

DRAFT DOCUMENT

HANDBOOK

QUALITY STANDARDS  
IN  
BASIC BIOMEDICAL  
RESEARCH



UNDP/World Bank/WHO  
Special Programme for Research and Training in Tropical Diseases (TDR)



UNDP/World Bank/WHO  
Special Programme for Research and Training in Tropical Diseases  
(TDR)

# **HANDBOOK**

## **QUALITY STANDARDS IN BASIC BIOMEDICAL RESEARCH**

Prepared for TDR by the  
Scientific Working Group on GLP



TDR/PRD/QSBR/01.1

This document is not a formal publication of the World Health Organization (WHO), and all rights are reserved by the Organization. The document may, however, be freely reviewed, abstracted, reproduced or translated, in part or in whole, but not for sale or for use in conjunction with commercial purposes.

The views expressed in documents by named authors, are solely the responsibility of those authors.

© TDR 2001

This document has been prepared as a result of the deliberations of a specialized Scientific Working Group (SWG), convened by the UNDP/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR). The SWG, composed of independent scientific experts, met in Geneva on 4-6 September 2000 to discuss various aspects related to good laboratory practice (GLP) and sound scientific working practices. They concluded that there was a pressing global need for the dissemination of information and guidance if developing countries were to comply with internationally established standards.

To this end, this document - a preparatory guide outlining the quality needs in biomedical research required in disease endemic countries - has been produced. The quality standards for basic biomedical research described in this document do not address the scientific content of a research programme or proposal, but they are concerned with the way the research work is both organized and performed.

This preliminary publication is intended to serve as a working document, the first step towards the development of an official set of guidelines on quality standards for basic biomedical research. It will be circulated internationally to scientists and researchers involved in biomedical research related to product development. Comments and suggestions will be canvassed, with a view to incorporating all such feedback into a revised, finalized set of guidelines, for publication in 2003.

Those wishing to contribute to the development of these guidelines should address all correspondence, to be received by January 2003, to the following:

TDR Communications Unit  
WHO, Avenue Appia 20  
1211 Geneva 27  
Switzerland  
Email: [tdr@who.int](mailto:tdr@who.int)

**Participants in the Scientific Working Group on GLP:**

Dr JP Seiler (Switzerland), chair  
Dr D Long (GLP Consultant, France), rapporteur  
Dr D Turnheim (Organization for Economic Cooperation & Development, France)  
Dr N Gawadi (H. Lundbeck, Denmark)  
Dr NK Nair (University of Sains Malaysia, Malaysia)  
Dr MT Ham (Ministry of Health, Welfare and Sports, The Netherlands)  
Dr Ch. K Maitai (University of Nairobi, Kenya)  
Dr CON Wambebe (National Institute for Pharmaceutical R & D, Nigeria)  
Dr M Arevalo (Institute de Immunologia del Valle, Colombia)  
Dr JF McCormack (Food and Drug Administration, USA)  
Dr G Murila (Kenya Trypanosomiasis Research Institute, Kenya)  
Dr P Palittapongkarnpim (National Center for Genetic Engineering & Biotechnology Thailand)  
Dr JM Sapin (agence française de sécurité sanitaire des aliments, France)  
Dr A Walubo (University of the Orange Free State, South Africa)  
Dr P Withers (Phoenix International, France)

**WHO Secretariat:**

Dr D Kioy (Preclinical Coordinator, TDR/Communicable Diseases [CDS] cluster/  
World Health Organization [WHO])  
Dr B Halpaap (TDR/CDS)  
Dr E Griffiths (Health Technology and Pharmaceuticals [HTP] cluster/WHO)  
Dr H Engers (TDR/CDS)  
Dr S Kopp-Kubel (HTP)

**Editorial Group:**

Dr N Gawadi (H Lundbeck, Denmark)  
Dr D Long (GLP consultant, France)  
Dr JP Seiler (Switzerland)  
Dr D Kioy (Preclinical Coordinator, TDR/CDS)

# TABLE OF CONTENTS

---

<b>BACKGROUND</b> .....	vii
<b>INTRODUCTION TO THE TDR QUALITY STANDARDS IN BIOMEDICAL RESEARCH</b> .....	1
AN OVERVIEW OF APPLICABLE QUALITY STANDARDS FOR DRUG OR THERAPEUTIC PRODUCT DEVELOPMENT .....	2
THE IMPORTANCE OF CHOOSING THE RIGHT CANDIDATE FOR FURTHER DEVELOPMENT .....	4
<b>SCOPE AND PRINCIPLES</b> .....	6
<b>THE TDR QUALITY STANDARDS</b> .....	7
<b>ORGANIZATION</b> .....	7
Quality policy .....	7
Physical resources .....	7
Personnel .....	8
<b>DOCUMENTATION</b> .....	8
Introduction .....	8
Protocol/study plan .....	9
Standard operating procedures (SOPs) .....	10
Good record keeping .....	12
Storage of records .....	13
Data sharing.....	14
<b>EDUCATION AND TRAINING</b> .....	14
Education.. .....	14
Training .....	14
<b>SUPERVISION/QUALITY ASSURANCE</b> .....	15
Verifying qualifications. ....	15
Verification of results .....	15
Reporting of results .....	16
<b>CONCLUSIONS</b> .....	16



## BACKGROUND

---

The need for quality standards for biomedical research was discussed at the first meeting of the Scientific Working Group (SWG) on good laboratory practice (GLP) issues at World Health Organization (WHO) Headquarters in November 1999. The delegates recognized a need to develop quality standards for research activities that lie outside the scope of the Organization for Economic Cooperation and Development (OECD) principles of GLP (or equivalent quality standards). The correct performance of research would affect the results in, and development of, health care programmes. Specifically, quality standards should address the need for universal acceptability and credibility of data arising from basic research. The Group considered that the key to such acceptance would be proper documentation that allows traceability. A task group was mandated to draft a document to address quality issues in basic research investigations (discovery stage), which draft document was subsequently discussed at the second meeting of the SWG in September 2000. This SWG recommended that a second draft be produced for wider consultation with the scientific community. This current volume serves as the second draft document as reviewed and approved by the SWG members.



# INTRODUCTION TO QUALITY STANDARDS IN BIOMEDICAL RESEARCH

---

The world's population is facing serious health challenges in the form of newly emerging diseases or disease patterns e.g. transmissible spongiform encephalopathies (bovine spongiform encephalopathy, Creutzfeldt-Jakob disease), human immunodeficiency virus (HIV) and Ebola; the emergence of multidrug resistant diseases or organisms e.g. malaria and tuberculosis; and increasing difficulties in treating 'old' diseases such as trypanosomiasis, onchocerciasis, diabetes, hypertension and cancer. The problem is worsened by the changing age patterns of populations, the faster population movements that promote the transmission of diseases, the new practices in land use, agriculture and forestry, and the changing world climate, to name but a few. As a result, there is increased demand for new drugs and new principles for treatment, based on new knowledge about the causes and mechanisms of diseases, and for new methods of vector control. The search for these commodities and principles engenders an increased need for scientific researchers and research programmes. With the continued restrictions in available funding, it is essential that basic scientific research as a whole, and especially in all fields connected with health issues, is conducted in a proper fashion using processes that minimize resource wastage and reduce the need for costly confirmation and repetition of work already performed.

Today, research facilities in many universities, hospitals, other government institutions, and industries, are used for basic scientific research relevant to the discovery and development of new products with potential usefulness in health care. Data from these activities need to be reliable to ensure a solid basis for the decision as to whether to invest in the further development of a product. Since these activities fall outside the regulatory scope, i.e. they are not covered by, for example, the principles of good laboratory practice, a need for guidance on quality standards applicable to these areas has been recognized.

It must be stressed here that the quality standards for biomedical research described in this document do not address the scientific content of a research programme or proposal, but are concerned with the way the research work is organized and performed. Usually the organization of such work is outlined and described in the study plan or protocol, a document explaining why and how the experimental work will be undertaken. It is clear that if the basic, underlying conditions of the experimental set-up are unclear or poorly documented, there may be fundamental

doubts as to the validity of the knowledge obtained, and its contribution to science. It should not be surprising, therefore, to find that some controversies in the scientific literature could probably have been resolved earlier, easier and better if the practical experimental conditions had been fully described, or if the supportive data had been properly collected.

### *An overview of applicable quality standards for drug or therapeutic product development*

Drug or therapeutic product development follows four well-defined stages:

**Stage 1** is the stage of basic scientific exploration and discovery of substances with the potential for yielding new drugs or product candidates. This stage is not covered by any officially recognized quality standard. The ethical conduct of work in this area of basic or applied research depends entirely on the individual scientist's judgement. Consequently, mutual acceptance of data from different laboratories has been difficult. **This research is the subject of this document.**

**Stage 2** is the stage of 'safety testing' of drug candidates in non-human models, usually animals. Such studies are termed 'non-clinical' as they are not performed in man. Safety tests include toxicology and safety pharmacology studies, with potential extension to pharmacokinetics and bioavailability. The studies are typically required to be conducted in compliance with international good laboratory practice (GLP)<sup>1</sup> standards or national regulations.

**Stage 3** encompasses clinical studies in man. Here, good clinical practice (GCP)<sup>2</sup> is the basis for quality standards, ethical research conduct and regulatory compliance. GCP must be instituted in all clinical trials from Phase I (to demonstrate tolerance of the test drug) through Phase II (where the dose-effect relationship is confirmed) to Phase III (full-scale, often multicentre, clinical trials in hundreds of patients to confirm therapeutic efficacy and safety).

---

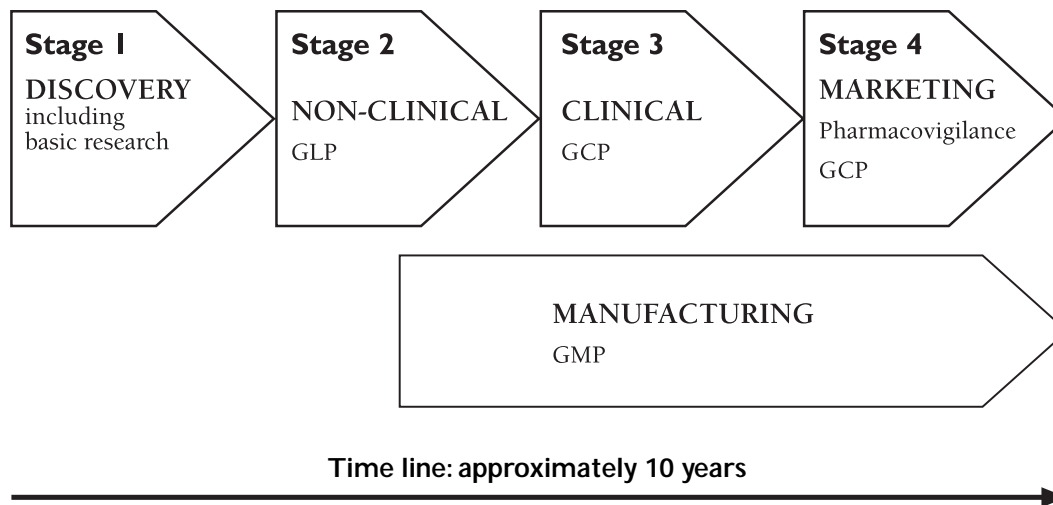
<sup>1</sup> TDR. *Handbook on good laboratory practice (GLP): quality practices for regulated non-clinical research and development*. Geneva, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), 2001

<sup>2</sup> WHO. *Guidelines for good clinical practice (GCP) for trials for pharmaceutical products*. Geneva, World Health Organization, 1995

In **Stage 4**, the post-approval stage, the drug has been registered and is available on the market. However, even after marketing, the safety of a drug in its 'normal' use is monitored through formalized pharmacovigilance procedures.<sup>3</sup> If there are any subsequent clinical trials (Phase IV) they must also comply with GCP.

From stage 3 onwards, throughout the rest of a drug's lifetime, good manufacturing practice (GMP)<sup>4</sup> applies to all manufacturing of bulk and formulated product.

These different steps in classical drug development are summarized in the diagram below:



These 'good practice' quality standards are supplemented by other existing WHO quality initiatives governing the activities of laboratories that typically support the drug life cycle, such as clinical chemical laboratories, chemical analytical laboratories, pathology laboratories.<sup>5</sup> In addition, International Organization for Standardization (ISO)<sup>6</sup> programmes for developing countries will support the development of standards for calibration and testing, again complementing the work of laboratories complying with the WHO good practices.

<sup>3</sup> WHO Programme for International Drug Monitoring, Uppsala, Sweden

<sup>4</sup> WHO. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials Volume 2: good manufacturing practices and inspection*. Geneva, World Health Organization, 1999

<sup>5</sup> see: <http://www.who.int>

<sup>6</sup> see: International Organization for Standardization Committee on Developing Country Matters (ISO/DEVCO)  
- <http://www.iso.ch>

### *The importance of choosing the right candidate for further development*

Research programmes are time consuming and require vast resources in the form of financial, human and technical efforts. This is true whether new basic principles are being established or new drug candidates being developed. The development of a new drug usually takes 10-12 years from discovery to registration and marketing, and the development costs for a new drug are currently estimated to amount to about US\$250 million dollars. It is also estimated that 5% of the development costs is spent at stage 1, the discovery stage, 10% on stage 2, the non-clinical testing stage, and the remaining 85% on stage 3, the clinical and registration stage. Clearly, it is essential to take extreme care that the right drug candidates for further development are selected in the early and cheaper stages, by the application and use of sound scientific principles in the conduct of basic exploratory and discovery studies coupled with an attention to high quality standards. Not only will investment in the wrong candidate waste resources and time, but will certainly block capacity which could have been used for the development of a more promising candidate.

The notion of quality in this area has two aspects: a fundamental, scientific one, and a practical, experimental one. When the underlying science is wrong or the working hypothesis is ill conceived, the results obtained by even the best conducted experiments will not lead to a true advance of knowledge. On the other hand, even the best science, the most brilliantly reasoned working hypothesis, will not return results and answers that are acceptable to the scientific community if they are not supported by flawlessly conducted (i.e. high quality) experiments.

It is often claimed that science is self-policing, in that the quality of research proposals and research results will be exposed to the scrutiny of peers, and that results will be challenged by attempts to repeat and verify experiments. However, the extent to which this process ensures the integrity of research and its results has been questioned. Broad and Wade<sup>7</sup> described many instances where spurious results were able to be published and to survive for some time. They traced the anomalies to organizational practices within the scientific endeavour itself. But also outright fraudulent machinations and manipulation of data may not be ruled out, as recent experience and some highly publicized cases have shown. A group of scientists from the American Institute of Medicine<sup>8</sup> therefore recommended closer surveillance of scientific activities in order to assure reliability of new scientific results, and a Danish group<sup>9</sup> came to similar conclusions. Both groups called for clear organization of work, clear definition and allocation of responsibilities,

<sup>7</sup> Broad W, Wade N. *Betrayers of the truth. Fraud and deceit in science.* Oxford University Press, 1982.

<sup>8</sup> Institute of Medicine. *Report of a study. The responsible conduct of research in the health sciences.* Washington DC, National Academy Press, 1989

<sup>9</sup> Andersen D, Attrup L, Axelsen N, Riis P. *Scientific dishonesty and good scientific practice.* Danish Medical Research Council, 1992.

close supervision of the scientific work, good data recording practices, good facilities for data storage and retrieval, and proper training of scientists and other staff.

It is not the intention of this document to stipulate the scientific nature of the research investigations, but to provide guidance that will enable scientists to organize their research and produce better substantiated and thus more credible results. It must be potentially possible for peers, scientific journals, potential development partners, or authorities to audit studies to verify authenticity and reliable reporting of results. This helps to validate the data and make the results acceptable to the scientific community at large, and makes it more likely that there will be commensurate returns on investment.

In this sense, this document does not deal with matters such as the definition and writing of research programmes, and the submission and peer-review of research proposals for purposes of requesting research grants. It is clear that each research programme will require a research proposal of high scientific quality to obtain funding. The research proposal will outline the biomedical context for, and provide the overall outline of, the programme, with reference to existing knowledge. As such it will describe and discuss the scientific principles and data upon which the proposal rests. It will also outline the general timeframe of the research programme, the main stages involved, and propose the individual component studies. Some of the publications cited above do provide guidance for institutions, institution heads and institutional supervisors in this area, and they should be consulted for the setting-up of 'good institutional practices'. A proper scientific concept, expressed in a peer-reviewed proposal for a research programme, would therefore ensure the studies are rooted in a basis of sound science.

## SCOPE AND PRINCIPLES

---

The proposed quality standards have been developed to cover non-regulated basic biomedical research, in particular the discovery and exploratory stages of drug development. They are concerned with the organizational, managerial, experimental side of research work. Production of credible research data is ensured by adhering to the basic principles and the key elements of sound study management.

# THE TDR QUALITY STANDARDS

---

The quality principles for basic biomedical research are described under the following headings:

- Organization
- Documentation
- Education and training
- Supervision/quality assurance

## *Organization*

### **Quality policy**

It is essential for each research institution to have a written policy describing the quality standards to be applied by all personnel in the conduct of experimental work, irrespective of its nature. Such a policy paper would also outline the responsibilities at the different organizational levels. The administration (director) of the organization should be visibly and fully supportive of these standards, and should implement mechanisms for their application, exercising at least some level of control over them.

### **Physical resources**

The research institution's administration is responsible for providing facilities of suitable size, construction and location, and for providing suitable equipment to meet the requirements of the research programme and its individual studies. Fulfilling the requirements of the study does not necessarily mean that 'state of the art' constructions or equipment have to be provided. Instead, the institution's administration, in cooperation with the leader of the research group or the study director, has to consider carefully the objectives of the research programme, including its individual component studies, and investigate and decide how to achieve these with the facilities and equipment available. Special attention should be paid to the risks for study integrity which can originate from the close spatial coexistence of different activities and studies. It is therefore important that care be taken to minimize any disturbances that could interfere with the validity of the study, especially with regard to minimizing the risks of confusion and mix-ups (of studies, test systems, test items, data). The purpose of such requirements is to ensure that the individual study is not compromised because of inadequate facilities or equipment.

All equipment should be suitable for its intended use. Equipment must be properly calibrated and maintained, if necessary by a qualified and certified agent, to ensure accurate and consistent performance. Records of repairs, routine maintenance and any non-routine work should be retained. This is to ensure the reliability of data generated and to prevent loss or corruption of data as a result of inaccurate, inadequate or faulty equipment.

### **Personnel**

Qualifications and training should be adequate for the activities that each person is to perform. The organization's administration should ensure that the responsibilities of staff at *all* levels are defined and documented in a job description. Aspects to be considered are: scientific field of activity, practical duties, supervisory duties/delegation, administrative and financial responsibilities, communication, and keeping knowledge and skills up to date. There must be sufficient financial support for education and training activities.

While it is important to ensure that all staff are knowledgeable and well versed in the relevant quality aspects of experimental work, its planning, recording and reporting, this is especially relevant to tutors, PhD students and post-doctoral fellows in university settings, who should be responsible for the full application of the quality standards required by the institution, and should not tolerate any deviation from them. This requirement holds also for any institution where new staff are employed on a temporary, project-related basis.

## ***Documentation***

### **Introduction**

Making a full record of all information is essential to allow the possibility for complete reconstruction of a study. It is the only way of demonstrating what actually went on at the time, and so the study record must not only contain the data generated, but also prove that all the required procedures were correctly carried out at the correct time. Consequently, if a complete record is not made, the study validity is compromised, as the missing data have to be considered non-existent or lost.

Documentation may be divided into two broad classes:

- prescriptive documents that give instructions as to what is to happen during the course of a study.
- descriptive records that describe what actually happened during the course of the activities.

The prescriptive documents include research proposals, study plans and standard operating systems. The records include raw data, any derived data, study reports and publications.

### **Protocol/study plan**

A protocol or study plan is a document describing in detail the proposed conduct of a study. Because it is the key document for communicating the intentions of the study to all contributing staff and sponsors, its contents and layout should be clear. Every study must therefore have a study plan.

In basic research, a protocol/study plan is usually part of a proposal. Nevertheless, this part of the proposal can stand on its own, particularly when considering the practical aspects of the study, the theme for this document. A research proposal is a document outlining the scientific context, overall objectives and scope of a study or a big research programme (or research thrust). Although the proposer, usually a research scientist(s), is responsible for the scientific content of the proposal, all research scientist(s) responsible for running the programme must be indicated here. Also the proposal should outline the main stages in the study or, in case of a big research programme, describe the individual component studies and indicate the general timeframe of each study and the programme. One would expect a review board or the management within the institution to approve the document, since resources and budget would have to be found to support the work. It is essential for each research institution to have a policy or guidelines describing the writing, verification and approval of research proposals, plans and individual study plans.

The study plan should describe the study design in detail, including the purpose, the intended methods, and the names of the persons who will carry out the study and interpret the experimental data. The information in the study plan should be sufficiently detailed to enable the study to be repeated exactly, if necessary. The study plan is, therefore, likely to contain details of the test material, the conditions of handling and storage of this material, the quality of reagents, the type of test system, and the observations to be made. The document should describe the methods for data collection, evaluation, verification and (if appropriate) statistical analysis. Where appropriate (for example, in research involving animals), the plan should discuss the ethical implications of the experiment. Proposed dates for key events should also be stated, and the names of involved personnel, including their exact duties. As noted above, procedures considered routine in the laboratory may be described in general documents of the institution, such as standard operating procedures (SOPs). Where applicable therefore, such procedures need not be explained in full detail in the study plan, but the respective SOP documents should be quoted and available.

In the case of an experiment that is based on previous preliminary work, this would normally be referenced in the plan to ensure traceability to the previous data, justifying certain parameters investigated in the main experiment. References cited in the study plan should either come from published peer reviewed sources, or from internal research reports where data or documentation are available. Both published sources and internal reports must be verifiable. The link between the proposed activities and the published material must be explicit.

Major changes to the study plan may need authorization. However, minor deviations from the plan may simply be recorded in the laboratory notebook, or they may be recorded in specifically designed data sheets which are then filed with the rest of the data.

The research scientist should ensure that the technicians responsible for the day-to-day conduct of experimental phases are familiar with the study plan and its associated procedures. Such instruction should be documented in the study notes.

### **Standard operating procedures**

SOPs are those documents which describe activities of a repetitive, routine nature in a very detailed manner. The existence of such standardized, approved written working procedures is unquestionably required by classical quality assurance techniques, indeed by good management. Remember the Deming quote:

*'Use standards [i.e. SOPs] as the liberator that relegates the problems that have already been solved to the field of routine, and leaves the creative faculties free for the problems that are still unsolved'. W. Edwards Deming*

Every institution, or laboratory or facility within an institution, will certainly already have a collection of standard procedures under various headings and in differing forms, e.g. recipes for the preparation of buffer solutions or tissue culture media, directions for the operation and maintenance of apparatus and instruments, or step-by-step descriptions of commonly performed activities. These should become integrated into a fully coherent system with a standard layout, which should be predefined by management. This should lead to centralized organization of formatting, numbering, issuance, modification and withdrawal, which will help avoid duplication of effort, incoherence, delays, lack of traceability and incomplete distribution. The system should thus encompass all standard activities and there should not be separate, conflicting systems for conveying directives to personnel, such as memos.

The best effects with such a system of standardized procedures can be expected if there is comprehensive coverage of:

- standard scientific techniques, equipment, etc.
- all critical phases of study design, management, conduct and reporting.
- 'scientific' administrative policy and procedures (e.g. format, safety and hygiene, security, personnel management).

Ideally, the individuals most familiar with the activity to be described in a SOP should also write the document. Furthermore, there should be somebody responsible for each SOP (author or person responsible) to handle queries and to keep each procedure updated. It is a good idea to impose a minimal requirement for periodic review.

SOPs should be immediately available to all individuals performing the respective tasks. Staff must fully understand the SOP and follow it rigorously. Deviations from the standard way of performing these activities should be handled like deviations from study plans, i.e. they have to be described, justified, signed and dated, in order to preserve the credibility of the system.

For reasons of traceability and easy use, a two-tier system of SOP is often the preferred approach. In such an approach, one tier may reflect general policies and procedures (e.g. protocol writing, review, approval, distribution and modification, SOPs, general rules for equipment use and maintenance, archives). The second tier may represent technical methods (e.g. methods of staining in histology, analytical methods, specific procedures for use and maintenance of equipment). It is advisable to present the SOPs (SOP manuals) as a binder with an up-to-date table of contents, logical chapter divisions and selective distribution, to avoid a mushrooming packet of dust-gathering paper that often gets misplaced. All alterations to SOPs have to be made through formal revisions; notes and changes as hand-written margin comments are not admissible.

All withdrawn SOPs, whether no longer used or superseded by a revised version, should be archived carefully in order to make a complete historical record of the test facility's procedures.

Properly designed SOPs will bring the following benefits to the laboratory:

- standardized, consistent procedures (person-to-person, test-to-test variability minimized).
- an opportunity to optimize processes.
- capture of technical and administrative improvements.
- demonstration of management commitment to quality as part of the SOP approval process.
- ease of documenting complicated techniques in study protocols and reports (a simple reference to the procedure should often suffice).
- continuity in the event of personnel turnover.

- availability of a training manual.
- a means of study reconstruction after the event, also after a lapse of years.
- a means of communication in case of audit, visits, technology transfer, etc.

The successful implementation of SOPs requires:

- sustained support from all levels of management with commitment to establishing SOPs as an essential element in the organization and culture of the laboratory.
- SOP-based education and training of personnel so that the procedures are performed in the same way by all personnel.
- a sound SOP management system to ensure that current SOPs are available in the right place.

### Good record keeping

The collection of data should be done in strict compliance with the rules of the institution. It is important to be able to identify who collected the data from a given procedure and when. This is why signing and dating the data is a necessity.

Raw data are defined as all original recordings made during the course of a study.

The data should indicate:

**What was done** – demonstrating compliance with the study plan.

**How it was done** – demonstrating compliance with practical, experimental instructions (in the study plan and relevant SOPs).

**When the work was performed** – demonstrating the existence of the events and their sequence in time.

**Who did the work** – demonstrating conformity with the responsibilities delegated by management to suitably qualified personnel.

Characteristics of the collection of good raw data are:

**Attributability** – data can be traced to their source, e.g. by study number, sample number, parameter. Unique identification of data pertaining to an individual study helps to prevent data mix-up.

**Originality** – raw data constitute the first recording of the observation. Raw data should not be recorded on scraps of paper for transcription into a final form. When a computer is recording the data, the electronic record is, in principle, considered to be the raw data.

To ensure these characteristics, data have to be recorded:

**Promptly** – data have to be recorded immediately the operation is completed. It is not acceptable to make the record some time after the job has been finished, since memory may fail or become inaccurate, which may lead to data loss or faulty records.

**Accurately** – the raw data have to be a true representation of the observation, and accuracy is thus absolutely central to the integrity of the study.

**Legibly** – data that cannot be read are useless, and records that are difficult to decipher raise doubts in the minds of the reader as to their credibility. Therefore, write legibly.

**Indelibly** – one of the common problems in research is that data are often recorded in pencil and are subject to subsequent changes without this being evident, which in turn may lead to suspicions of deliberate tampering with data. Use of indelible and waterproof ink eliminates this problem. Any changes to raw data should be made so as not to obscure the previous entry. The person responsible for the change (or the person approving it) should then sign and date the change, and the reason for the change should be indicated, if necessary. It is furthermore necessary to check the robustness of the print-out from instruments: some fade quickly at room temperature or when stored in plastic folders. In such cases, an authorized (signed and dated) photocopy should be prepared for storage.

Data should be recorded and organized in a way that supports and facilitates both recording and all subsequent processes (e.g. data entry, reporting, audit, archiving).

At the end of every study, all raw data pertaining to the study should be collected, together with the study plan and a final report or summary of the results, and combined into a single package of information. This study information package should then be archived in order to guarantee the integrity of the data and of the study. When single data sets from a finalized study are needed for another study, there should be formalized procedures for the retrieval of studies or study parts from the archives (see also section on data sharing).

### **Storage of records**

The records retained are a great deal more than a just a compilation of papers or a set of figures. The collected data represent the value (in time, resources and economic potential) of the research done. Therefore the administration and physical placement of the storage facilities must be of a quality that matches the assets laid down in the data.

Access to the storage facility should be limited to authorized personnel, and the facility must protect records from physical damage, interference and loss. Stored material should be logically and practically arranged to facilitate rapid retrieval. It is furthermore advisable to allocate a person to be responsible for the archive.

The institution should retain all records for at least the period of time it takes to develop the product. It is recommended to either follow the national guidance or to stipulate a period of 10-20 years after publication. In some countries there are national archives for research data. If such facilities exist, they should take priority over institutional storage facilities.

### **Data sharing**

Each institution should endeavour to regard its data as part of its assets, potentially available to all personnel. It is good practice for the institution to provide for regular seminars where staff present their work to one another for discussion. Similarly, the institution should encourage an atmosphere where staff can see one another's data, and may freely access these if they wish to verify a study.

Data sharing can be practised through the agency of a national archive as described above. Any researcher should be able to access data for the purpose of verifying or repeating a study, or for further developing the studies in a research programme. There is no reason to re-invent wheels.

Finally, it should be acceptable practice to ask for raw data from a colleague outside one's own institution, for the purposes cited above, and if patent rights are not infringed.

## ***Education and training***

### **Education**

Education includes the qualification(s) that staff have on joining the research institution. Staff may become further qualified through a structured course of study while at the institution. Any qualification usually results in the award of a diploma or degree from a recognized academic institution. These qualifications must be suitable for the type of research activity envisaged; they should be documented in the person's curriculum vitae (CV) and be verifiable.

### **Training**

It will be necessary to train staff (at all levels) in specialized or new techniques. Such training should be offered routinely, and will help to keep the general level of expertise at the research institution up to date. Such training should also be documented, either in the CV or by means of separate training records.

## *Supervision/quality assurance*

### **Verifying qualifications**

The institution's administration must implement a procedure for verifying staff qualifications as stated in their CVs.

### **Verification of results**

In the first instance, the scientist has primary responsibility for the quality and reliability of his/her data. The administration of the research institution, however, also has a critical role in ensuring the quality and reliability of the data collected at the institution. Production of quality and reliable data requires strict supervision. This supervision is often at two levels: 1) supervision related to the scientific content, often requiring some level of confidentiality, and 2) supervision to ensure that the systems used to generate data are sound.

The validity of scientific research depends on how well it will withstand scrutiny. The scientists responsible for the conduct of the experiment must therefore ensure that there are verification procedures in place that will confirm the integrity and quality of the data. The signature of a responsible scientist should attest that sufficient verifications at all levels have been made to ensure this.

Verification activities may also need to be performed by someone from outside the organization who is responsible for testing, in which case this verification is named an 'audit'. An audit means the systematic scrutiny of all raw data in a study and the verification of their correct representation in the final report or publication. While it is unusual to implement systematic independent auditing in research institutions, it is only through care at the level of data acquisition and data recording that the study can be validated at all by audit. A successful audit relies on the traceability and transparency of all events contributing to the study.

It is also possible to organize external third party audits by professionals who look at the systems, studies or specific data. This approach is particularly relevant as research which falls outside the regulatory scope of GLP, GMP and GCP is not inspected by national regulatory monitoring authorities.

**Reporting of results**

The research institution should have a policy or guidelines for scientific evaluation and reporting of results. There are many ways to do this. The institution could choose to authorize a superior or peer to inspect a portion of the raw data, and to evaluate the technical and scientific content of the report. This person would assure management that the report is a fair and complete account of the activities as documented in the raw data. After this, the report would be circulated to the rest of the scientific staff for discussion and comments before sending the final report out of house. Internal reports used as the basis for further work would need equally rigorous treatment.

It is also possible to organize an external review of the work done. Academic institutions are familiar with the practice of an external examiner who assesses PhD theses; the external review of research work would work in a very similar manner.

***Conclusions***

The need for quality standards in biomedical research at the drug discovery stage has been articulated through several meetings held under the auspices of WHO. It is indisputable that selection of successful drug candidates for further development must be based on reliable data obtained by using sound scientific research principles. The proper organization of resources, writing of study plans and SOPs, education and training, documentation and supervision is the hallmark of universally acceptable, high quality and reliable data. It is hoped that wide application of the quality standards as proposed in the present guidance document will accomplish the intended purpose, i.e. will lead to cost-effective, accelerated discovery research and associated advantages.



**WHO/TDR**  
**Avenue Appia 20**  
**1211 Geneva 27**  
**Switzerland**  
**Tel: (+41) 22-791-3725**  
**Fax: (+41) 22-791-4854**  
**E-mail: [tdrnews@who.int](mailto:tdrnews@who.int)**  
**Web: [www.who.int/tdr](http://www.who.int/tdr)**