, and some types of data. An index would greatly simplify storage and assist in subsequent archiving of the material. Computerized material that is being archived should be prepared for use by a standardized word processing package. There are instances where computerized data with a set format may be incorporated into existing data base files, complete with established fields and labels. The data base can be indexed for subsequent retrieval of information.

Types of Media to Be Archived

Standard media are:

- **Original paper**. Includes signed documents and raw data (if collected on paper). A standard filing system (preferably computer-based) will be needed, together with an index.

- **Microfilm**. An alternative for paper documentation, including signed documents and raw data. Microfilming reduces space requirements and makes access and retrieval simpler for most purposes. Microfilm storage should be compatible with HPB library equipment and, perhaps, indexing systems.

- **Magnetic storage**. Includes computerized data and text. Using standard floppy disks makes the information more transportable. This type of storage permits the material to be searched electronically and to be calculated or plotted from new perspectives.

Storage Containers for Archiving

Papers should be stored in appropriately sized boxes. The proper containers should be obtained for tissue storage.

Storage Environment of Archived Material

The environment for the storage of each material should be specified (e.g., for materials requiring refrigeration, for magnetic media).

Software/Hardware That Stores/Retrieves the Archived Material

Indexing systems for archived text, data, and tissues should be designed to run on standard computer hardware (preferably the IBM PC and compatibles), using an appropriate standard data base package. Text should be converted to an HPB standard word processor format. Where possible, computerized data should be converted to an HPB standard data base format.

13.4 Indexing and Retrieving Archived Material

A separate data base file must be used to index all studies stored in the archive. This file should contain only that information necessary to permit computerized searches of salient features and to indicate where and how the study materials are stored. When study materials are archived, project personnel should be requested to complete a form that asks for information such as:

a. animal species,

b. substances studied,

c. exposure concentrations and durations,

d. tests used,

e. parameters measured,

f. organs studied,

g. important dates,

h. names of personnel,

i. location of study,

j. location of raw data, tissues, protocol, SOPs, reports, and documents,

k. major findings,

l. basic GLP information,

m. data base file names,

n. text file names, and

o. security information.

The archivist enters the information provided on this form into the data base.

The archivist provides information to the staff on how to retrieve data using the index system. Any duly authorized person is to have retrieval access to the archive.

For security reasons, visitors to the archive must be accompanied by the archivist or by a deputy archivist appointed for the duration of the visit. (An exception to this procedure may be made in the case of *bona fide* visitors conducting approved research.) For each visit, a log book should record the date, the length of the visit, the names of the visitors, and the reason for the visit.

Only on-site consultation is to be permitted under normal circumstances. If a valid requirement for removing archived material occurs, the person requiring the material should complete a separate SOP form, which is to be countersigned by that person's Division Chief.

13.5 Storing Archived Material

The storage units used for archived material depend on the material being stored, including:

a. laboratory books and record sheets;

b. magnetic tapes and disks;

c. tissues, laboratory test samples, and preserved wet materials; and

d. standard operating procedures, protocols, and résumés.

Laboratory Books and Record Sheets

Laboratory books and record sheets should be stored in locked filing cabinets in the laboratory until they are full or, perhaps, until the end of a fiscal year. They should then be moved to central storage. Notebooks should preferably be hard-backed, and the accompanying loose-leaf datasheets should be coded to a notebook page. All raw data - for example, printout tapes - could be stored stapled to a loose-leaf page or in a properly coded envelope book.

Magnetic Tapes and Disks

Magnetic media for computers require special storage conditions to ensure the longest possible life. An expert should be consulted to determine the best conditions.

Tissues, Laboratory Test Samples, and Preserved Wet Materials

The storage of tissues and related materials cannot be centralized. For safety reasons, most cannot be taken outside the building. Furthermore, they often require special storage equipment such as deep-freezers, temperature-controlled rooms, and liquid nitrogen.

Each division within the Directorate should be provided with storage units that are set aside solely for the purpose of storing such materials. The storage units should be equipped with alarm systems to detect malfunctions. The project leader, in collaboration with the Director, should decide how long to hold test specimens in storage.

Standard Operating Procedures (SOPs), Protocols, and Résumés

SOPs and experimental protocols should be stored as described for other paper and electronically stored data. A computerized cataloguing system should be developed and maintained for all SON, protocols, and staff résumés.

13.6 Duration of the Archive

The planning for a project should include planning the length of time that materials and information must be held in storage following the end of a project. For example, if wet specimens are to be kept, an estimate of the length of time that these must be stored should be given to the archivist.

To avoid overcrowding archive facilities, all materials should be stored only for a designated maximum duration, after which the material could be relocated to a more permanent storage place. The usual duration is five years, except in the case of documents and other materials for which there might be a legal requirement for longer storage.

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3. *Occupational Safety and Health*. Canada Labour Code (Part IV).

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GLOSSARY OF ACRONYMS AND INITIALISMS

The acronyms and initialisms most commonly associated with Drugs Directorate laboratory activities are:

ACS	-	American Chemical Society
AECB	-	Atomic Energy Control Board of Canada
AOAC	-	Association of Official Analytical Chemists
AR	-	Analytical reagent grade
ASTM	-	American Society for Testing and Materials
BDR	-	Bureau of Drug Research
BB	-	Bureau of Biologics
BP	-	British Pharmacopoeia
CAP	-	College of American Pathologists
CTFA	-	Cosmetics, Toiletries and Fragrances Association
DD	-	Drugs Directorate
DID	-	Drug Identification Division
DO	-	Drug official (method)
DTD	-	Drug Toxicology Division
EP	-	European Pharmacopoeia
GC	-	Gas chromatography
GLP	-	Good laboratory practice
HPB	-	Health Protection Branch
IR	-	Infrared
MS	-	Mass spectometry
NBS	-	National Bureau of Standards
NMR	-	Nuclear magnetic resonance
NF	-	National Formulary
OD	-	Optical density
PCD	-	Pharmaceutical Chemistry Division
QA	-	Quality assurance
SOP	-	Standard operating procedure
TC	-	To contain
TD	-	To deliver
USP	-	United States Pharmacopeia

Appendix A
Drugs Directorate Staff Involved in the Preparation of this Guide with Their Affiliations at the Time of Involvement

Steering Committee:	B. Lodge (Co-ordinator) (DID) T. Cyr (PCD) S. Swierenga (DTD) W. Yarosh (BB)
Instrumentation:	B. Lodge (Coordinator) (DID) H. Beckstead (DID) R. Brien (PCD) D. Long (BB) A. Menzies (DTD)
Data Handling:	S. Hills (Co-ordinator) (BB) N. Beaudoin (PCD) G. Carignan (PCD) J. Ethier (DID) G. Lauriault (DID) A. Pakuts (DTD)
Analytical Methods:	E. Lovering (Co-ordinator) (PCD) B. Black (DID) W. Nitchuk (BB) S. Qureshi (DTD)
Sample Handling:	S. Desjardins (Co-ordinator) (DTD) P. Lacroix (PCD) D. Latham (DID) D. Long (BB) N. Mousseau (PCD)
Reagents:	B. Becker (Co-ordinator) (BB) A. Bayne (PCD) M. Burton (DTD) S. Callahan (DID) C. Savard (DID) L. Whitehouse (DTD)

Reference Standards:	H. Avdovich (Co-ordinator) (DID) T. Fanok (BB) S. Laganière (PCD) S. Liakopoulou (DTD)
Inspection:	D. Kindack (Co-ordinator) (DID) R. Downie (DTD) B. Foster (PCD)
Personnel Records:	B. Mallett (Co-ordinator) (BB) D. Bura (DTD) N. Curran (PCD) C. St. Onge (DID)
Archives:	M. Girard (Co-ordinator) (DID) A. Beaubien (DTD) R. Sears (PCD) B. Wachmann (BB)
Environment:	J. Peart (Co-ordinator) (BB) B. Flann (DID) N. Jordan (PCD) R. Wood (DTD)
Electronic Data:	J. Zamecnik (Co-ordinator) (DID) L. Brunet (PCD) M. Girard (DID) D. Gubiani (PCD) S. Hills (BB) C. Paul (DTD)