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Formulation of an Audit System for Testing Laboratories Under the Requirements of EN ISO/IEC 17025:2000

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ABSTRACT

According to the fish export regulations published by the government of Sri Lanka, an approval complying with the applicable requirements of the standard ISO/IEC 17025:2000 is mandatory, when obtaining the services from the testing laboratories.

The objective of this project was to formulate an audit system for evaluation of testing laboratories by studying the criteria considered under the Intentional Standard EN ISO/IEC 17025:2000.

A common technique to guide an audit is by completing an evaluation list, which addresses all components of the system. Therefore, to formulate the audit system for testing laboratories, a checklist was constructed with a scientific base. The criteria for the checklist was established as clearly and unambiguously as possible, by analysing the pinpoints or critical control points for the management and technical requirements of the standard through literature review and by studying the quality system of an established chemical laboratory. Furthermore, a path for analysing histamine in fish, using High Performance Liquid Chromatography was observed by following a practical sample, from arrival at the chemical laboratory until the result report was issued. Vital knowledge gained for that part of the process is by personal communications and by comparison of the critical control points found in theory and practice. For the analysis of critical control points, a logical decision tree was used along with some practical experience. The identified critical control points and their elements were used to establish the criteria for the audit checklist.

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1 INTRODUCTION

1.1 General

The total fish production in Sri Lanka has increased by about 65% or just over 12,000 Mt over the last decade. The fish exporting industry has become a good source of foreign exchange earning in Sri Lanka now. In 2000, foreign exchange earnings from fish and fishery products doubled to approximately 10 billion Rupees, which is over 100% increase compared to the previous year earnings. Japan is the main market for Sri Lanka's shrimp/prawn and tuna exports. European Union countries, USA and other non-EU countries are among other major importers of Sri Lanka (NARA 2001). Exporting countries must comply with the requirements of the importing countries.

1.2 Fisheries and quality control

In accordance with the European Union legislation the Fishery Product Quality Control Unit was established under the Department of Fisheries and Aquatic Resources in Sri Lanka in 1999. This unit has been operating since January 1999 to fulfil the European Union requirements. The main objective of the unit is to ensure that the fish products exported meet the international standards through the enforcement of the Fish Product (Exports) Regulations 1998, made under the Fisheries and Aquatic Resources Act. The Fishery Product Quality Control Unit is responsible for the approval of fish processing establishments, regular inspections of fish processing establishments processing fish for export, inspection of landing sites and fishing boats including official sampling of products, water and ice, issue of health certificates for consignments of fish/fishery products exported, approval of testing laboratories from which the services are obtained to the fisheries sector and monitoring of chemical residues in farmed shrimps etc. As a whole, the Fishery Product Quality Control Unit is responsible for the quality and safety of the fish and fishery products exported from Sri Lanka (NARA 2001).

In Sri Lanka, the laboratories conduct chemical and microbiological analysis of fish products, processing water and ice for the fishing industry. In addition to that, the microbiological analyses of swab samples are also carried out for the verification of the cleanliness of the production environment. Among the chemical parameters, histamine is an important parameter in the laboratory analysis of fish products in the sense of safety aspects. Many samples of tuna fish (one of the main exporting fish species in Sri Lanka) are tested for histamine, under the official and processing control systems annually, although the cost of analysis is very high. The recommended test method principle used for the analysis of histamine by regulations is the High Performance Liquid Chromatography (HPLC). Furthermore, the analysis of histamine for certain fish species including tuna is mandatory according to the fish export regulations in Sri Lanka (Sri Lanka 1998).

1.3 Approval of testing laboratories

Fish importing regulations, especially those set by the European Union require the use of accredited testing laboratories approved and evaluated by the relevant Competent Government Authorities responsible for the export inspection. These official evaluations are for the purpose of checking and ensuring the adequacy of required control systems (The European Commission 1991 and 1994).

Accreditation is the "formal recognition that a testing laboratory is competent to carry out specific tests or specific type of tests" (The International Organization for Standardisation 1996). The practical meaning of accreditation can be defined as recognition and acceptance of test data across national boundaries, reduction of re-testing, and an increase of opportunities in international trade by mutual acceptance of laboratory test results.

Approval of accredited testing laboratories performing the analyses for the fisheries sector is mandatory according to the regulations that are published by the government of Sri Lanka. These laboratories shall be evaluated from time to time within a specified time period decided by the Competent Authority for export of fish products (Sri Lanka 1998 and 2002).

The Department of Fisheries and Aquatic Resources is the Competent Authority for fish products in Sri Lanka. It has already approved the laboratories for testing of fish products under the provisions of the Fish Product (Exports) Regulations 1998, the national regulation for the exporting fish products and the amendment to the regulations 2002. These laboratories fulfil the applicable requirements of ISO 17025 and have already been accredited by the certified accreditation bodies (Sri Lanka 1998 and 2002).

To check the conformance to necessary requirements, the Department of Fisheries and Aquatic Resources has to carry out the annual evaluations of these approved laboratories. The Fishery Product Quality Control Unit of the Department of Fisheries has become responsible for these evaluations now. Therefore, the findings of this project will be beneficial for this responsibility as well as for the other related work of the Division/Department.

The International Standard EN ISO/ IEC 17025:2000 “The General Requirements for the Competence of the Testing and Calibration Laboratories” is used as a guiding tool, when carrying out periodic evaluations for confirmation and recognition of the competence of approved testing laboratories, as well as for the accreditation purposes (The European Committee for Standardisation 2000).

With the previous criteria in mind, the aim of the project is to formulate an audit system for the evaluation of testing laboratories. Identification of the Critical Control Points of an established quality system, by studying the steps throughout the analysis of histamine (a one of the important parameters concerned in the laboratory analysis of fish products), using the High Performance Liquid Chromatography was used as a practical example.

In this project the special focus will be on parts of the standard that concern their direct relationship with the test result.

Furthermore this project is basically focused on the testing laboratories which have alredy been accredited. Therefore when formulating the audit system it was assumed that the laboratories fulfil all the basic requirements concerned by an accreditation body. Although the whole laboratory system is discussed throughout the project, the audit system comprised only with the neccessary critical control points directly influence the proper functioning of the system.

2 LITERATURE REVIEW

2.1 General requirements of the EN ISO/IEC 17025:2000

The International Standard EN ISO/IEC 17025:2000 specifies the necessary requirements that a testing or a calibration laboratory should have, if they intend to demonstrate that they are operating according to a quality system. This International Standard has been introduced as the result of the revisions to the ISO Guide 25 and the EN 45001 respectively. (The European Committee for Standardisation 2000).

According to the standard EN ISO/IEC 17025:2000 certain management requirements shall be fulfilled by the laboratory under the sub clauses of the standards such as;

1. Organization, quality system and document control
2. Review of requests tenders and contracts
3. Sub contracting of tests and calibrations
4. Purchasing services and supplies
5. Services to the client
6. Complaints
7. Control of non-conforming testing and calibration work
8. Corrective action and preventive action
9. Control of records, internal audits and management reviews

The standard has some specific technical requirements that the laboratory has to fulfil to be able to prove their technical competence. The tests and/or calibrations must be in compliance with the sub clauses of the standard such as:

1. General requirements
2. Personnel, accommodation and environmental conditions
3. Test and calibration method
4. Method validation
5. Equipment
6. Measurement traceability
7. Sampling, handling of test and calibration items
8. Assuring the test and the calibration results
9. Reporting of results, to demonstrate their capability.

2.2 Quality system for testing laboratories

There are certain basic elements that need to be considered for a laboratory quality system (Garfield 1992). These elements are:

1. Organization, quality policy and quality system
2. Personnel
3. Premises
4. Equipment
5. Purchasing services and supplies
6. Document control
7. Traceability
8. Internal Audits
9. Corrective actions
10. Customer complaints

These basic elements play a major role to ensure the overall quality of the laboratory and the test or calibration result it produces. When taking into consideration each element in detail, it is obvious that these factors are the functional properties of the laboratory body. Below is a brief description on what is required by the standard EN ISO/IEC 17025 (2000) for the elements concerned above. The requirements were clarified using the Nordic Committee on Food Analysis (1994) whenever necessary.

1) **Organisation, quality policy and quality system** – To carry out the testing or calibration work complying with the required recognised standards, as the basic organisational requirement, the laboratory shall have obtained accreditation from a recognised accreditation body. Furthermore the organisational structure must be documented and the responsibilities of each employee must be clearly identified. This is to ensure that the laboratory performs testing correctly. This includes the managerial and technical personnel with the necessary authority to attend to the quality system. Furthermore the laboratory shall have an appointed person responsible for the quality assurance. When concerning the quality policy, the laboratory's objectives and commitment to maintain and implement a quality system shall be clearly defined in the system's documentation (Quality Manual).

2) **Personnel** - The laboratory management shall employ personnel with necessary knowledge and experience. The management shall ensure the competence of all the employees who carry out specific tasks (e.g. operating equipment, perform test and/or calibrations, evaluate results, and sign the test reports and calibration certificates). The management of the laboratory must take the responsibility that the competence of the personnel is kept up to date by relevant training. Personnel performing the specific tasks shall have enough qualifications in the field of education, training and experience etc. Furthermore there must be sufficient staff during holidays and in case of illness, especially for the microbiological laboratories.

3) **Premises** – To perform laboratory work analytically correctly and reliably the laboratory should have appropriate and sufficiently spacious premises. The premises should be arranged in such a way, which facilitate good house keeping and minimises the transportation within the laboratory (e.g. people, sample, media etc.) while carrying out the work procedures.

All working surfaces and floors must be constructed with materials that are easy to clean.

The premises must be well lit. The general light intensity must be at least 5oo Lux. But the light intensity requirement depends on the nature of the work carried out at each work area.

The laboratory premises must be well ventilated. The ventilation shall be balanced and constructed in order to prevent draught and dust formation and spreading of fungal spores and other micro-organisms. In microbiological laboratories air of the laboratory must be regularly monitored (once a month). Installation of UV lamps or efficient air filters may be necessary. Concerning the microbiological laboratories the ventilation system must be constructed in a way, which prevents the passage of air to adjacent premises.

The laboratory must be provided with sufficiently large cold storage or freezer facilities for storage of samples, media and solutions according to requirements. The storage facilities must be arranged to provide separate storage spaces for different items.

The laboratory must have separate areas for cleaning of glassware and other utensils, sterilisation purposes, preparation of media, storage of chemicals and for the work with particularly virulent materials (e.g. infectious micro-organisms).

Microbiological and chemical work should be carried out in separate rooms. Unauthorised persons should not be allowed to enter the premises.

There should be changing rooms /or changing places attached to the laboratory to prevent the cross contamination through outside clothes.

4) **Equipment** – The laboratory shall be furnished with the instruments, glassware and other equipment required for the work to be carried out. The reliability of the test results is greatly affected by the standard of the equipment used.

The equipment shall be calibrated or checked before being put into service. The equipment should be placed in appropriate places of the laboratory, accessible for easy cleaning.

All the major apparatus/equipment shall have authorised personnel appointed by the laboratory.

All the equipment in the laboratory should have defined requirements on accuracy, and there must be a programme for routine maintenance, checking and calibration of the equipment with decided frequency.

Instruments should be checked at least at the start and at the end of the analytical series.

The results must be documented in the records of the equipment after each check.

5) **Purchasing services & supplies** – There should be established procedures for the purchase, reception and storage of reagents and other laboratory materials as well as for services. The purchased items should be further checked for the compliance with the required standards. The records should be kept available for the verification purposes.

6) **Document Control** – There should be an established document control system. According to the standard these documents include regulations, standards, other normative documents, test and or calibration methods, drawings, software, specifications, instructions and manuals.

All the quality system documents need the approval for use by the relevant authority.

Quality system documents of the laboratory shall reflect the document path and the reliability.

The laboratory shall have the procedures for handling of quality and technical records.
Concerning control of data, there should be procedures for calculations and data transfers. The medium for handling of data should be identified with the suitability and integrity.

7) **Traceability** - Concerning the technical data the laboratory shall maintain records within a defined time period. These include the original observations, derived data and sufficient information to establish an audit trial, calibration records, staff records and copy of each test report or calibration certificate etc.

It is important that all major data on the analytical activities are documented in a way that analysis can be performed again under conditions as similar as possible to the original.

All the readings and calculations must be clearly and legibly noted using permanent pens. The documents should be signed and dated.

If any alterations are done to the records they shall be signed by the person responsible for the correction/change. Concerning the electronically stored records suitable preventive measures shall be taken to protect the data.

Primary data such as delivery notes, receipt of samples, sample pre-treatment, notes on important part of the determination etc. and the analytical report must be kept filed.

All the documents should be arranged in a way so as to enabling the related documents can be traced back from the analytical report to the original receipt of the sample at the laboratory.

8) **Internal audits** – For the verification of the activities related to the quality system, the laboratory shall carry out internal audits based on a decided frequency and established procedures.

This internal audit programme shall be handled by trained and qualified personnel and shall address all the elements of the quality system.

9) **Corrective actions** – The corrective action procedures shall be established with the personnel responsible for implementation.

The procedures for corrective action shall be followed by an investigation to determine the causative reason for the deviation.

This involves analysis of plausible causes and identification of potential corrective actions for where such actions are needed.

After implementation, the results of the corrective actions should be monitored to check the effectiveness.

10) **Customer complaints** – The laboratory shall have standard procedures for the handling of complaints. Records of the all complaints, investigations and the relevant corrective actions taken by the laboratory should be recorded and maintained.

The proper functioning and monitoring of the above key components must be evaluated from time to time to ensure the continuous compliance to the required standards.

2.3 Quality control system for the equipment

The quality control system for the equipment is also an essential part of the laboratory quality assurance system.

That would include that all the equipment be entered into the laboratory's preventive maintenance programme, ensuring, as far as possible, that the equipment is operating

with the reliability required. The actions include specification checks, calibrating, cleaning, lubricating, reconditioning, adjusting and testing.

Therefore, after approval for usage each piece of equipment should be entered into the inventory of the laboratory and the schedule for preventive maintenance. It includes necessary components that would ensure the required quality control of the equipment.

Inventory – The permanent inventory record shall be established for each piece of equipment and the software significant to the test and/or calibration performed. This inventory record shall include:

Name of the item
Model number
Serial number
Manufacturer name and address
Date checked against specifications
Date placed in service
Cost of the item
Laboratory location and, if available, manufacturer instructions.

Definition of service tasks – For each piece of equipment quality assurance performance checklist shall be maintained. This should be a bound book and can be kept near the equipment or in a suitable location. These records included:

Name of the item
Frequency of necessary services
Standard reference materials or other materials to be used
Any damage or malfunction or repair to the equipment
Date of breakdown
Date of return to service etc.

Interval establishment – The frequency for the service and calibration work to be carried out must be clearly established and recorded. The frequency depends on the type of equipment, supplier recommendations, maintenance conditions and servicing history, extent and severity of use, age, tendency of the item to wear or drift, environmental conditions (ambient temperature, humidity, vibrations etc.) and the quality of the measurement sought. The way checks are made, the information (e.g. results, acceptance criteria etc.), the name of the person carrying out the checks, and date and the due date of the next calibration should be recorded.

Personnel assignment monitors – The responsible person and their alternates shall be assigned for preventive maintenance duties for each piece of equipment to ensure their duties are performed as per scheduled programme.

Special instructions – If special items such as special monitoring devices, techniques, materials and/or piece of equipment are required for checking the performance of equipment, that must be mentioned in the notebook to facilitate the maintenance of the supporting devices along with the main piece.

Training – A programme should be established for the training of personnel in the performance of difficult maintenance and repair tasks.

Operating the system – To make sure the preventive maintenance jobs are carried out as scheduled, a reminder scheme must be established to notify the monitors in advance.

Records and documentation – After completing the maintenance task, records should be documented in the appropriate notebook.

Surveillance – a responsible person must carry out a review of "recording notebooks" periodically to ensure the proper monitoring of the preventive maintenance work. Their reviews must also be recorded (Garfield 1992, The European Committee for Standardisation 2002).

2.4 Quality control system for histamine

2.4.1 Formation of histamine in fish and its importance

Histamine is a biogenic amine included in the category of Scombrotoxin. This toxin forms as a result of microbial activity due to time/temperature abuse of certain species of fish and can cause consumer illnesses. Scombroid poisoning illnesses are most closely linked to the development of histamine in the fish. In most cases histamine levels in illness-causing fish have been above 200 ppm, often above 500 ppm. However, there is some evidence that other chemicals (e.g. biogenic amines, such as putrescine and cadaverine) may also play a role in these illnesses. Histamine poisonings have primarily been associated with the consumption of tuna and other marine fish such as mahi mahi, and bluefish. However, there are some other species that are also capable of developing elevated levels of histamine when temperature abused (FDA 2001).

Histamine or scombroid fish poisoning is among the top three seafood-related public health problems reported in the United States. Epidemiological data from Hawaii between September 1989 and September 1999 indicate that mahi mahi and tuna were the leading fish species implicated in illnesses due to histamine poisoning at 54% and 25% respectively. Imported "seafood" was responsible for 48% and imported mahi mahi was responsible for 45% of the total number of illnesses (Kaneko 2000).

Certain bacteria produce the enzyme histidine decarboxylase during growth at high temperatures. The enzyme reacts with free histidine, a naturally occurring substance (amino acid) presents in large quantities in some fish. The result is the formation of histamine (FDA 2001).

2.4.2 Safety aspects and control

Formation of histamine is accelerated with the temperature increase of the product. Although histamine-forming bacteria are able to grow within a wide range of

temperatures, they grow rapidly at high-abuse temperatures (e.g. around 21°C). The growth at moderate-abuse temperatures (e.g. around 7°C) is relatively slow comparing to the growth at high temperature. When the temperature of the product is around 32°C, the bacterial growth is quite high. It is very clear that the histamine development occurs mainly as a result of high temperature spoilage. However, the opportunity for formation of histamine at moderate abuse temperatures is also considerable (FDA 2001).

After formation of the enzyme histidine decarboxylase, it can produce histamine continuously even though the bacteria are not in an active stage. This enzyme has the ability to activate at or near refrigeration temperatures. Even at frozen conditions this enzyme can remain stable. After thawing the frozen product, the enzyme is reactivated and continues rapidly to produce histamine. When concerning the preservation methods, it is clear that freezing can inactivate the enzyme forming bacteria while cooking can inactivate both bacteria and the enzyme it self. Once histamine is formed, it cannot be eliminated by the above preservation methods such as heat treatment (including retorting), freezing or by any other method. However for the cooked fish products it is necessary to re-contaminate the product with the responsible bacteria for the formation of additional histamine. Therefore, development of histamine is more likely to occur in raw and unfrozen fish (FDA 2001).

The bacteria associated with histamine development are commonly present in the marine environment. They naturally found on the gills and in the gut of live, marine fish. At this stage these bacteria do no harm to the fish. Upon death, the defence mechanisms of the fish can no longer inhibit bacterial growth, and histamine-forming bacteria start to grow and produce histamine. Evisceration and removal of the gills in a sanitary manner can reduce, but not eliminate, the number of histamine-forming bacteria. However, if the evisceration /gilling and gutting is carried out under unhygienic conditions, it may accelerate the development of histamine in the edible portions of the fish by spreading the bacteria to the flesh of the fish (FDA 2001).

Morganella morganii is the main contributor to histamine formation in fish. Because of its prevalence it can produce high level of histamine. The potential for histamine formation is increased when the flesh of the fish is directly exposed to the enzyme-forming bacteria. This occurs when the fish are processed (e.g. filleting). Any exposure time above 4.4°C significantly reduces the expected shelf life. For this reason, fish that have not been previously frozen should not be exposed to temperatures above 4.4°C for more than 4 hours. Extended frozen storage (e.g. 24 weeks) or cooking minimises the risk of additional histamine development by inactivating the enzyme-forming bacteria and, in the case of cooking, the enzyme itself. As previously mentioned, recontamination with enzyme-forming bacteria and significant temperature abuse is necessary for histamine formation under these conditions. Such recontamination may not be likely to occur if the fish is processed under proper hygienic conditions (FDA 2001).

Because of this, processing control systems require the proper preventive measures to control further formation of histamine during processing and until dispatch. This

includes a control system for required factors, monitoring and verifications to check the effectiveness. These verifications include in house and external laboratory testing of the product.

2.4.3 Detection of histamine

Chemical testing is used for the detection of histamine in fish flesh. The design of the sampling plan also affects the validity of this analysis. The amount of sampling required to accommodate such variability is large. For this reason, chemical testing alone will not normally provide adequate assurance for the controlling of this chemical hazard. The reason is that, generally histamine is not uniformly distributed in spoiled fish. Therefore, 50 ppm has been set as the guidance level and, if 50 ppm is found in one section, it is considered that there is a possibility of exceeding 500 ppm in other sections. In addition to that, it is also reasonable to assume that, without proper controls during refrigerated (fresh chilled) transportation between suppliers/processors, scombrotoxin-forming fish species will contain unsafe levels of histamine upon receipt by the final processor. However, these conditions are not similar for cooked or frozen fish or fishery products (FDA 2001).

Chemical compounds can be analysed at various levels of accuracy. The level of accuracy depends on the method used. Selection of a test method principle for a particular kind of analysis depends on various factors. This can be the actual need for accuracy, time limits, technical skills required, the cost, availability of reagents and/or equipment used. For the analysis of histamine there is no simple, inexpensive, but highly accurate method. Regulatory authorities require a very accurate measurement to make necessary decisions on product safety. For this purpose costly and sophisticated analytical equipment is required. However, routine in-plant monitoring systems can use low cost and simpler techniques with less accuracy (Pan and James 1985). At testing laboratory level, HPLC (High Performance Liquid Chromatography) is widely used to detect histamine in fish as the most accurate method principle.

2.5 Critical Control Points

The requirements that laboratories need to fulfil are explained in detail in the international standard EN ISO/IEC 17025:2000. For auditing purposes the abstract or pinpoints of the each requirement should only be considered. For this purpose the Critical Control Points (CCPs) of each requirement should be analysed. Control of these points is necessary for the reliability of the test result.

Although Critical Control Points are most often used in HACCP systems (Hazard Analysis and Critical Control Point systems) in the food industry, they can also be applied for the other systems.

Hazard Analysis and Critical Control Point System is always a safety assurance system, although this method can also be applied to the laboratory quality system.

Critical Control Point is a point, step or procedure at which control can be applied and a hazard to the safety of the output can be prevented, eliminated or reduced to an

acceptable level (Dillon and Griffith 1996). At this point, step or procedure, the control or the requirement in place is essential.

A control point (CP) is a point at which the lose of control at the same point does not cause a significant effect or it is controlled by prerequisite programmes.

A simple logic tree is shown in Figure 1, which is used to distinguish between a control point and a critical control point.

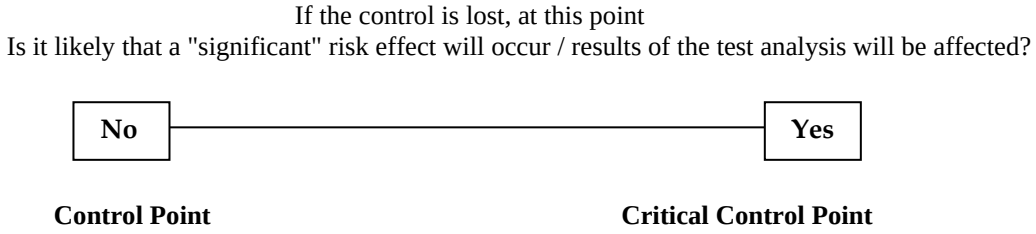
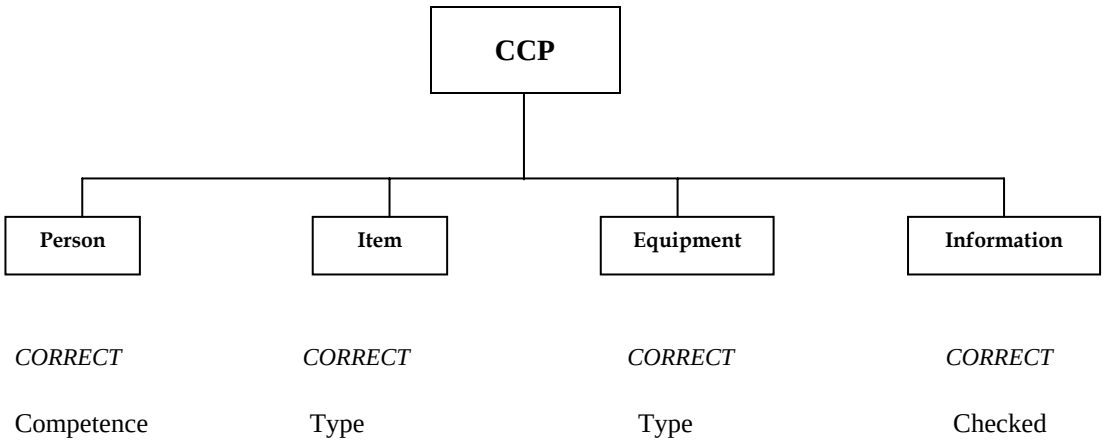


Figure 1: Simple logic tree, to distinguish between critical control points and control points.

The common technique to guide the audit is to complete an evaluation checklist. The checklist for the audit should focus on the critical control points. The auditor must consider all parts of the process when constructing a checklist. A critical control point can consist of up to four elements (Figure 2) and they are:

Person – someone to perform or supervise the task
Item – something to work on
Equipment – tools and facilities
Information – software or knowledge received or generated



Training	Condition	Condition	Content
Identification	Capability	Capability	Edition
Motivation	Quality	Identification	Condition
	Identification	Location	Identification
			Distribution

Figure 2: Elements of a critical control point that can be used to guide the auditor to find the key activities in a critical control point (Dillon. and Griffith 1996).

2.6 Proficiency testing

Validation of results is an important control step of the laboratory quality assurance programme. It provides a check on the laboratory's analytical results. This check is an extra check in addition to the daily monitoring programmes. Result validation or proficiency testing is a systematic programme. In this programme samples of known composition are analysed to evaluate the laboratory's ability to perform the analyses at an acceptable level of competence. These proficiency tests include both intra-laboratory and inter-laboratory sample examinations (Garfield 1992).

2.6.1 Intra-laboratory proficiency testing

Intra-laboratory proficiency testing is conducted for the periodic assessment of the performance of individual analysts and the overall laboratory. This testing programme helps to establish a record of instrument, performance, demonstrate and prove the reliability of analytical methods, detect training needs and reveals the need for upgrading the laboratory quality system. Intra-laboratory performance testing consists of the examination of check or reference, “blind” or “double-blind” samples, and extensive use of primary and secondary standards. A "blind sample" is a sample whose composition is known to laboratory management, but unknown to the analyst. With a “double-blind sample”, the analyst doesn't know the composition of the sample or whether it is a check sample to evaluate the analyst. The double blind sample is sent to the analyst as a routine sample. This is very important to evaluate the true quality of the system (Garfield 1992).

2.6.2 Inter-laboratory testing

The inter-laboratory proficiency testing has a number of advantages. Inter-laboratory test programmes can be defined as proficiency tests, inter-laboratory surveys, check samples, or round robin programmes (ring tests). In these programmes, samples are distributed for analysis to laboratories by external organisations. The inter-laboratory test programmes are held most of the times as voluntary participation programmes. This kind of programme is for instance used as part of a system of laboratory accreditation or certification, to estimate the accuracy and precision of results between laboratories, or to upgrade the overall quality of laboratory performance. (The purpose of the inter-laboratory programme can vary, but is always stated in the documents of the sponsoring organization).

Government agencies also conduct another form of inter-laboratory testing for the accreditation of laboratories. For this purpose, considering the result of the government laboratory as standard, the split samples are analysed by both the government lab and the laboratory seeking accreditation. Maintaining the quality control charts for the laboratory and individual charts for analysts are also considered requirements. This testing is the part of the accreditation. Collaborative testing is used as a special form of inter-laboratory proficiency testing to evaluate the performance of a method. For this purpose carefully prepared homogeneous samples are analysed under actual working conditions in several labs. This is to confirm whether the method is a reliable one (Garfield 1992). A description on how to make a control chart is in Appendix II.

3 METHOD

The audit system is based on finding the critical control points in theory and in practice, throughout the whole chain from the arrival of the sample until the result has been reported. It is important to distinguish between critical control points and other points in the chain (receiving of the sample to result report) in order to make the system efficient but not unnecessarily complicated.

3.1 Data collection

Using the information gathered and summarised from the literature review the basic laboratory system was studied. All the necessary components of the laboratory quality system were clarified by personal communication with experts.

The procedure used for analysis of histamine in one of the chemical laboratories of the Icelandic Fisheries Laboratories in Reykjavik was observed in practice. Further information was collected from practical observations, method description followed by the Icelandic Fisheries laboratory and from the NMKL (NORDISK METODIKKOMMITTE FOR LIVSMEDEL = Nordic Committee on Food Analysis) guidelines. Based on the above information, a test method description was written on analysis of histamine. In Appendix I is a draft to a document that includes a format with all the necessary information for a method description of histamine analysed by HPLC.

3.2 Identification of the critical control points

3.2.1 Testing laboratory and organization

To check compliance with the standards by the laboratory and for evaluation purposes, the critical control points of the each requirement should be identified in theory. Therefore, the focus is on the management part and the technical part because they are the vital parts to be fulfilled in the standard. In this context critical control points for each requirement coming under the standard was identified.

3.2.2 Test method

When considering the requirements specified in the standard for the testing and calibration laboratories, all requirements are to produce technically valid data and results. That means each and every test method is followed by the specified requirements automatically from arrival of the sample until the final results are issued, in an established quality system. Therefore, to study the application of the requirements and to identify the critical control points of an established laboratory system in practice, one whole chain of a sample path was studied in Iceland. A fish sample arriving at the chemical laboratory of Icelandic Fisheries Laboratories in Reykjavik for the analysis of histamine was used as an actual sample to follow the steps.

3.3 Comparison of theoretical system to actually working system

Critical Control Points analysed for the requirements in theory were compared with the critical control points observed for the actual working system. For this purpose, each and every critical control point analysed for the requirements in theory was discussed with its relevant practical application. The critical control points identified throughout the sample path in the test method for histamine was used as practical points. Whenever necessary the critical control points identified in the requirements in theory were elaborated and made more understandable and specific, using the practically identified critical control points. Confirmed critical control points were included in the audit checklist.

4 RESULTS

1.1 The critical control points in theory

As stated earlier, when identifying the critical control points, only the most distinguished parts of the requirements, which can cause significant risk to the test results, were taken into consideration. All the critical control points of concern to an accreditation body, when obtaining the accreditation are not considered here for this purpose.

4.1.1 Management requirements

The following numbers will be used according to their placement in the standard.

Paragraph 4.1 Organisation
Although the laboratory shall have particular legal requirements for accreditation purposes, here, as the main organisational requirement, the laboratory shall have obtained accreditation from a recognised accreditation body. Furthermore it should have the organisational structure with defined responsibilities of the personnel.

***CCP_1*:** Valid document of accreditation
***CCP_2*:** Organisational structure with clearly defined responsibilities

Paragraph 4.2 Quality system
Regarding the quality system requirement, the laboratory shall have a quality system document addressing all the required elements of the system. The appropriate personnel shall implement the document. The personnel responsible for appropriate chapters must be made aware.

***CCP*:** Approved Quality Manual

Paragraph 4.3 Document control
The laboratory, as the part of its quality system, shall establish and maintain the procedures for the document control. In this procedure each task shall be clearly identified (Figure 3).

***CCP_1*:** Identified suitable formats for each document category
***CCP_2*:** Defined responsibilities for preparation of each type of document
***CCP_3*:** Issuing authority
***CCP_4*:** Responsible person for maintenance and storage
***CCP_5*:** Traceably records for the required documents

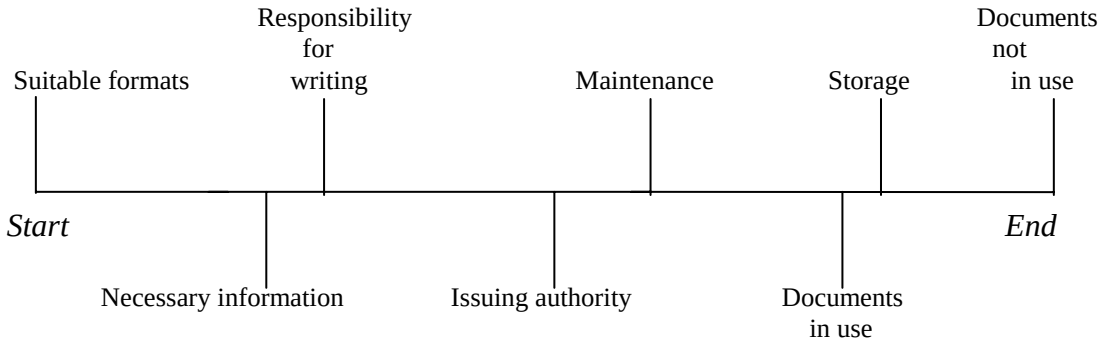


Figure 3: Lifetime of documents. This shows the path of a document from its origin until disposal.

Paragraph 4.4. Review of requests, tenders and contracts
Procedures for the review of requests, tenders and contracts shall be established and maintained by the laboratory. Each contract shall be acceptable both laboratory and to the client.

***CCP*:** Agreement between the lab and the customer

Paragraph 4.5. Subcontracting of tests and calibrations
When the laboratory subcontracts work whether for unforeseen reasons or on a regular basis, the subcontracts shall be given to a competent subcontractor. The subcontractors should comply with the required standards.

***CCP_1*:** The established criteria for the selection of subcontractors

***CCP_2*:** Selection responsibility; the responsible person for the judgement
***CCP_3*:** Records of the evidence of competence
***CCP_4*:** Register of all sub contractors

Paragraph 4.6. Purchasing services and supplies
The laboratory shall have the procedures for purchasing services and supplies to maintain and ensure the quality of the purchased supplies, reagents and consumable material that affect the quality of the tests.

***CCP_1*:** Criteria for purchasing of services
***CCP_2*:** List for the required standards and list of reliable sources
***CCP_3*:** Checking system at the receipt, record keeping system and availability of such records

Paragraph 4.7. Service to the client
The responsibility of the laboratory is to provide good co-operation and ensure the confidence. Affordability to clarification of the request and reasonable access to relevant areas for witnessing of work performed is also important.

For this requirement there is no critical control point.

Paragraph 4.8. Complaints
There should be a policy and established procedure for action on customer complaints. Customer complaints are very important feedback, which can be used to improve the quality system of the laboratory. A chart showing the handling of customer complaints is shown in Figure 4.

***CCP_1*:** The designated personnel responsible for handling the complaints
***CCP_2*:** Recording at the date of receipt
***CCP_3*:** Keeping records or documents of the complaint
***CCP_3*:** Records of date of the investigation
***CCP_4*:** Records on date and the corrective action taken

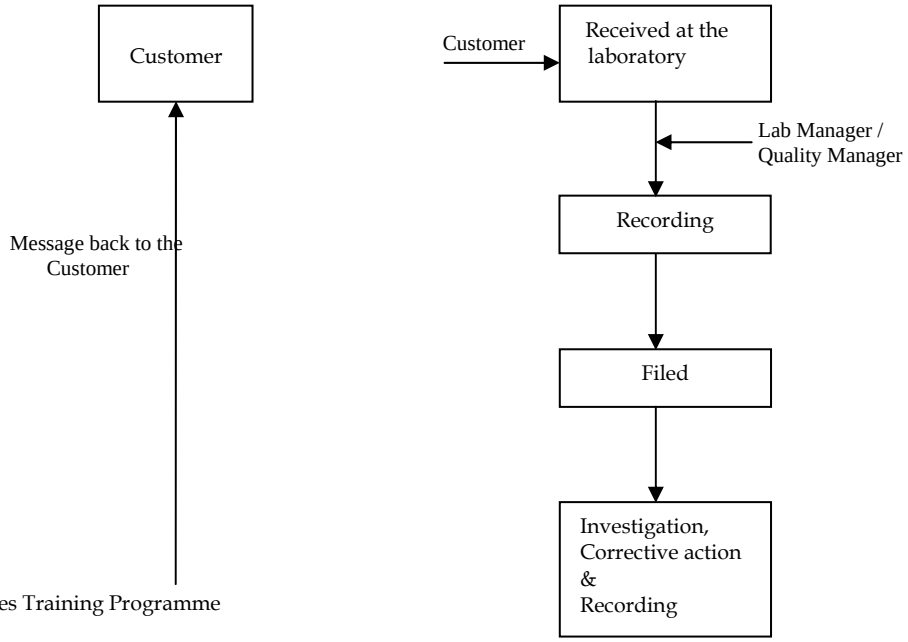


Figure 4: Customer complaint path, which shows the handling of the complaints ending in an improvement of the quality system and response to the customer.

Paragraph 4.9. Control of non-conforming testing and/or calibration work
Procedures for the control of non-conforming work according to the significance shall be available. These procedures are used whenever deviations of procedures or client requirements are observed.

***CCP_1*:** Previously identified non-conforming work
***CCP_2*:** Designated personnel for the management
***CCP_3*:** List of well-defined actions

Paragraph 4.10. Corrective action &
Paragraph 4.11. Preventive action
When concerning corrective and preventive actions, the laboratory shall have an established policy and procedures for the corrective actions when non-conforming work or departures from the policies and procedures in the quality or technical operations have been identified. There shall be established preventive actions for the identified potential sources of non-conformances in the technical and quality system. Preventive measures are for the initiation before the deviation is occurred.

CCP_1*:* Properly identified root causes
***CCP_2*:** Identification of the relevant corrective or preventive measures
***CCP_3*:** Person responsible for the implementation
***CCP_4*:** Records of the action taken / initiation of actions including the dates and time
***CCP_5*:** Evidence ensuring the effectiveness
Paragraph 4.12. Control of records
The laboratory shall have the procedures for the control and traceability of quality and technical records including identification, collection, indexing, access filling, storage, maintenance and disposal etc. These records include the records on quality matters, original observations, records for each test or calibration, staff records and copies of each test or calibration certificates issued etc.

***CCP_1*:** Responsible personnel for maintenance
***CCP_2*:** Storage system ensuring the protection, security and traceability
***CCP_3*:** Disposal system

Paragraph 4.13. Internal audits
To check compliance to the requirements continuously and for verification purposes the laboratory shall carry out internal audits according to a predetermined schedule

and procedures. A trained and qualified person, who is independent to the activity to be audited, shall carry out these audits.

***CCP_1*:** Latest internal audit and records on follow-up activities

Paragraph 4.14. Management reviews
The laboratory's executive management shall organise management reviews according to a predetermined schedule and procedures for the review of the quality system and testing and calibration activities. The typical period for conducting a management review according to the standard is once every 12 months. The management reviews shall take into account; the suitability of policies and procedures, reports from managerial and supervisory personnel, the outcome of recent internal audits, corrective and preventive actions, assessments by external bodies, the results of the inter-laboratory comparisons or proficiency tests, changes in the volume and type of work and the clients feed-back.

Results of the reviews should be fed into the relevant systems. Findings from the management reviews and the actions on the findings are important.

***CCP_1*:** Review of the latest management review and corrective action on deviations stated

4.1.2 4.1.2. Technical requirements

The following numbers will be used according to their placement in the *standard.*

Paragraph 5.1. General
There is no distinguished critical control point here at this step because all items are discussed in detail.

Paragraph 5.2. Personnel
The responsibility of the laboratory management is to ensure the competence of the personnel operating specific equipment, performing tests or calibrations, evaluating results, signing test reports or calibration certificates. Personnel performing specific tasks shall be qualified on the basis of appropriate education, experience or demonstrated skills as required.

***CCP_1*:** Description of the necessary knowledge
***CCP_2*:** List of personnel working at the lab and their responsibilities
***CCP_3*:** Information on education, previous experience, performance, training and training programmes

Paragraph 5.3. Accommodation and environmental conditions
The laboratory shall be provided with energy sources, lighting and suitable environmental conditions. The laboratory shall monitor, control and record

environmental conditions as required by the relevant specifications. Measures shall be taken to prevent cross contamination. A system for monitoring, controlling and recording of environmental conditions required. Availability of required measures for prevention of cross contamination is also needed.

All these requirements are considered when accreditation of a chemical laboratory is obtained. Therefore when concerning an audit system for a chemical laboratory, there is no critical control point at this requirement because the test result is not affected by the microbial contamination of the environment. On the other hand for a microbiological laboratory there is a critical control point here.

CCP: System for monitoring, controlling and recording of environmental conditions

Paragraph 5.4. Test and calibration methods and method validation
Sub-paragraph 5.4.1. General

The laboratory shall use appropriate methods and procedures for tests and calibrations within the scope of the laboratory. These include the methods and procedures for sampling, handling, transport, preparation of the items to be tested.

Basically the above requirements are considered before obtaining accreditation by the relevant accreditation body. Therefore, there is no critical control point here for this audit system.

Sub-paragraph 5.4.2. Selection of methods
The laboratory shall use methods, which meet the needs of the client and which are appropriate. Methods published in the international, regional or national standards are preferred. The laboratory should ensure that it uses the latest editions of the standards. Laboratory developed methods or methods adopted by the laboratory may also be used if they are appropriate for the intended use and if they are validated. The laboratory shall confirm that it can properly operate the standard methods before introducing them.

***CCP_1*:** List of accredited /validated methods

Sub-paragraph 5.4.3. Laboratory developed methods
Methods developed by the laboratory for its own use, they shall be planned by and assigned to qualified personnel equipped with adequate resources.

***CCP_1*:** Evidence for validation before use

Sub-paragraph 5.4.4. Non standard methods
When it is necessary to use methods not covered by standard methods, it shall be subject to agreement with the client and shall include a clear specification of the requirement. The method used shall have been validated appropriately before use.

***CCP*:** Evidence for validation before use

Sub-paragraph 5.4.5. Validation of methods
The validation is the confirmation by examination and providing the objective evidence that specific requirements are fulfilled. The laboratory shall validate non-standard methods, laboratory-designed methods, standard methods used outside their scope and modifications of standard methods to confirm that the methods are used as intended. The laboratory shall record the results obtained, the procedure used for the validation and a statement as to whether the method is fit for the intended use.

***CCP_1*:** Recorded procedures /methods used
***CCP_2*:** Documented system for results
***CCP_3*:** Statements that prove the fitness of the method

Sub-paragraph 5.4.6. Estimation of uncertainty of measurement
For a calibration or testing laboratory performing its own calibrations, there should be appropriate procedures for estimating measurement uncertainty. Testing laboratories shall have and apply procedures for estimating uncertainty of measurement.

***CCP_1*:** Identification of all the components of interest during analysis/calibration
***CCP_2*:** Calculated uncertainty according to approved references
***CCP_3*:** Uncertainty given in the result report/calibration certificate

Sub-paragraph 5.4.7. Control of data
The laboratory shall have appropriate procedures for the control of data. Concerning *control of data*, there should be procedures for calculations and data transfers. The medium for handling of data should be identified with the suitability and integrity.

***CCP_1*:** Procedures for calculations (methods, responsibility, handling of data and verification)
***CCP_2*:** System for protecting data (if computers or automated equipment are used)

Paragraph 5.5. Equipment
The laboratory shall be equipped with all the items necessary for the correct performance of tests and calibrations. Before being placed in service, all equipment shall be calibrated or checked to establish that they meet the laboratory's specification requirements and comply with the relevant standard specifications.

CCP_1: Approval for use
***CCP_2*:** Established preventive maintenance programme for each piece of equipment
***CCP_3*:** Authority for use – authorised personnel
***CCP_4*:** Records regarding technical and quality records as stating in chapter 2.3

Paragraph 5.6. Measurement traceability
This applies to equipment used for tests and calibrations having a significant effect on the accuracy or validity of the results. Therefore, before being put in service, each item should be calibrated. The laboratories shall have reference standards and reference materials. Reference standards shall be calibrated by a certified body. These reference standards in the laboratory shall be used only for the calibration purposes.

***CCP_1*:** Calibration programmes for the equipment
***CCP_2*:** Maintaining of reference standard and reference materials
***CCP_3*:** Calibration certificate issued by appropriate personnel

Paragraph 5.7. Sampling
For carrying out sampling the laboratory shall have a sampling plan and procedures. Sampling process should include important factors to be controlled, like temperature, to ensure the validity of the results. The records should be maintained regarding the sampling activities.

***CCP_1*:** Sampling plan and factors to be controlled with procedures to be followed
***CCP_2*:** Recording system – decided sample report format

Paragraph 5.8. Handling of test and calibration items
The laboratory shall have procedures for the transportation, receipt, protection, storage, retention and disposal of tests and calibration items including the provisions necessary to protect the integrity of the test or the calibration item.

***CCP_1*:** Procedures from receipt until disposal (Recording, responsible person, handling system etc.)
***CCP_2*:** Storage facilities
***CCP_3*:** Registration to ensure traceability

Paragraph 5.9. Assuring the quality of test and calibration results
Assuring the quality of the result is an essential part of the quality control system. Therefore, the laboratory shall have quality control procedures for monitoring the validity of the tests and the calibrations undertaken. For this purpose use of certified reference materials or internal quality control using secondary reference materials, participation in inter-laboratory comparisons or proficiency testing programmes, replicate tests or calibrations using the same or different methods can be included in relevant monitoring programmes.
***CCP_1*:** Use of certified reference material or secondary reference materials
***CCP_2*:** Participation in intra-laboratory and inter-laboratory proficiency test programmes and review of results and their records as evidence.

Paragraph 5.10. Reporting the results
The results of each test or calibration carried out by the laboratory shall be reported, accurately, clearly, unambiguously and objectively in accordance with any specific instructions in the test or calibration methods.

***CCP_1*:** Formats with required information (uncertainty, dates etc.)

4.2 The critical control points for the test method histamine

To identify the critical control points of the test method a practical fish sample was used. The sample was followed from arrival until the result report was issued. The

results of the observations and information collected throughout the sample path are summarised as follows:

Reception of the samples on arrival
At the reception, on arrival at the laboratory, the sample and the accompanying documents (sampling report/delivery note) should be checked. The accompanying documents should contain necessary information. The information on the accompanying document should match with the sample label. The sample containers/packages and the transport conditions (temperature control) should be considered, where necessary. The samples, which are not fulfilling the requirements, should be rejected (Nordic committee on Food Analysis 2002, The European Committee for Standardisation 2000).

The samples, which are accepted, should be registered with necessary information, i.e. sample code, time of arrival, date of arrival, temperature (when required), nature of the sample received, information required for the issue of the results etc. (Nordic committee on Food Analysis 2002, The European Committee for Standardisation 2000).

***CCP_1*:** Checking of the sample on arrival
***CCP_2*:** Registration of the sample (with correct information)
***CCP_3*:** Use of calibrated thermometers if thermometers are needed
***CCP_4*:** Traceability from arrival until sample is analysed, signatures

Reception at the analytical laboratory
When the received sample is submitted to the analytical laboratory it should be recorded again in the laboratoriy's recording system with the neccessary information.

***CCP_1*:** Recording with neccessary information
***CCP_2*:** Handled and signed
Environmental conditions
The laboratory layout shall be arranged to preclude cross-contamination of the samples and provided with suitable temperature conditions for particular samples as well as for particular equipment. Lighting facilities should be provided according to the requirement of the area concerned.

These basic facilities are considered and should be fulfilled by the chemical laboratory at the accreditation stage.

Therefore above requirements are not considered as critical control points here for this purpose.

Storage of the samples
The storage facilities for the samples should be arranged in a way protecting the samples from contamination and providing the suitable temperature conditions.

***CCP_1*:** Use of calibrated cold storage facilities
***CCP_2*:** Procedures for storage

***CCP_3*:** Records of storage

Test method
A test method description written according to a published recognised standard shall be used.

***CCP_1*:** Validity of the method description at the time of use
***CCP_2*:** Handled and signed
Sample preparation – grinding of the sample
The whole sample should be minced mechanically to ensure the homogeneity. All the steps of the mincing should be carried out fast and minced sample must be packed in a clean container. Proper running condition and cleanliness of the equipment, adequate supply of clean sample containers should be in place as prerequisites.

***CCP*:** Handled and signed

Sample preparation – weighing of the sample
Accurate amount of the sample (50.0 g) should be weighed for the extraction and the reminder should be stored at refrigerated or freezer conditions until the results are reported.

***CCP_1*:** Use of calibrated scale
***CCP_2*:** Weighing and recording
***CCP_3*:** Handled and signed

Sample preparation – extraction
The weighed sample should be homogenised for 2 min until well mixed in 50 ml 10% TCA and the extract should be filtered through Whatman 542 filterpaper (or similar) under vacuum. The extract should be made up to 100 ml in a volumetric flask. After being well mixed, a small amount is filtered through a 0.45 μm micro filter.

(Trichloroacetic acid solution 10% w/v – 200 g Trichloroacetic acid is dissolved in deionized water and diluted up to 2 L in a volumetric flask before the extraction)

When following the procedure, use of the reagents under quality control, clean glassware, use of standard measuring equipment, use of standard filters etc. are also important but considered prerequisites to this point.

***CCP_1*:** Homogenising
***CCP_2*:** Preparation of the TCA solution, date of preparation
***CCP_3*:** Handled and signed

Preparation of reagent O-pthalaldehyde (OPA)
For this preparation, 90.0 mg of OPA should be weighed in to a 10 ml volumetric flask and dissolved with 1 ml of methanol. After that, 0.2 ml 2-mercaptoethanol must be added to the solution and made up to 10 ml with boric acid buffer at pH 10.8 and

mixed thoroughly. This solution should be made fresh every two days and stored in a refrigerator. Solids and solvents should be measured very accurately.

(Boric acid buffer (0.4 M, pH 10.8) - 24.73 g boric acid and 21 g potassium hydroxide is dissolved together and pH is adjusted to 10.8 with 6 M KOH. This solution is diluted up to 1 L in volumetric flask).

At this step, the use of the reagents under quality control, clean glassware, use of standard measuring equipment, use of standard filters are also important but considered prerequisites to this point.

***CCP_1*:** Adjusting the pH
***CCP_2*:** Calibration status of the scales at the time of the usage
***CCP_3*:** Handled and signed

Sample preparation – derivatization
At this step, 0.25 ml of the sample/ standard should be added to 0.5 ml OPA reagent in a screw-capped test tube (measuring sample, standard and OPA reagent should be done very accurately). The mixture should be kept in dark for exactly 3.5 minutes. Then 2 ml ethylacetate is added and centrifuged for 1 min. After waiting until phase separation (exactly 3.5 min. or after clear separation) an aliquot from the top phase is pipetted in a vial for injection.

Same as the above steps, when following the procedure, use of the reagents under quality control, clean glassware, use of standard measuring equipment, use of standard filters are also important but considered prerequisites to this point.

***CCP_1*:** Keeping in dark
***CCP_2*:** Handled and signed
Preparation of the HPLC set up & auto injection
Solvent A - deionized water

Solvent B - (Mixture of 10% acetonitrile & 90% Sodiumhydrogenphosphate)

Buffer substance of 23.4 g should be measured in to a volumetric flask dissolved and made up to 2 L with deionized water. The buffer solution is mixed with acetonitrile in the ratio1:9 (buffer to acetonitrile). Before use, the solvent mixture should be filtered through a 0.4 μm filter.

Solvent C - (Mixture of 60% acetonitrile & 40% Sodiumhydrogenphosphate)

Buffer substance of 23.4 g should be measured into a volumetric flask dissolved and made up to 2 L with deionized water. The buffer solution is mixed with acetonitrile in the ratio 6:4 (buffer to acetonitrile). The solvent mixture should be filtered through a 0.4 μm filter before use.

Solvent D - (100% acetonitrile)

100% acetonitrile is filtered through a 0.4 μm filter before use.

All the solvents should be degassed before being poured into the solvent reservoirs and the solvent reservoir containers should be very clean without any particulate matter. Solvent reservoirs should preferably be continuously degassed after connection to the pumping system to avoid trapped air bubbles inside the passages. The loading passages must be flushed away by the solvents to prevent the cross-contamination depending on the previous injection.

After the preparation of the equipment the standard and the sample vial should be placed in the channel for auto sampling in two separate occasions. For this method auto sampling is carried out and therefore the sample loop is pre decided according to a programme. Furthermore the standard is also under the same injection procedure and therefore, it will not affect the accuracy of the result.

At this step also when following the procedure, use of the reagents under quality control, clean glassware, usage of standard measuring equipment, usage of standard filters are also important but considered prerequisites to this point. Concerning the preparation of the equipment it is assumed that a qualified experienced person appointed by the laboratory handles it.

***CCP_1*:** Calibration status of the HPLC equipment at the time of use
***CCP_2*:** Calibration status of the scales at the time of use
***CCP_3*:** Handled and signed

Calculation
Using the previously prepared standard curve the results of the samples are quantified and results are expressed as g kg^{-1} or mg kg^{-1} (Appendix I, 6.4 and 6.5).

***CCP_1*:** Validity of the prepared standard curve for quantification
***CCP_2*:** Handled and signed

Reporting of results
The results of the analysis should be reported in a decided recognised format clearly and accurately. Here the results are reported according to IFL "sample handling system".
***CCP_1*:** Reporting with required information (format, date.....etc.)
***CCP_2*:** Measurement uncertainty given according to previously described rules
***CCP_3*:** Issuing by the authorized personnel

4.3 Audit system

4.3.1 Evaluation of testing laboratories - checklist

The checklist is a guide to the auditor. It makes it easier for the auditor to follow all the components of the system and to record the non-conformities. This is the basic record use to write the audit report.

This audit checklist is the result of the comparison of critical control points coming under each requirement of the standard in theory, and the critical control points identified in practice for a whole sample chain for the test method histamine. See Appendix III for the cross-references to the standard, found by the comparison and Appendix IV for the checklist. This checklist is based on the requirements of the International Standard EN ISO/IEC 17025:2000 and the critical control points for quality system identified from an accredited chemical laboratory. Note: This checklist is just a draft because there may be different requirements between various laboratory systems.

4.3.2 Audit report

The audit report plays an important role when reporting the results of an audit. This report is always followed by a checklist and elaborates the necessary areas coming under the checklist in a detailed manner. Particular observations, which cannot be addressed as non-conformities, are also pointed out in this report. The auditor's opinion, the activity plan for rectifying the deviations including the name of the responsible person, date and signatures for the acceptance and evidence etc. is also included in this report. The necessary feed back to the auditor by the laboratory is confirmed with the specified time periods according to the activity plan of the report.

5 DISCUSSION

The Intentional Standard EN ISO/IEC 17025:2000, the "General Requirements for the Testing and Calibration Laboratories" specifies two categories of requirements for laboratories to comply with as management requirements and technical requirements.

The management requirements are mainly for the laboratory to demonstrate that it is operating a quality system and under good administration practices. These requirements are explained as 14 sub-requirements, which testing and calibration laboratories shall fulfil to prove the competency. These requirements are reviewed in detail in sub-chapters 2.1 and 2.2.

The technical requirements coming under the standard focus on the laboratory's technical competence and the ability to produce technically valid results. The technical requirements are also reviewed in chapters 2.1 and 2.2 in detail.

These management and technical parts are always interrelated. Without a good management system the technical applications cannot be established. Therefore, whenever the requirements for testing/calibration laboratories are considered, it is important to consider the connection between them.

This project is basically focused on testing laboratories which have alredy been accredited. Therefore, when formulating the audit system, it was assumed that the said laboratories fulfilled all the basic requirements of an accreditation body, to avoid making the system unnecessarily complex. Thus, although the whole laboratory system was discussed throughout the project, the audit system dealt only with the neccessary critical control points, which directly influence the proper functioning of the system.

Identification of the critical control points coming under the requirements is important to establish the criteria to formulate the audit system. In this project, critical control points of the requirements in theory and in practice were identified. The sample path in testing for histamine was observed to identify the critical control points in practice.

Identification of the critical control points can be carried out in two ways. One method is a logical way using a simple logic tree or a decision tree. The other way is through the experience gained by observing the relevant applications.

If a significant risk can occur to the product (test result) at a particular point due to the loss of control, and whenever that damage can not be rectified at a subsequent step it can be considered a critical control point. After identification of these specific points, which are deemed critical to the safety of the product (e.g. the test results), the next step is establishing the target levels. For some incidents it will be relatively easy to establish target values and there may be no critical limits.

For most critical control points of the laboratory system requirements only target values can be assigned. For example, if the critical control point is the status of having an approved document, target is the “approved document available”. Absence of the document is unacceptable and the presence of the document is the acceptable condition. However the decisions on targets or critical limits should be based upon good evidence and not decided by guesswork (Dillon and Griffith 1996).

An audit system can be formulated based on the identified critical control points and their target values or critical limits. To formulate an audit system it is necessary to have predetermined/identified-targeted points which should be looked in to and the relevant decision levels/ target values for each point that enable to take the necessary decisions effectively.

In this project the audit system is based on the comparison of the critical control points found for the necessary requirements both in theory and in practice. Comparison of two sets of critical control points is important in assessing the system in a realistic way. Therefore, this comparison study helps to find the relevant locations of the standard connected to each practical application. Furthermore this is immensely beneficial as a learning process to identify the appropriate locations of the standard accurately for each conformance in practice. It will help the auditor when reporting the non- conformances referring to those locations in the standard.

The critical control points for the requirements from the beginning such as organization, quality system, document control, review of requests, tenders and

contracts, subcontracting of testing and calibrations and complaints are obvious in both the theoretical and practical systems. The next requirement, 4.7 Services to the client was excluded because there are no critical control points affecting the test result at this step.

Concerning the critical control points for the requirements as 4.9 Control of non-conforming testing/calibration work, 4.10 Corrective action, 4.11 Preventive action it was revealed that it is very important to have personnel communications, observe the practices and check the quality and technical records to get a clear picture of the practices instead of just filling a check list.

The requirements and their critical control points for control of records, internal audits, management reviews and personnel are not complicated. They are rather obvious and understandable in both the theoretical and actual systems. To check the control of records, a practical example can be used by taking one chain of records for a test item. In the case of internal audits and management reviews, as an outside evaluation authority, more information can be obtained from communication with the laboratory manager and the quality manager other than only checking the records.

As for requirement 5.3 Accommodation and environmental conditions, there are no critical control points for a chemical laboratory. There would be in the case of a microbiological laboratory. The basic requirements are considered when obtaining the accreditation for both laboratories. But the laboratory environment is not continuously monitored in a chemical laboratory as for a microbiological laboratory. The requirement 5.4.1 Test and calibration methods and method validation in general was excluded and not discussed in this project. As mentioned before this requirement and its CCPs are considered at the accreditation level. The accreditation authority is carrying out annual evaluations for the continuous monitoring of the system.

The critical control points under the requirement, 5.4.2 Selection of methods is important to check the methods that the laboratory is currently using and to check the status of accreditation or suitability of methods whenever necessary.

If the laboratory is using "laboratory developed" and "non-standard" methods as per 5.4.3 and 5.4.4 respectively the validation before use is very important as to the critical control points identified at requirement 5.4.5. The results of the above two methods shall be compared against the results given for the same parameter by recognised standard methods. So there should be objective evidence for the validation of a method before use. Therefore, the laboratory should record the results obtained, procedures used for the validation and statements on the fitness for the intended use. The validation can also be done by using reference standards and reference materials, comparison of results achieved with other methods as mentioned above, inter-laboratory comparisons etc. or combination of above techniques (The European Committee for Standardisation 2002).

Discussing the critical control points of requirement 5.4.6, estimation of uncertainty of measurement, for some instances the nature of the test method preclude rigorous, metrologically and statistically valid calculation of uncertainty of measurement. For

that kind of situations the laboratory should have to attempt to identify all the components of uncertainty to do a reasonable estimate. This avoids, giving a wrong impression of the uncertainty when reporting the results. This estimate can be based on the knowledge of the performance, the method, measurement scope and the same time using the previous experiences and validation of data. The degree of rigor used in uncertainty estimation depends on various factors. They are the requirement of the test method, the requirement of the client and the existence of the narrow limits required for the decisions to particular requirements (for e.g. EU limits). In cases where well recognised test methods are specifying their limits to the values of the major sources of uncertainty of measurement and method of presentation of calculated results, the laboratory can follow them instead of using their own estimations and expressions. Sources contributing to the uncertainty can be included such as reference standards and reference materials used, methods and equipment used, properties and the condition of the item used for testing or calibration and the person handled etc. (The European Committee for Standardisation 2002). However, as revealed at the comparison and the discussion, for the auditing purposes, personnel communications are very important to clarify and better understanding of the situations, requirements and practices they are dealing with.

The critical control points for requirement 5.4.7 Control of data and the necessary requirements for the equipment under 5.5 are also discussed, compared, and clarified. The detailed information on these requirements has been reviewed in chapters 2.2 and 2.3. This information is also useful to clarify the critical control points under these requirements.

The comparison of the critical control points relevant to requirement 5.6 Measurement traceability in theory with the relevant practical points for the test method histamine made it easy to clarify the criteria for the requirement. Here it reveals clearly the importance of the calibration of equipment involved in the test method, maintaining the reference standards and reference materials up to date with required calibrations and the availability of the calibration certificates as evidence.

The critical control points of the two systems are very obvious for requirement 5.7 Sampling.

The handling of test and calibration items, requirement 5.8 of the standard, also gives very practical experiences when comparing the theoretical and the practical critical control points. Under this requirement, for storage facilities, only the availability of the required storage facilities is concerned. All the requirements should be fulfilled by the laboratory for the storage facilities and its' continuous monitoring is considered and checked by the accreditation authority. The auditor can observe the storage practices such as how they store the items to prevent cross contamination etc. Furthermore, this practical experience gives knowledge to follow the path of a test item, for the required traceability, by following the registration record.

Critical control points identified for requirement 5.9 Assuring of test and calibration results are very obvious. Discussing the practical applications reveals the importance of maintaining control charts. A detailed description on control charts is in Appendix

II. As to requirement 5.10 and its theoretical and practical comparison, the critical control points for both systems are very clear and specific. When reporting the results, specific instructions should be followed, such as measurement uncertainty. If measurement uncertainty is given in the method for test or calibration results it is necessary to mention it on the test report.

An audit system contains chain of activities such as direct checking, personnel communications, random checking, recording in the checklist, results (including the opinions of the auditor), open discussion with the responsible personnel and activity plan for the non-conformances. According to the agreement in the audit report, the laboratory should send the necessary feedback to the auditing authority regarding the corrective measures taken on the deviations pointed out in the audit. The auditor should also be aware of the time limits given to rectify the deviations.

6 CONCLUSIONS

The objective of this project was to formulate an audit system for evaluation of testing laboratories under the International Standard EN ISO/IEC 17025:2000. The results of the project can be summarised in the following points.

1. The common technique to guide an audit is by following an evaluation system checklist, which addresses all the components of the system.

2. Therefore, to formulate an audit system for testing laboratories, a checklist should be constructed with a scientific base.

3. The criteria for the checklist should be established clearly and unambiguously. The analysis of the pinpoints or critical control points of each requirement in the laboratory system is necessary to cope with this task.

4. For the analysis of critical control points, both logical decision tree and/or practical experiences can be utilised.

5. The identified critical control points and their elements can be used to establish the audit checklist.

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APPENDIX - 1

Draft to the document that includes a format with all necessary information

Name of the lab:
Date of issue: 1st,December 2002
Issue: 01
Traceability: C:/ Sepalika / Quality methods / Validated methods/ Histamine 01
Responsible person:
Author: Sepalika Wickramasinghe

Method Description for the Analysis of Histamine Using High Performance Liquid Chromatography

1. Scope

This method can be specified as a reference method of analysis for the determination of histamine in fish and fishery products according to the requirement of *Council Directive 91/493/EEC of 22 July 1991, laying down the health conditions for the production and the placing on the market of fishery products* issued by the European Commission.

2. Field of Application

This method can be applied for the quantitative determination of histamine in fish and fish products and has been proved as a sensitive, simple and selective method for the analysis of histamine, by scientific studies.

3. Principle

Histamine is extracted with trichloroacetic acid and derived with O-phthalaldehyde. The Histamine OPA Fluorophore is separated by reverse – phase high performance liquid chromatography under gradient elution conditions and the fluoresence of the separated stable product is measured fluorometrically.

4. Reagents

4.1 Distilled water or deionized water
4.2 Acetonitrile, HPLC grade
4.3 Methanol, HPLC grade
4.4 Ethyl acetate, HPLC grade
4.5 Boric acid
4.6 Sodium dihydrogenphosphate dihydrate, extrapure
4.7 Potassium hydroxide
4.8 Trichloroacetic acid, extra pure
4.9 O-Ophthalaldehyde (OPA), 97%
4.10 Histamine dihydrochloride

5. Apparatus

5.1. HP 1050 Series Pumping System
5.2 HP Automatic Injection System
5.3 Varian 9070 Fluoresence Detector
5.4 Windows Chemstation Data Handling System
5.5 HPLC RP – column; Hypersil BDS C18; 5μm 250*4.0 mm;HP or Thermoquest/Hypersil; part no.28105-030
5.6 Guard columns; Lichrospher 100 RP -18; 5μm 4x4 mm; HP
5.7 Chromocol Ltd. UK, Vials (2 – CV) & caps (11 – Ac7)
5.8 Ultra-Turrax T25 homogenizer janke & Kunkel
5.9 Vortex – Genie Model K-550
5.10 Radiometer PHM80 Portable pH meter
5.11 Analytical balances AE 160 & AE 200
5.12 Glassware – Glassware and plastic containers as per the requirement Gilson pipettes, filters, Whatman 542 (or similar) filter papers, millipore 0.4 μm solvent filters cat.no. HTTPO 4700, Millipore 0.45 μm sample filters Cat no. HAWPO 4700

6. Procedure

6.1. Preparation of solvents/buffers

Solvent A - deionized water

Solvent B - (Mixture of 10% acetonitrile & 90% Sodiumhydrogenphosphate)
First, 23.4 g of the buffer substance is measured in to a volumetric flask dissolved and made up to 2 L with deionized water. The buffer solution is mixed with acetonitrile in the ratio1:9 (buffer to acetonitrile). Before use, the solvent mixture is filtered through a 0.4 μm filter.

Solvent C - (Mixture of 60% acetonitrile & 40% Sodiumhydrogenphosphate)

To prepare solvent - C, 23.4g of the buffer substance is measured in to a volumetric flask dissolved and made up to 2 L with deionized water. The buffer solution is mixed with acetonitrile in the ratio 6:4 (buffer to acetonitrile). Before use, the solvent mixture is filtered through a 0.4 μm filter.

Solvent D - (100% acetonitrile)

100% acetonitrile is filtered through a 0.4 μm filter before use.

Boric acid buffer (0.4 M pH 10.8)

For this preparation, 24.73 g of boric acid and 21 g Potassiumhydroxide are mixed together and the pH of the solvent mixture is adjusted up to 10.8 by adding 6 M KOH. The mixture is diluted up to 1 L in a volumetric flask.

Trichloroacetic acid solution (10% w/v)

200 g of the Trichloroacetic acid is diluted in deionized water and diluted up to 2 L in a volumetric flask.

Preparation of the reagent O-phthalaldehyde

First, 90.0 mg of OPA is weighed into a 10ml volumetric flask and 1ml of methanol is added. The mixture is mixed until dissolved well and then 0.2 ml of 2-mercaptoethanol is added. The solvent mixture is made up to 10ml with Boric acid buffer at pH 10.8. After mixing thoroughly, the solution is stored in an amber bottle in a refrigerator. The solution must be prepared every two days.

6.2. Extraction of histamine

Fist, 50.0 g of minced fish sample is weighed accurately in to a container and blended with 50 ml 10% TCA solution. The mixture is homogenized and the clear extract is filtered through Whatman 542 filter paper (or similar) under vacuum and made up to 100 ml in a volumetric flask and thoroughly mixed. Small amount of filtered extract is again filtered through a 0.45 μm filter. The filtrate should be stored at 4°C.

6.3. Derivatization

For derivatization step 0.25 ml of sample/standard is mixed with 0.5 ml O-phthalaldehyde reagent in a screw cap test tube. The solution is kept in a dark place for exactly 3.5 minutes. After kept in dark 2 ml of ethylacetate is added and vortexed for 1 min.

6.4. Standards and quantification

As the first step, 100.0 mg of histamine standard is weighed in to a volumetric flask and made up to 100 ml with10% TCA. A stock solution is made by mixing the amine 10 mg/100 ml in concentration. Suitable dilutions are made for the standard curve preparation (eg.1/2, 1/4, 1/8, 1/16, 1/32, 1/64). Quantification of samples is done by area measurement determined using a concentration versus standard area plot.

6.5. Calculation

Two or more runs of each standard are carried out and by liner regression (R^2> 0.99) the samples are quantified and the results are expressed as g kg^{-1} in the sample.
The following formula, which is constructed according to the standard curve and the chromatograph (area percent report), is used for the calculation:

$$\text{Histamine con}^{n}\ \text{g/kg} = \left[\frac{\text{Area} + C}{m}\right] \times F \times 1000 / \text{Weight of the sample}$$

F = histamine con^{n} of one diluted standard/dilution factor

APPENDIX - II

Procedure for Making a Control Chart

Importance of using the control charts was mentioned several times in the main text, while discussing the requirements and/or applications use to determine the quality level of a laboratory. Therefore, the following discussion is based on the NMKL Procedure No.3 (1996), to discuss more about the control charts. Although this discussion is focussed on the chemical laboratories according to the NMKL procedure No.3 the same procedure can be applied for the microbiological laboratories.

General

The use of control charts is a suitable way of documenting internal quality control in food chemical laboratories. When auditing the system, control charts can be used to verify the effectiveness of the quality control applications. A control chat is a diagram intended to examine whether a process is under statistical control. In the chart, the values of one or more characteristics (average, standard deviation, variation width, etc.) are plotted and compared to given limits.

By determining the analytical characteristics of a control material several times, commonly used control charts are obtained. Here the results of the determination are plotted against the code of analysis. The code of analysis can be a date or a number. In this plot, codes of analysis are marked on the horizontal axis, while the results of the determination are on the vertical axis. The control material can be defined as a certified reference material, another reference material or an internally prepared control material. A test portion from the control material is removed before the analysis and it is used as the sample. In this analysis, results of the several determinations which are carried out at the same time on the control sample are plotted as the average. Normal control chart is consisted of horizontal lines defining the average line, warning line and action limit lines. These lines originate from the normal distribution N (μ, σ^2) ((μ, = true or accepted value, σ^2 = Variance) which is considered to be applicable to the random variation of the values.

Therefore, whenever possible constructing and use of control charts is very important. This can be done continuously for all the routine analyses. These control charts and their results should be made available to all person involved in the analytical work.

A control chart demonstrates the quality level of the laboratory. It displays that the laboratory is running a predetermined quality control system. These charts are helpful to increase the confidence in work. In other hand control charts can be defined as kind of guiding tools which can be used to detect the deviations at an early stage and to take corrective actions in time.

It is important that control charts are constructed on the basis of measurements carried out in the laboratory, not on published performance characteristics like trueness, precision, that are possibly stated in the method in question.

When control charts demonstrate the results of the analysis is under statistical control, it is good evidence to prove the reliability of the results obtained from the unknown test items. Storage of the control chart documents parallel to the correspondence lifetime of the test results records is very important. Control charts are good indicators to prove the correctness of the results when analytical results are in question.

It is important that it is made clear to all members of the staff that control charts are used to ensure that any abnormalities are detected at an early stage, not in order to put pressure on the staff.

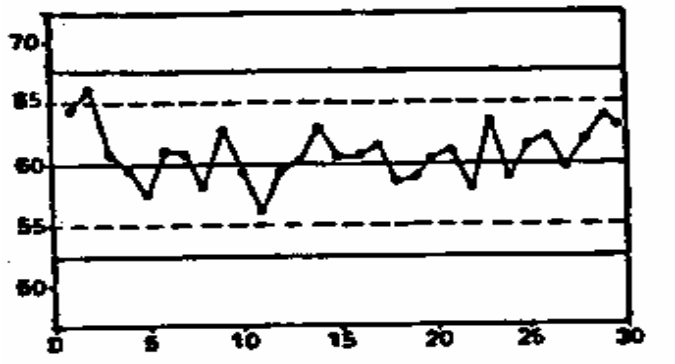

Figure 5: Control chart with warning and action limits in which results from 30 determinations have been recorded.

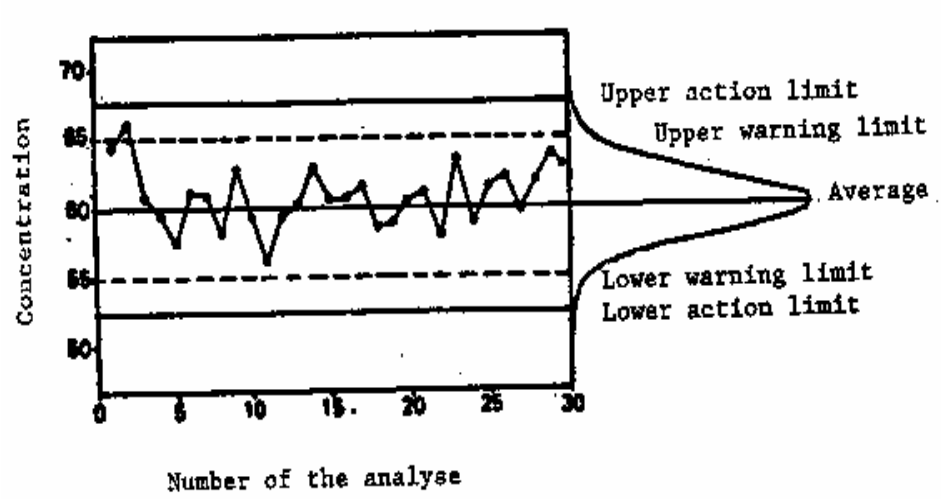

Figure 6: Average, warning limits and action limits in relation to the normal distribution of the results.

The warning and action limits on the control chart are determined by the estimated standard deviation.
Upper action limit = average + 3x standard deviation
Upper warning limit = average + 2x standard deviation
Lower warning limit = average - 2x standard deviation

Lower action limit = average - 3x standard deviation

The factors 2 and 3 corresponds to the probability levels 95% (= significance 5%) and 99.7% (= significance 0.3%).

Use of control charts

The control charts are constructed considering that if only “normal” random errors occur then probability is 95% for the obtained value to be within the warning limits. The probability to be the obtained value within the action limits is 99.7%. This justification is based on considering that the standard deviation is estimated from 30 or more observations. Use of the results of few samples to construct a control chart is unimportant. When constructing a control chart using the results obtained by the analysis of control materials it is expected that the results lie above and below the centre line with the same frequency.

There are simple rules for the interpretation of the control charts according to the NMKL procedure No.3 (1996) as below.

The following observations should be seen as indications that something out of the ordinary has occurred, i.e. that the analysis is no longer under statistical control (Quality Assurance Principles for Analytical Laboratories, AOAC).

- one result is outside either action limit
- two successive results are outside the same warning limit
- seven successive results are on the same side of the central line
- seven successive results form a rising or falling straight line (indicating a clear trend, irrespectively of which side of the centre line the result is on).

Therefore, the laboratories' responsibility is to establish suitable acceptance limits for the analytical work. If there is any detectable abnormality, it should be noted in the control chart. In such a situation that analytical work should be stopped and the reason for the deviation found. After taking corrective measures, the work should be restarted. Results of the analytical work should be released only by proving the abnormality has been corrected and under statistical control by analysing the control materials.

Although any internal quality control system is not 100% perfect, it is important to construct control charts based on control materials analysed together with unknown samples. This will be a simple method for monitoring the quality of the analytical work.

APPENDIX - III

Critical Control Points in Practice for Test Method Histamine - Reference to EN ISO/IEC 17025: 2000

Step No.	Test method step	Critical control points identified at each step	Relevant reference to the standard
1.	Reception of the sample on arrival	***CCP_1:*** Checking of the sample on arrival	5.8 Handling of the test and calibration items
		CCP_2: Registration of the sample (with correct information)	5.8 Handling of the test and calibration items
		CCP_3: Use of calibrated thermometers if thermometers are used	5.6 Measurement traceability
		CCP_4: Traceability from arrival until sample is analysed, signatures	4.12 Control of records
2.	Reception at the analytical laboratory	***CCP_1:*** Recording with necessary information	5.8 Handling of the test and calibration items
		CCP_2: Handled and signed	4.12 Control of records
3.	Environmental conditions	Here there are no critical control points for a chemical laboratory.	5.3 Accommodation and environmental conditions
4.	Storage of the samples	***CCP_1:*** Use of calibrated cold storage facilities	5.6 Measurement traceability
		CCP_2: Procedures for storage	5.8 Handling of the test and calibration items
		CCP_3: Records of storage	4.12 Control of records

5.	Test method	***CCP₁:*** Validity of the method description at the time of use	4.3 Document control 5.4.5 Validation of methods
		CCP₂: Handled and signed	5.12 Personnel
6.	Sample preparation - grinding of the sample	***CCP₁:*** Handled and signed	5.12 Personnel 4.12 Control of records
7.	Sample preparation - weighing of the sample	***CCP₁:*** Use of calibrated scale	5.6 Measurement traceability
		CCP₂: Weighing and recording	4.12 Control of records
		CCP₃: Handled and signed	5.12 Personnel 4.12 Control of records
8.	Sample preparation - extraction	***CCP₁:*** Homogenising	4.12 Control of records
		CCP₂: Preparation of TCA solution and date of preparation	4.12 Control of records
		CCP₃: Handled and signed	5.12 Personnel 4.12 Control of records
9.	Preparation of reagent-Opthalaldehyde (OPA)	***CCP₁:*** Adjusting pH	4.12 Control of records
		CCP₂: Calibration status of the scale at the time of use	5.6 Measurement traceability
		CCP₃: Handled and signed	5.12 Personnel 4.12 Control of records
10.	Sample preparation - derivatization	***CCP₁:*** Keeping in dark	4.12 Control of records
		CCP₃: Handled and signed	5.12 Personnel 4.12 Control of records

11.	Preparation of the HPLC set up and auto injection	***CCP₁:*** Calibration status of the HPLC equipment	5.6 Measurement traceability
		CCP₂: Calibration status of the scales at the time of use	5.6 Measurement traceability
		CCP₃: Handled and signed	5.12 Personnel 4.12 Control of records
12.	Calculation	***CCP₁:*** Validity of the prepared standard curve for quantification	5.4.7 Control of data 5.12 Personnel
		CCP₂: Handled and signed	5.12 Personnel
13.	Reporting the results	***CCP₁:*** Reporting with required information	5.10 Reporting the results
		CCP₂: Measurement uncertainty given according to the previously described rules	5.10 Reporting the results
		CCP₃: Issued by the authorized personnel	5.12 Personnel

APPENDIX - IV

Evaluation of Testing Laboratories - Checklist

(In this evaluation checklist the same numbers coming under the standard are used for easy reference)

Name & address of the laboratory:	
Approval number:	**Date:**
Evaluation authority:	**Report number:**
Auditor:	

4.Management Requirements

4.1 Organization

- Valid document of accreditation
- Organizatinal structure with defined responsibilities

The valid document of accreditation should be available.

Comments:

4.2 Quality System

- Approved quality manual

Approved quality manual is necessary.

Comments:

4.3 Document control

- Identified formats
- Defined responsibilities for preparation
- Issuing authority
- Responsible person for maintenance & storage
- Traceability records for required documents

Comments:

4.4 Review of requests tenders and contracts

- Agreement between the lab and the customer

Comments:

4.5 Subcontracting of tests & calibrations

- Established criteria for selection
- Responsible person
- Records on competence
- Register of all subcontractors

Comments:

4.6 Purchasing services /supplies

- Established criteria
- List of required standards and reliable sources
- Checking and record keeping system

Check records for the purchased items should be made available.

Comments:

4.8 Complaints

- Designated personnel
- Recording at the receipt
- Keeping the document of complaint
- Records of the date of investigation & corrective action

It is important to note the feedback to the customer & the improvements to the quality system. Records on the investigations and the corrective action taken are important.

Comments:

4.9 Control of non-conforming testing and calibration work

- Previously identified non-conforming work
- Designated personnel for management
- List of well defined actions

Comments:

4.10 Corrective action
4.11 Preventive action

- Properly identified root causes
- Identification of measures
- Designated personnel for implementation
- Records on actions
- Evidence for effectiveness

For 4.9, 4.10 & 4.11 observing the practices, personnel communications & checking of the technical and quality records are important.

Comments:

4.12 Control of records

- Responsible personnel for maintenance
- Storage system ensuring protection & security
- Disposal system

Practical example can be used to check the system. Chain of records connected to a test item can be followed.

Comments:

4.13 Internal audits

- Latest internal audit and follow - up audit activities

Latest internal audits and their findings are important. Actions on non - conformances and records on corrective actions should be considered.

Comments:

4.14 Management Reviews

- Review of latest management review & corrective actions on deviations stated

Corrective actions on the deviations pointed out at the management reviews are important. Check that the management reviews are conducted as per the required frequency.

Comments:

5. Technical requirements

5.2 Personnel

- Description of neccessary knowledge
- List of personnel & their responsibilities
- Information on education, experiences, performance, training and training programmes

Experienced qualified personnel for specific tasks are important.

Comments:

5.3 Accommodation and environmental conditions

- System for monitoring, control & recording of required environmental conditions

This should be specially considered for the microbiological laboratories. The records of monitoring activities can be checked. For chemical laboratories this part is excluded.

Comments:

5.4 Test and calibration methods and method validation
5.4.2 Selection of methods

- List of approved methods

A list of approved test methods should be available. Check all the methods currently used are included.

Comments:

5.4.3 Laboratory developed methods

- Evidence for validation before usage

The results of the validation should be available.

Comments:

5.4.4 Non-standard methods

- Evidence for validation before usage

The results of the validation should be available.

Comments:

5.4.5 Validation of methods

- Recorded procedures or methods
- Documented system for results
- Statements prove the fitness of the method

If the laboratory is using the methods as per 5.4.3 & 5.4.4 accuracy of the validated results should be checked against the results of the standard methods.

Comments:

5.4.6 Estimation of uncertainty of measurement

- Identification of all components of uncertainity during analysis
- Calculated uncertainty according to the directions of the approved references
- Uncertainty given in the result report

Personnel communications are also important for clarifications.

Comments:

5.4.7 Control of data

- Procedures for calculation
- System for protecting data

Calculation methods/ standard curves etc. for all test methods & electronic or any other system for protecting of data.

Comments:

5.5 Equipment

- Approval for usage
- Established preventive maintenence programme for each piece of equipment
- Authority for usage
- Records regarding technical & quality records as stated in 2.3

Approval document and the preventive maintenance note book can be checked. Referring to 5.2 authority can be confirmed. Records on the calibration and maintenance etc. are important.

Comments:

5.6 Measurement traceability

- Calibration programme for equipment (e.g. HPLC set up, scales, weights, burettes)
- Maintaining of reference standards & reference materials
  - name
  - date (standards up to date)
  - checking records
  - storage
  - authority
  - calibration
- Calibration certificate issued by the appropriate personnel

The reference standards are the secondary standards, which are calibrated against the primary/ national standards and are the working standards /"in-house" reference standards. Reference materials are also "in-house" reference materials calibrated against RMs/CRMs.

Comments:

5.7 Sampling

- Sampling plan & procedures
- Recording system

If the laboratory is carrying out sampling the above requirements are considered**.**

Comments:

5.8 Handling of test and calibration items

- Procedures for receipt and handling
- Storage facilities
- Registration to ensure the traceability

Check the storage facilities are available as to the requirement. Path of a received test item can be followed from result report to the arrival of the sample**.**

Comments:

5.9 Assuring the quality of test and calibration results

- Use of certified reference materials or secondary reference materials
- Participation in proficiency tests
  - intralaboratory
  - interlaboratory
- Review of results

Control charts can be used as source of evidence.

Comments:

5.10 Reporting the results

- Formats with required information
- Repoerting according to required specifications

Reporting the measurement uncertainity in the result report is important.

Comments:

Number of conformaties:

Number of non-conformaties: