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World Health Organization
Department of Control of Neglected Tropical Diseases
WHO Pesticide Evaluation Scheme (WHOPES)

Quality control of pesticide products

Guidelines for National Laboratories

Collaborative International Pesticide Analytical Council

Food and Agriculture Organization of the United Nations

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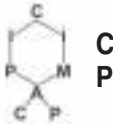

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1. Introduction

The aim of this document is to provide a general guidance for the establishment or strengthening of national pesticide quality control activities, irrespective of the use of the product, whether public health or agricultural. Though the end-use of a product may differ, the quality control schemes are very similar, and a laboratory combining products of both areas may prove synergistic and allow a rational use of resources. This document focuses on laboratories involved in the post-registration analysis of pesticide products to ensure that the data generated are of a sufficiently high standard to stand external scrutiny. Reference is also made to laboratories engaged in pre-registration testing of products.

The scope of the guidelines is not restricted to the control of quality in conducting specific analyses, but extends to the full range of management activities related to the operation of the laboratory, including organization, staff, procedures, and the facilities involved.

This is a guidance document with quality assurance requirements for laboratories involved in product testing. In general, accreditation according to ISO/IEC 17025[1] through a national body seems to respond better to the specific needs of an official quality control laboratory than the quality assurance scheme under Good Laboratory Practice (OECD Series on the Principles of Good Laboratory Practice and Compliance Monitoring[2]), which is mandatory for the elaboration of studies necessary for national registration in countries of the Oganisation of Economic Co-operation and Development. The emphasis of accreditation is on quality management and competency, while offering more flexibility with respect to the analysis of samples arriving at short notice—a situation often seen in official quality control laboratories. The outline of the document and the points covered refer very often to the requirements of the Standard ISO/IEC 17025. In order to maintain a simple wording, the assumption was made that samples are submitted to the control laboratory by a body outside the lab organization. The term “customer” is used in that context.

2. Organization and management

2.1 Structure, responsibilities and authority of individuals in the laboratory

It is essential that official laboratories engaged in the quality control of public health and agricultural pesticides possess an awareness of the national and international regulatory framework within which both the pesticide industry and the national registration authorities operate. The pesticide manufacturers have to comply with national pesticide standards and, depending on national legislation, also the FAO and WHO specifications for pesticides.

It is essential, therefore, that laboratories engaged in the development and use of methods of analysis of pesticides must possess up-to-date test equipment and have trained and competent staff. It is also important that laboratory staff are able to hold a pragmatic dialogue with technical staff among regulators and manufacturers, to deal with disputes and promote beneficial change. This section of these guidelines deals in more detail with some of the key aspects.

All staff in the laboratory will impact on the quality of the data generated, and must therefore have clear and agreed job descriptions. These must cover all the accountabilities that the jobholder takes on, together with a clear description of the purpose of each one.

Each job must be captured within the organization chart for the laboratory, providing an instant overview of key areas of responsibility, and a clear structure for the organization. Thus, the overall purpose of one job will become a key accountability for the person who manages that jobholder. In particular, this will allow all aspects of dealing with non-conformance to be defined, together with appropriate corrective and preventative actions.

Specified staff will have accountability for quality assurance within the facility, and for quality auditing.

2.2 Quality assurance schemes

2.2.1 Management review

It is recommended that a management review of all systems and procedures should be carried out at an agreed frequency, usually once a year. Each review should identify any improvements needed, whether in terms of organization, training, or changes to any particular procedures or analytical methods. These requirements should be documented in an agreed improvement programme, with action dates. To facilitate this review, it is useful to identify some key points which might include:

- a judgement of available resources (staff, rooms, sample capacity, etc.)
- adherence to calibration protocols
- adherence to maintenance schedules
- results of proficiency testing programmes, if available
- results from collaborative testing programmes.

2.2.2 Quality system

It is essential that the key elements of the operation of the laboratory, which impinge on quality, are captured in the Laboratory Quality Manual. This will refer to key procedures, quality planning, and record keeping. Quality planning should ensure that all buildings, equipment, resources, skills, processes, etc. are available and up to date, in order to meet customer expectations, with the ability to change as requirements change. Important aspects of the quality system are traceability of results (archiving of raw data, electronic files, etc.) and documentation of standard operation procedures, including reference material and instrumentation (see below).

2.2.3 Customer orders and contracts

Procedures must be established to cover contract and order agreements with key customers. These must include:

- a process for ensuring customers requirements are properly checked and clear before acceptance;
- a process for amending contracts;
- procedures to cover receipt, storage, and disposal of samples;
- systems for recording contracts and orders, and for filing.

2.3 Document and data recording

Procedures are needed to define how all key documents and laboratory results and other data are controlled and archived for a specified period of time.

Documents will include:

- all analytical and physical test methods
- all product specifications
- all laboratory operating procedures
- all safety health and environmental control procedures.

There must also be a documented system, with associated operating procedures, to ensure that all documents are written consistently, issued to where they are to be used, readily available when the method described is being carried out, and removed or replaced when they are out of date. Nevertheless, systems should be kept as simple as possible, and documents may be kept as hard

copy or electronically. It is particularly important that a procedure is in place for the updating or modification of methods or operating procedures, including the appropriate approvals by qualified staff.

Consistent systems for the maintenance of records must be in place. These should cover:

- all test results
- samples
- calibration and maintenance records
- training records
- certificates of analysis from suppliers
- customer orders.

Records must be kept to demonstrate the effective operation of the quality system, and should be used as a basis for review and improvement. Procedures should indicate what, how, and for how long, records are kept, and how they are maintained and disposed of. All records should be clear, legible, and readily retrievable, and stored to minimize deterioration or loss.

Quality records include:

- records of management reviews and audits
- customer contracts and orders
- suppliers lists
- supplier history records
- analytical and other test results
- calibration and maintenance records
- records of non-conformances or concessions issued
- customer complaints
- training records and plans
- audit records and plans.

2.4 Internal quality audits

Procedures must be in place to cover regular audits of all systems and procedures in use in the laboratory. These should be carried out by a team of trained auditors. The audit procedure should include:

- planning the audit programme;
- planning individual audits, using checklists;
- carrying out the audits;
- documenting results;
- ensuring laboratory supervisors are committed to correcting deficiencies;
- carrying out follow-up audits, to ensure corrective action is taken.

Procedures should be available to describe how to deal with corrective actions, and to identify preventative actions to avoid future problems. Corrective actions may cover:

- effective handling of customer complaints;
- effective investigation of procedural non-conformances;
- controls to ensure corrective action is taken.

Preventative actions may include:

- analysis of key quality measures, for example, errors, concessions, audit results, quality records, customer complaints;
- actions to prevent future non-conformance;
- actions arising from management review.

2.5 Participation in international ring and collaborative studies

It is recommended that official laboratories establish internal quality assurance measures as a routine procedure. As formulated pesticides are generally not available as standard reference materials, internal quality assurance measures such as: use of independent reference solutions (e.g. reference solutions prepared from a different standard reference material by independent weighing and dilution); analysis of formulations with standard additions of known amount of the active substance(s) are strongly recommended.

Furthermore, laboratories should be encouraged to take part in as many CIPAC or AOAC collaborative studies as possible. This not only provides the opportunity for laboratories to be involved at an early stage in the implementation of new methods, but also provides a reference point for the laboratory in terms of overall competence. As indicated earlier, few schemes yet exist, and the scope of this programme is limited to determination of the active ingredient in formulations. Nevertheless, the use of laboratory proficiency testing programmes is highly recommended to provide important benchmarks, such as the Check Sample Program of the Association of American Pesticide Control Officials (AAPCO) initiated by the Office of the Indiana State Chemist at Purdue University in the United States of America.[3]

3. Staff qualifications and training

At all levels in the organization, staff must be competent to carry out the tasks that fulfil their key accountabilities, as described in their formal job descriptions. In assessing their competency to carry out their tasks fully and well, formal qualifications, experience, and other personal characteristics must be considered. For staff engaged in carrying out analytical work, proficiency testing schemes provide one mechanism for assessing the competence of the analyst, as well as providing information on the robustness of the analytical procedures.

Personnel must be fully trained in all the tasks they are authorized to carry out. Training must be supported by up-to-date training records, which must also identify training needs. Each member of staff will need an agreed training programme. Careful adherence to these programmes will allow staff to take on a wider range of activities in the laboratory, and enable promotion, when opportunities arise. Training programmes should not be restricted to technical aspects of the job, but should cover personal development and management skills.

Everyone whose work covers quality critical activities should be included in a training programme, to ensure they have the appropriate skills. Training may be on-the-job, through recognised courses, and/or involve further academic study. Training procedures should include:

- developing a training plan, by identifying needs and planned training dates;
- regularly reviewing training needs;
- auditing that agreed objectives have been met.

Staff working in pesticide control laboratories must have an adequate scientific background, with a good knowledge of physical sciences. However, in addition they also need to possess a number of key competencies, including the ability to see problems through, to think analytically and logically, to be able to assess the impact of their work, and to think creatively, as well as the ability to work to focus on detail. It is useful to develop a list of four or five key competencies for each level in the organization chart as an aid in staff assessment and identification of future training needs.

The ability to work with, and analyse, highly complex chemicals, and to utilize modern analytical equipment requires knowledge of chemistry to degree level, coupled with additional training in the use of the types of analytical and test equipment discussed below. A good knowledge of computer based systems for record storage is essential.

In order to meet the laboratory safety procedures, it is essential that staff are fully familiar with all safety, health, and environmental requirements, and are tested through regular assessments and drills.

It is important that all aspects of the management system, including training programmes, records, and associated procedures are regularly audited. These audits should be carried out by trained staff who are familiar with the work being carried out, but are not involved in the activities on a daily basis.

4. Facilities

4.1 Library and access to electronic databases

It is essential that staff have access to all appropriate library facilities. Key information is increasingly available electronically, and access to the Internet is essential for gathering information on FAO and WHO specifications. Staff should have access to CIPAC[4], AOAC[5] and ASTM[6] methods, together with background information held in the "Pesticide Manual"[7] as well as information provided by pesticide manufacturers.

4.2 Laboratory facilities and safety provisions

In order to obtain results of appropriate quality, laboratory facilities have assumed much higher importance in the past few years. Some of the key characteristics are:

- modern buildings of solid construction, with smooth, easily cleaned floors and other surfaces;
- location away from sources of vibration;
- good electrical supply (particularly uninterrupted supplies for microprocessor controlled equipment);
- air-conditioning;
- piped supply of high quality gases, including nitrogen, helium, hydrogen, and compressed air for use in chromatography;
- good drainage and waste disposal systems;
- adequate bench space for sample preparation, and location of equipment;
- provision of fume hoods, where required, for handling volatile, dusty and/or toxic materials;
- provision of areas for collation of data, preparation of reports, storage of laboratory documentation;
- modern safety systems including fire detection and suppression, gas alarms, mandatory wearing of safety spectacles, use of protective gloves and clothing, etc.

4.3 Areas for storage of data, samples, standards, and reagents

Separate, secure areas should be available for filing and archiving of data. Sensitive information should be held in fire-proof cabinets, including back-up copies of computer discs.

Product samples should be kept in sealed sample jars in well ventilated, air-conditioned or temperature controlled areas and kept for a minimum of 3 years.

Chemicals and reagents should also be kept in well ventilated temperature controlled areas, with flammable solvents kept in fire-proof containers. Materials should be stored to allow use on a "first in first out" basis, and provision made for disposal of materials exceeding stated shelf-lives.

5. Equipment

5.1 Range and type of equipment

It is essential that the laboratory be equipped with up-to-date systems covering a wide range of analytical and physical test equipment, including:

- capillary gas chromatograph with flame ionization detection (FID), operating in split and splitless modes;
- packed column gas chromatograph with FID detection;
- high performance liquid chromatograph, with ultraviolet detection and column oven;
- mass selective detector for capillary gas chromatograph;
- a modern laboratory data system, or computing integrator to process the data from chromatography and other equipment;
- all accessories to be used in conjunction with the range of chromatographic equipment;
- ultraviolet and infrared spectrophotometers
- laboratory balances, operating down to 0.1 mg sensitivity;
- wide range of laboratory volumetric glassware;
- laboratory ovens, desiccators, and refrigerators for drying and storage of samples, and reference materials;
- water baths, suspensibility jars and Crow receivers for testing suspensibility and emulsion stability of pesticide suspensions and emulsions;
- range of hydrometers and density bottles for specific gravity and density measurements;
- range of test sieves for particle size measurement;

- rotary evaporators for solvent removal;
- range of laboratory thermometers;
- pH and titrimetric apparatus, preferably in the form of autotitrators;
- ultrasonic baths for sample dissolution;
- bulk and tap density apparatus.

The range of equipment may vary according to the tests that are aimed to be performed.

5.2 Procurement of equipment

Analytical equipment should be purchased from major suppliers that have a proven track record in supplying equipment which is fit for the purpose. No major items of equipment should be purchased without clear evidence that it will meet requirements and, where possible, demonstrations should be carried out to evaluate the system. It is important, particularly with computer controlled equipment, that the supplier can maintain and service the devices at short notice. This may indeed be a key consideration when evaluating alternative suppliers.

Clear procedures should be established for the purchase of equipment, in line with Section 7.1.

6. Chemicals

6.1 Quality and type used

All chemicals and reagents should be sourced from reputable laboratory chemical suppliers and should be adequate for the tasks for which they are to be used. In particular, laboratory gases and solvents used for chromatography must be of high purity as defined by instrument and column suppliers. Attention should also be given to specific requirements for chemical purity indicated in analytical methods.

6.2 Analytical standards

Analytical standards are particularly important, and only certified reference materials should be used. These should be sourced primarily as indicated in the CIPAC / AOAC methods, or from pesticide manufacturers[a] or recognized national / international standards agencies and commercial providers of reference materials.

In cases of dispute, it is recommended that the laboratories involved use analytical standards from the same batch, to avoid any particular bias. It is

[a] Article 4.1.5 of the International Code of Conduct on the Distribution and Use of Pesticides[8] requires pesticide industry to "provide, at the request of a country, methods for the analysis of any active ingredient or formulation that they manufature, and provide the necessary analytical standards".

also very important that analytical standards are stored according to instructions- usually in a refrigerator, in sealed, moisture-free bottles, or in accordance with information supplied by manufacturers or other suppliers.

6.3 Procurement of chemicals

Chemicals and reagents must be purchased from reputable suppliers and checked against agreed quality criteria. Procedures should be available covering all aspects of purchase as indicated in Section 7.1.

6.4 Safe handling and storage

No chemical should be handled without clear knowledge of the material hazards. For particularly toxic materials, laboratory protocols should be available and followed covering each particular use to which the chemical is put.

Toxic and volatile materials should always be handled in fume hoods. Appropriate rubber or neoprene gloves must always be worn, together with approved safety spectacles and laboratory coats or overalls. Good quality footwear should be worn, and no open-toe sandals.

All chemicals must be stored in secure, temperature controlled areas, with good lighting and ventilation, in accordance with prescribed storage conditions and local safety regulations. Flammable materials should be kept in fire-proof cabinets, both in general stores and in the laboratory.

6.5 Waste disposal

Laboratory staff must have a good knowledge of local waste disposal legislation, and procedures must be strictly followed.

Waste materials, including solvents and other organic matter, should be collected and stored in suitable containers, and sent for appropriate, safe disposal or treatment. Liquid waste containing chlorinated solvents must be kept segregated, to avoid potential exothermic reactions and allow separate disposal or incineration.

The wastewater from laboratory sinks should pass to an appropriate water treatment system.

7. Operational procedures for quality control

7.1 Procurement of materials and services

It is important that purchased materials and services meet the overall requirements of the laboratory. This will require:

- an up-to-date list of all approved suppliers
- a process for the approval of new suppliers
- a process for receipt of certificates of conformance or analysis
- a system for dealing with substandard materials or services.

Examples of materials are:

- laboratory reagents
- laboratory equipment and consumables
- labels
- software.

Examples of services are:

- external maintenance and calibration
- cleaning contractors.

7.2 Sample registration and traceability

It is vital that the laboratory has an area where incoming samples are received and logged. Samples must be clearly labelled, and a sequential reference number must be added.

This number is the key identifier for the sample as it progresses through the various work locations in the laboratory, and enables the sample to be tracked at all times.

When work is complete, records filed and results dispatched, samples may be stored in reference number order, for easy retrieval and to ensure traceability of data.

Laboratories may increasingly use computerized laboratory information management systems, with bar coded samples, such that information (as raw data) from all stages of analysis can be automatically recorded and used to

compile final results sheets and reports, following comparison of each set of data with appropriate specification limits.

7.3 Analytical and physical test method and validation

The laboratory must have available the full range of validated test methods as controlled documents. These may be generated and validated in-house, but at least should be based on appropriate CIPAC or AOAC procedures. It is recommended that, wherever possible, methods used should have been demonstrated to be sufficiently robust, through collaborative study, and for referee purposes. CIPAC or AOAC approved methods should be used exclusively—or ASTM methods for some physical characteristics.

Where it is necessary to develop in-house procedures, these should be carefully validated, in accordance with generally accepted validation schemes (e.g. the Sanco Document 3030)[9] before being applied to test samples.

It is strongly recommended that where methods are to be applied for the first time in the laboratory, or by an operator who is unfamiliar with the procedure, a previously analysed sample should be checked in replicate, to ensure adequate accuracy and precision.

Where impurity profiles of technical materials are being determined, it is important that methods should include details on the use of blanks and spiked samples, to check for possible interference, and on levels of recovery, which should be carefully defined. Such checks must be carried out prior to analysis, and the recovery and other defined criteria fully met.

7.4 Product specifications

In most cases, products should be checked against the appropriate specification, either provided by the manufacturer or the WHO or FAO specification. If none of these is available, it is essential that appropriate tests be applied, as indicated for each product type in the *Manual on the Development and Use of FAO and WHO Specifications for Pesticides*.[10] An indication of acceptable ranges for some of the standard tests may be found within this document, or by referring to FAO and WHO specifications for similar product types. Alternatively, specifications provided by reputable manufacturers may be used.

7.5 Special laboratory procedures

In addition to the test methods described earlier, laboratories will require standard operating procedures for all key activities undertaken, which should be held as controlled documents. In particular, procedures will be required to cover the following:

- sample receipt, handling and storage, including use of expiry dates;
- calibration programme and check requirements on specific instruments;
- procurement, storage and use of analytical standards and other calibration materials;
- storage, use and disposal of reagents and test solutions (including control of expiry dates);
- equipment cleaning protocols;
- selection of new equipment and suppliers;
- procedures for data processing and storage of electronic information;
- maintenance programmes and procedures;
- standard operating procedures for all laboratory equipment.

Careful management of all samples and stock solutions is vital, with good labelling and strict adherence to shelf-lives.

It is also important for laboratories to develop and document procedures for dealing with disputes concerning analytical data, rather than operating on an ad hoc basis. Rapid resolution can often be achieved by dialogue between laboratories, sharing of information and data, and where appropriate retesting and swapping of samples.

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