ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE (APIC)

GUIDELINE for QUALIFICATION & MANAGEMENT of CONTRACT QUALITY CONTROL LABORATORIES

10 January 2012

Content

INTRODUCTION

Over the last decade the pharmaceutical industry has made a dramatic shift in how it is outsourcing many activities that historically would never have been anticipated before. We have seen a dramatic shift in where product and materials are manufactured and this change has also been reflected in where and how these products are tested and evaluated. To help facilitate this new environment this organisation developed guidance for Supplier Management and published this in January 2010. This guidance focused on supplier of materials to API manufacturers however, we also see the need to develop this guidance into phase 2 and also define guidance for Laboratory Contract Life Cycle Management.

Link to Supplier Management Guideline :
http://www.apic.cefic.org/publications/publications.html (bottom of the page)

Our aim is to ensure that this guidance ensures that patients worldwide and at any time can have confidence in the quality, safety and efficacy of medicines. The cGMP regulations for final medicinal products are clearly defined in each country and region. The content of the regulations may vary but the objectives are the same:
- To deliver high quality, safe medicines manufactured and distributed following controlled procedures to treat diseases and
- To prevent deaths, serious illnesses, adverse events or product recalls resulting from deficiencies in the manufacturing and distribution processes.

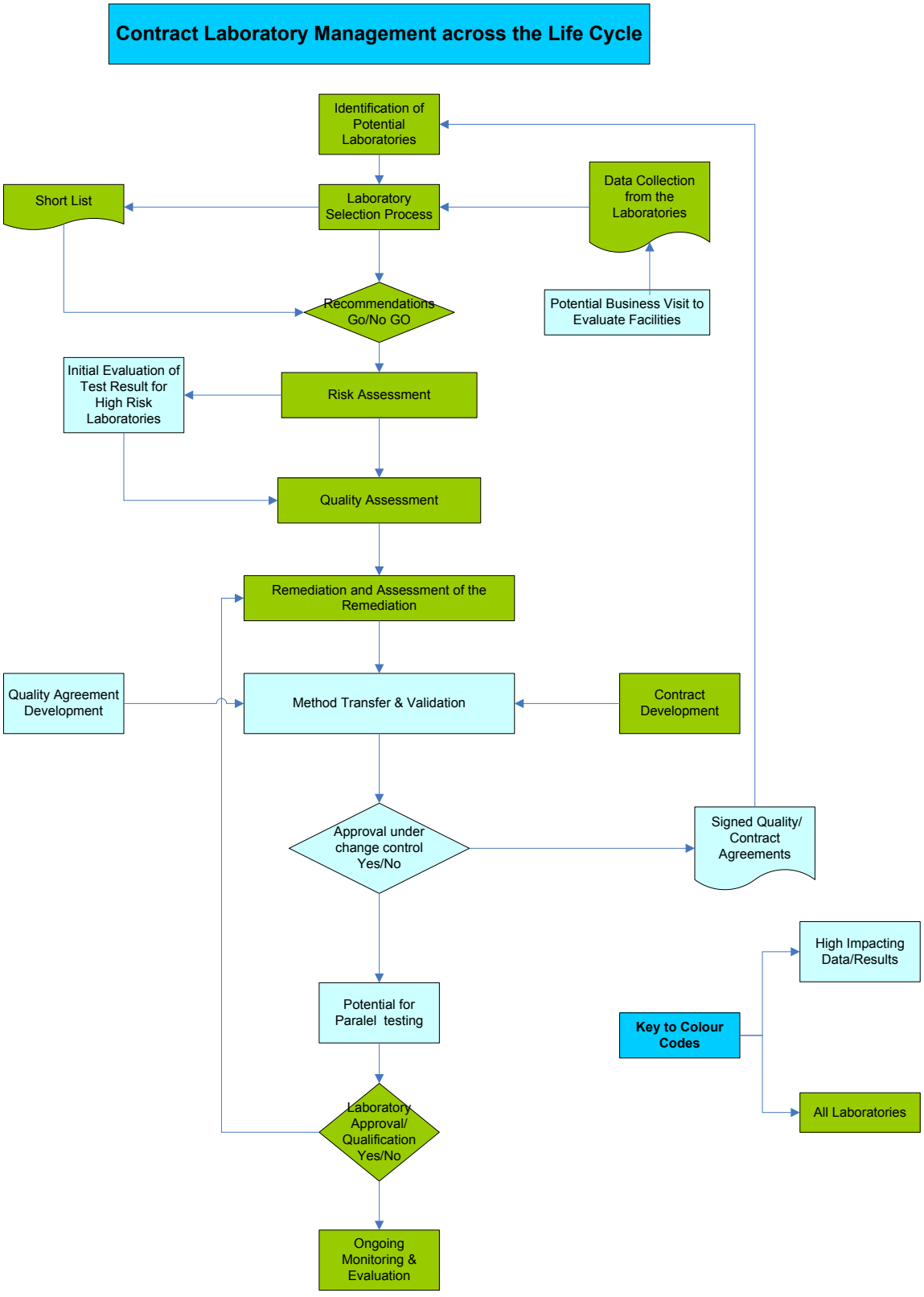
It has been well documented and communicated where systems have been inadequate and in case deficient in managing the full product life cycle, resulting in patient impact and the loss of trust with our customers. In the last number of years the pharmaceutical industry, and the Regulatory Authorities and inspectorates have taken action to address these deficiencies for the future. This is ensuring that appropriate cGMP practices are applied.

The ever increasing infiltration of counterfeit medicines and falsified APIs into the supply chain continues to worry Regulatory Authorities and Industry at large and serves as a constant threat to the patients. It is therefore essential that we qualify and manage the entire supply chain for medicines and all other inputs to this process.

The scope of this guidance document is to share the best practices of APIC member companies on systems to be implemented to adequately manage contact laboratories through the complete life cycle of the product, including

- Identification of Potential Laboratories
- Risk Assessment
- Quality Assessments
- Ongoing Supplier Management (Monitoring and Evaluation)

Our guidance covers Laboratory management over the entire product lifecycle as described in the Contract Laboratory Management Flow Chart below:


Contract Laboratory Management across the Life Cycle
Identification of Potential Laboratories
Short List
Laboratory Selection Process
Data Collection from the Laboratories
Recommendations Go/No GO
Potential Business Visit to Evaluate Facilities
Initial Evaluation of Test Result for High Risk Laboratories
Risk Assessment
Quality Assessment
Remediation and Assessment of the Remediation
Quality Agreement Development
Method Transfer & Validation
Contract Development
Approval under change control Yes/No
Signed Quality/ Contract Agreements
Potential for Paralel testing
Key to Colour Codes
High Impacting Data/Results
All Laboratories
Laboratory Approval/ Qualification Yes/No
Ongoing Monitoring & Evaluation

In the appendices we also provide specific assessment documents as examples to help with contact laboratory evaluation based on best practice sharing by the Task Force members as listed below:

- Contract Laboratories Potential Identification Selection
- Contract Laboratories Questionnaires
- Risk Assessments Tool

The target audience for the guidance document is primarily API Manufacturers while it may also be used by medicinal product manufacturers.

Based on the complexity of testing there should be increasing Levels of GMP applied to assess the risk to patients and we recommend that companies follow ICH Q9 for their Quality Risk Management process and use the ICH Q9 definition of Risk:-
"Risk is the combination of the probability of occurrence of harm and the severity of the harm to the patient or consumer".

The Contract Laboratories must be approved using the Company's Change Control Procedures.

Guidance:
The quality system requirements for Contract Laboratories must follow the full life cycle management for identification, selection, approval, qualification and ongoing monitoring and evaluation.

In some cases we have seen that Regulatory Agencies has taken the approach to inspect some Contract Laboratory Companies and this has been well documented, however this does not mean that Pharmaceutical Companies can rely on these spot inspections. It is still our responsibility to manage the oversight and ensure that testing being completed is as per the cGMPs as outlined in the Quality Agreements developed.

Having a team selection process would appear to be a best practice and to have this take place in the early part of the evaluation process is very helpful to project timing and this approach is outlined.

The Quality Assessment is a critical step and should be carried out before any Quality Agreement is put in place. With this evaluation the level of risk can be assessed and some mitigating steps can be outlined and agreed through the Quality Agreement. Any other issues that arise during the laboratory assessment should be addressed by the selection team. Template documents for both the Quality Assessment and the Risk Assessment can be found in the Appendices to give detailed guidance.

The decision to audit or not audit of a Contract Laboratory must be based on a documented Risk Assessment and if deemed necessary this audit must be completed before any testing that is performed by the laboratory and then at a frequency in line with the ongoing evaluation and risk. For any new testing methods transfer and validation must be considered and the outcome documented.

If the specifications for the test results are communicated to the contract laboratory by the contract giver then an OOS procedure must be in place, and in the event of an out of specification result an investigation must be completed and documented by the laboratory.

The main steps of Laboratory Management are described in each chapter but we should also reference existing APIC guidance documents which are very much applicable to further clarify expectations and provide consistency to the processes. e.g.:
- Quality Agreements
- Auditing Guide,
- APIC Audit Programme
- APIC Quick Guide for API Sourcing
- APIC ICHQ7 How to do Document
- APIC Quality Management System Guide for API manufacturers

These documents are available on the APIC website: WWW. APIC.CEFIC.ORG
In the appendices we also provide specific assessment documents as examples to help with supplier evaluation based on best practice sharing by the Task Force members listed below:

- Buggy Tom (DSM ANTI-INFECTIVES)
- Stilgenbauer-Voigt Ingrid (BASF)
- Vandeweyer François (JANSSEN PHARMACEUTICA)
- Counihan Eileen, Chair (MERCK SHARP & DOHME)
- Storey Anthony (PFIZER)
- Macedo Maria José (Hovione FarmaCiencia SA)
- Genot Véronique (Abbott Healthcare Products B.V.)

We hope you will find the content of this guidance and the templates useful in the evaluation and management of contract laboratories ensuring safe APIs and medicines for the health, safety and quality of life of our patients worldwide.

If you have any comments or suggestions for improvement please contact the APIC Secretary at:

CEFIC Active Pharmaceutical Ingredients Committee (APIC) Av. E. Van Nieuwenhuyse 4 / box 2 B - 1160 Brussels Tel : +32 2 676 72 02 or +32 2 676 72 44 - Fax : + 32 2 676 73 59 E-mail : pvd@cefic.be or abo@cefic.be

For further details on APIC and for other APIC Guidance documents see:
www.apic.cefic.org

CHAPTER 1: IDENTIFICATION OF POTENTIAL LABORATORIES

Selection of independent contract laboratories and contract research organizations to perform laboratory studies, research, testing, experiments, evaluations, assays, examinations, and analysis requires careful consideration. While contract laboratories can be used either to supplement your company's in-house laboratory or to perform all your laboratory testing, one must thoroughly evaluate the laboratory, its capabilities, credentials, experience and its relationship with its clients.

Identification of Potential Contract Laboratories is usually serviced by the Purchasing Department together with or in cooperation with the QC unit and QA experts. However this identification must always be based on pre-defined requirements. Following items can be considered depending on the need:

- Evaluate the need for the Laboratory to be GMP compliant or not.
- Impact of generated data and results on GMP and on product quality (release)
- Experience with method development and/or method validation according to GMP requirements
- Experience with Specifications, QC activities and approval of QC results according to GMP requirements
- Laboratory Accreditation
- Accreditation of former inspection history
- Availability of equipment for analytical support
- Availability of technical knowledge and expertise
- Adequacy, availability and suitability of laboratory equipment and resources
- Cost competitively
- Innovative and technical competencies
- Responsiveness and communication
- Sampling handling, transport and frequency

Laboratory Selection Process:

Depending on whether your company will be using the laboratory long-term or short-term, your company will also want to consider the size of the laboratory and its relationship with its clients. If your company is entering into a long-term contract, you will want to ensure that the laboratory is responsive and available to your needs. If your company is small and has limited in-house laboratory, scientific or technical resources, you will want to ensure that the laboratory is available to answer questions regarding laboratory test methods, laboratory data, and laboratory test results especially for unexpected, out of specification or aberrant laboratory testing results.

Depending on the impact of generated data and results related to GMP, a documented risk assessment by a cross functional team is performed (see Chapter 3 and related tool in appendix 3) and/or a criticality evaluation approach is advisable to decide if a potential

business visit is needed in order to evaluate the facility prior to or as part of the selection process. The risk assessment must performed involving a cross functional team.

Depending on the criticality evaluation, a (cross functional) team will be formed. Representatives of the Procurement, QC and QA audit skilled experts will always be part of the Selection Evaluation Team. Resulting from the criticality evaluation the team can be extended with representatives as appropriate from other areas such as:
- Project Management Team
- Analytical Development
- Analytical Equipment Qualification
- Analytical Technique Specialists
- Regulatory Compliance
- Other Technical expertise as required (Legal, Safety & Health, ...)

A list of questions, which your company may want to consider when selecting new contract laboratories, is attached in Appendix 1.
The appendix differentiates between team on site visits during the selection process and a selection made based on a questionnaire.

The Appendix 1 questionnaire can be used by the team as a guidance and covers topics such as:
- General key (minimum) selection criteria
- Analytical result supply assurance
- Quality & Regulatory compliance
- Procurement & cost
- Innovation and technical knowledge
- Responsiveness & communication

Outcome:
Each member of the Laboratory Selection Team documents the collected information and formulates a decision and/or action proposal related to his/her expertise field.
An overall report will be issued by the team. The combined information must be used to formulate a final recommendation to Senior Management.
A short list with potential contract laboratories is issued. If critical issues (Quality, Safety, Health, Environment, Regulatory, Business continuity, and social responsibility) are identified and do not have a clearly defined actions for remediation, this information must be escalated to Senior Management. If Critical Quality and GMP issues are identified an accurate and approved mitigation plan must be available before the Quality Assessment can be initiated.
Senior Management is responsible for the final Go/No-Go decision for the laboratories that are specified on the short list provided by the team.

CHAPTER 2: RISK ASSESSMENT

Risk Assessment should include criteria related to the service provided by the laboratory and criteria related to the performance of the laboratory selected.

Criteria related to the service provided should include the impact of the test result to be provided by the Laboratory (e.g. test result to be included in the COA, test result for development purposes, test results included in regulatory submission document) and the level of detection of a possible error.

Criteria related to the performance of the laboratory selected should include the level of certification/accreditation of the Quality Systems, the experience in the activity and possible subcontracting activities.

Recommended criteria and respective weights are listed below.

Criteria related to the service:

- Criticality of the service (weight 45%) - Refers to the criticality of the analytical testing that will be provided by the Contract Lab, depending on the use and its importance for the owner.
- Stage of product life cycle (weight 10%) - Refers to the clinical phase of finished product (for manufacturing processes under development) up to validated manufacturing processes at commercial stage; for miscellaneous uses, validated status should be considered as the worst case scenario;
- Detection of error (weight 5%) - Refers to the level of verification performed by the requester upon service completion that would detect a possible error from the contracted lab, e.g. a known sample is tested in parallel. A report with full details is verified before accepting service output.

Criteria related to the performance of the Laboratory:

- Quality systems (weight 25%) - Aims to consider the impact of having (or not) a formal Quality System in place as well as the being inspected by EU (or other) Health Authorities ; it considers also the credibility of the certification and the adequacy/compliance of it when compared to the user requirements;
- Experience in the service (weight 10%) - Covers the experience that the Contract Laboratory may have on the performance of the service that will be provided. Level of expertise in the required technology should also be considered.
- Complexity of Supply Chain (weight 5%) - Aims to measure the level of security of the supply chain, considering the areas with higher risk factors and the level of control of the supply chain and its parties.

Assigning a level for each criterion is a multidisciplinary task, the output is a percentage of risk which assigns a Risk Level.

High Risk: % Risk between 75 and 100
Medium Risk: % Risk between 50 and 74

Low Risk: % Risk between 0 and 49

Using the following formula :

$\% \text{ Risk} = \Sigma (Ci * wi) / \Sigma wi$

Wherein Ci corresponds to each Criterion and wi to the respective weight.

Attached Matrix can be used as an aide-memoire for the classification of each Criterion. It should be seen as a tool and a suggestion that can be adapted to each reality.

The level of risk will define the level of oversight that is required to qualify a Contract Laboratory, meaning that as higher the risk as higher the detail required to support the Qualification of the Laboratory.

CHAPTER 3: QUALITY ASSESSMENT

The extent of the Quality Assessment of Quality Control Contract Laboratories will be dependent on the outcome of the Quality Risk Assessment as described in the previous Chapter.

Risk can be classified as High, Medium or Low depending on the impact of the results generated, the Lifecycle Stage of the Product and the track record of the laboratory.

The level of Risk may then be used to decide the level of Quality Assessment required.

The following criteria should generally lead to classification of High Risk:-.

- Test results being contracted out that will be used to Release Registered Intermediates or API's.
- Laboratories where there are no current Certifications or accreditations available.
- Laboratories that generate data used in Regulatory submissions.
- Laboratories that are listed in Regulatory Submissions and may be subject to inspection.

The key elements that should be considered in each Quality Assessment and how they should generally be applied to High, Medium and Low Risk are summarised in Table1.

The Contract Giver should decide on the relevant steps of the Quality Assessment to be followed in each case. The Quality Assessment should be documented and approved by Senior QA Management.

Table 1: Key Elements of Quality Assessments for Quality Control Contract Laboratories.

Requirement	Low Risk	Medium Risk	High Risk
Contract Laboratory Quality System Questionnaire	√	√	√
Review of information on Certifications of laboratory and Quality System (ISO17025-if relevant for test results being contracted out, ISO 9001 Quality System, others),	√	√	√
Review of information on GMP Compliance level of Contract laboratory and inspection history / Certification	*√	*√	*√
Review of Historical Performance of Contract laboratory	*√	*√	*√
Review of relevant analytical methods of Contract Laboratory	√	√	√
Sample testing-comparison of results from Contract Giver and Contract Laboratories	X	**√	*√

Contract Laboratory Audit	X	**√	√
Method Transfer and Validation	**√	***√	***√
Purchasing Contract with Quality Clause	√	√	√
Quality Agreement	X****	**√	√

* - if available or applicable
** - should be considered and decision documented
***- expected unless pharmacopoeia methods will be used
√- expected
X- not normally expected
X**** - Not expected as long as there is a Quality Clause in the Purchasing Contract defining the division of responsibilities.

1. Format of the Quality Assessment

1.1 Contract Quality Control Laboratory Questionnaire

Information on the quality system including laboratory certification and the main laboratory procedures in place in the Contract Laboratory should be requested for all contract laboratories usually in the form of a Contract Laboratory Questionnaire.

Information should be requested and reviewed for the following topics:

- Laboratory management structure and organogram
- Laboratory organogram including numbers of analysts
- and Quality Control- areas of expertise
- Laboratory Quality System – ISO 9001, ICH, GMP, GLP, GCP
- Information on Laboratory Certifications – ISO 17025, If scope is relevant for test results being contracted out,
- Copies of Certificates should be requested
- History of cGMP compliance Inspections – copies of inspection certificates or reports should be requested
- List of equipment
- List of analytical techniques
- Index of SOP's
- Expertise in validation of methods in accordance with ICH Q2-Validation of Analytical Procedures – Text and Methodology.
- Approach to verification of pharmacopoeial methods and methods received from customer
- Approach to compliance with Pharmacopoeia-general chapters
- Equipment controls-level of qualification and calibration is there a Validation Master Plan? If yes copy should be provided.
- Short summary of approach to periodic re-qualification and re-calibration of instruments
- Preparation and / or control of samples in the laboratory

- Preparation and control of reference standards
- Preparation and control of reagents
- Use of LIMS, chromatography data systems and /or other automated systems
- Computer System Validation, compliance of software, change control and deviation SOP's related to software
- Laboratory notebooks, analytical test records
- Information on verification and approval of laboratory data / release of results
- Raw data handling
- Analysts Training
- Laboratory Change Control,
- Laboratory Deviation SOP, OOS SOP
- Retain sample control
- Training
- Document control
- Document retention / archiving policy

1.2 Initial Evaluation of Contract Laboratory Test Methods and Results

A review of the analytical methods that will be used by the Contract Laboratory should always be done. The laboratory may use their own methods or analytical methods may be provided by the Contract Giver.

For High Risk, an initial evaluation of the test results from the contract laboratory should be considered before an audit is performed, if the laboratory already has capability to provide test results prior to method transfer and validation.

The relevant specifications, analytical methods and reference standards for the tests to be performed should be provided by the customer where applicable.

This evaluation of the initial test results provided by the contract laboratory, usually based on samples provided by the customer, should be carefully evaluated with results from the customer laboratory, where this is applicable.

Any changes related to the analytical methods or equipment to be used in all phases of the Quality Assessment should be handled according to the Change Control procedures of both the Contract Giver and Contract QC Laboratories.

Any issues from this initial evaluation of test results should be resolved before progressing to the next step of the Quality Assessment.

1.3 Audit of Quality Control Contract Laboratories

A prior approval audit of a High Risk Quality Control Contract Laboratory should be done as a core part of the Quality Assessment.

For a Medium Risk, the Contract Giver should decide if an audit is required or not of the Quality Control Contract Laboratory based on the Performance Track record of the Laboratory, for example, if Certification or Regulatory inspections have been satisfactorily completed or if a Third Party Audit report is available for review.

The decision whether to audit or not the laboratory should be justified and documented by the Contract Giver.

The auditing standards should be agreed in advance with the Contract Laboratory as part of defining the Audit Agenda to avoid disagreements on the scope during the audit.

In the case that the laboratory will provide QC test results used for release of a registered intermediate or API or for cGMP Controls related to the manufacture of registered intermediates or API's, the relevant ICH guidelines including ICH Q7 should be the auditing standards.

In other cases where an audit will be performed, the auditing standard should be defined in advance by the Contract Giver.

The APIC Audit Programme – Aide memoire to ICH Q7 - is recommended as guidance on the expected GMP and laboratory practices of a Quality Critical Contract Laboratory where ICH Q7 GMP Compliance is required.

The most relevant ICH Q7 Chapters for audit assessment are:-

- Chapter 2 Quality Management
- Chapter 3 Personnel
- Chapter 6 Documentation and records
- Chapter 11 Laboratory controls
- Chapter 12 Validation
- Chapter 13 Change Control
- Chapter 15 Complaints and Recalls

The checklist that was completed during the initial laboratory evaluation should also be verified during the audit (Reference: Annex 1).

A qualified Quality Auditor, from Quality Assurance and/or a QC Expert would be the recommended audit team.

Depending on the country where the Quality Control Laboratory being audited is situated and the written and spoken languages of the contract laboratory, an interpreter may be necessary.

The auditors should focus on the effectiveness of the Laboratory Controls for the following procedures:-

- analytical method development and validation if applicable
- analytical method transfer and validation

- verification of pharmacopoeial methods
- implementation of the analytical methods to be used
- preparation of reagents
- verification of the accuracy of the analytical test results
- traceability of all instruments, procedures, reference standards, reagents and personnel involved in generating the test results
- control of reference standards
- periodic qualification, calibration, monitoring and verification of equipment and instruments
- QC / QA review and approval of QC results to be reported to the Contract Giver

Quality System Procedures and Practices should also be assessed for:-

- personnel qualification and training
- document control
- management of change
- Laboratory deviation investigations and, where applicable, Out of Specification (OOS) investigations and reporting to Contract Giver
- internal audits
- management of Corrective and preventive actions (CAPA)
- complaints handling

In the closing meeting of the audit, the Lead Auditor should present the audit findings and the evidence for any audit observations of deficiencies in Laboratory Controls, Quality Systems and cGMP Compliance standards, for review and agreement with the Contract Laboratory auditees and Senior Management.

The Lead Auditor should also advise the Contract Laboratory on likely approval or not and agree timelines for the Audit Remediation Process.

Guidance on Classification of Audit Observations is given in the APIC Audit Programme Guidance document – http://www.apic.cefic.org/publications/publications.html

1.4 Remediation and Assessment of the Remediation

Remediation of any Critical or Major Observations from the audit would be required before the Contract Laboratory could be approved to perform testing on behalf of the Contract Giver.

The need for a Follow Up audit should also be considered.

Any other issues found during the Quality Assessment should also be clearly documented and a remediation plan agreed with the Contract Laboratory.

For example, if there is a need to purchase new equipment, provide new reference standards or perform analytical method validation or to ensure that valid Inspections and laboratory Inspection Certificates are available.

2. Completion of Quality Assessment

All of the data related to the Quality Assessment should be collated and reviewed by the multi-disciplinary project team.

If the review of the data, (not only the result of the audit), is un-satisfactory then a decision must be made on whether further remediation is to be considered or the quality assessment is a NO GO.

If the Quality Assessment is satisfactory then the decision is GO.

Final decision to recommend approval of the contract laboratory should be taken by a Senior QA Manager of The Contract Giver.

2.1 Method Transfer and Validation

Inter-Laboratory Protocols for Method Transfer and Validation for High and Medium Risks are recommended for all methods transferred to Contract Quality Control Laboratory. The acceptance criteria may vary depending on the level of Risk.

Validation of analytical methods should be done in accordance with the ICH Guideline Q2 (R1)- Validation of Analytical Procedures –Text and Methodology.

In the cases where validation has already been done by the Contract Giver and a copy of the validation report is provided to the Contract Laboratory, the acceptance criteria for transfer of the methods should be needed only for inter-laboratory validation (precision / reproducibility) as specified in the ICH Guideline Q2 (R1).

The acceptance criteria for precision and reproducibility should define the number of samples to be tested including testing of samples on different days with different analysts and, if possible, with different instruments, with the acceptable variation defined based on the data in the validation report of the method.

For Low Risks, the acceptance criteria for Method Transfer and Validation may simply be comparison of results obtained for same sample or batch in the contract QC and Contract Giver QC Laboratories within acceptable Relative Standard Deviation.

Method Transfer and Validation Protocols should be approved by QC/QA Managers of both the Contract Giver and Contract Acceptor.

3. Purchasing Contract / Quality Agreement with Contract Quality Control Laboratory

In all cases, a Purchasing Contract should include a Quality Paragraph that should be reviewed and approved by both the Contract Giver and Contract Acceptor. Typically, Quality Assurance and Quality Control personnel and Procurement are involved in the review, and others as appropriate, for example, Legal department, Production and Project managers.

The Quality Paragraph should define the analytical tests or services being contracted out, the relevant analytical methods, reference standards and specifications to be followed or used, how any laboratory deviations should be investigated and reported, how proposed changes should be managed and how the QC results should be reported.

A Quality Agreement defining in more detail each party's responsibilities should be prepared and approved by both parties at least for High and Medium Risks.

In the case where the laboratory is only responsible to report the result, the Contract Giver should review and decide if OOS Investigation is required. In the case where QC test results are released by the Contract Laboratory in line with specification, the contract laboratory should perform laboratory investigation of any OOS result and report conclusions to the Contract Giver.

Contract Giver will then decide on next steps including any re-testing or re-sampling and re-testing.

The detail contained in the Quality Agreement will depend on the level of Risk, the types of analyses being contracted out and the Quality System / laboratory standards in place in the Contract Laboratory.

An example of a Quality Agreement for Contract Laboratories is being developed by the relevant APIC Task Force and should be available later in 2012.

Development of the Purchasing Contract and where appropriate the Quality Agreement may start after satisfactory Quality Assessment and signed documents should be available before the Contract Laboratory is approved under the Change Control Procedure of the Contract Giver.

3.1 Approval of the Contract Quality Control Laboratory

Following completion of the Quality Assessment, any Method Transfer and Validation Activities and when signed Contracts and Quality Agreements are available, the use of the Contract Quality Control Laboratory for the related test results should be approved following the Contract Giver's Change Control Procedures.

The QC/QA responsibilities of the Contract Giver for verification of the test results for compliance with specification, where applicable, and inclusion for example in the Certificates of Analysis of the Intermediate or API should be documented as part of the Change Control Procedure of the Contract Giver, in addition to the Purchasing Contract and Quality Agreement.

The frequency of periodic verification of the accuracy of the contract laboratory test results and for periodic evaluation of any adverse trends related to the test results should also be documented in the change control record of the Contract Giver.

The Quality Paragraph of the Purchasing Contract and the Quality Agreement should be periodically reviewed to ensure they are still accurate, for example as part of the Annual Supplier Evaluation or Product Reviews.

CHAPTER 4: ONGOING SUPPLIER MANAGEMENT (MONITORING AND EVALUATION)

After the approval of a new contract laboratory, a periodic evaluation should be performed. For this evaluation different elements should be considered. The following chapter will define the activities for the ongoing evaluation and finally re-define the status of the qualification.

1. Responsibilities

The evaluation should be under the control of the Quality Unit but completed as part of a multi-disciplinary team. The Quality Unit is responsible for the ongoing evaluation and the classification of the supplier. Other departments should give their input to ensure that all relevant aspects are taken into account.

2. Elements of monitoring and rating

2.1 Ongoing monitoring

All agreed activities should be assessed according to defined criteria. These criteria should be a result of the risk assessment (see Annex 3).

At least the following aspects should be taken into consideration:

- Test documents (reports, protocols)
- Documentation of OSS results
- Evaluation of change control including risk management
- Customer complaints regarding analytical results
- Ongoing review of any trends in analytical data for contract lab involved
- Adherence to agreed timelines

All deviations should be monitored and managed according to the company's complaint procedure.

2.2 Periodic evaluation

Regular, typically on an annual basis, the supplier's performance should be assessed. For low risk quality control contract laboratory a periodical evaluation may not be required.

The following data should be evaluated:

- All results
- Adherence to agreed timelines
- Adherence to Quality Agreement

- Cross check of values on COA
- Trend analysis
- Audits results (own audits, authorities or third parties – if agreed upon)
- Customer complaints regarding analytical results
- Changes (methods, equipment and specifications)
- Responses on audit and remediation plan
- Response times for complaints and questions
- Changes in certification/accreditation status
- Results of inter laboratory performance test (if necessary)
- Turnaround of personnel
- Development of costs

2.3 Rating (classification)

After the periodic evaluation it could be appropriate to classify the contract laboratory according to an objective rating system. This rating system gives an indication about performance and satisfaction. The following categories are an example for a rating system:

- Completely satisfactory: approval
- Mainly satisfactory: limited approval (ongoing use)
- Partially satisfactory: conditional approval (no high risk quality control activities until corrective actions are in place)
- Not satisfactory: disqualified until actions are taken

The result of the rating has an important impact on the frequency of re-audits, re-evaluation, extent of sampling and testing. To manage this rating the company should have a system in place to manage this rating. Rating results should be reported to the management (e.g. as part of the Management Review).

2.4 Quality Review meeting

In order to develop a trustful relationship and take all opportunities to maintain and improve the quality of the service, the results of the periodic evaluation should be shared with the supplier. This should be mandatory for high risk quality control contract laboratory.

Depending on results and need for an exchange of information this could be either in person or in written form.

In this review the monitoring results should be presented and, if necessary, discussed. If there is a need for corrective actions they should be defined and timelines for improvement agreed.

In addition to that a meeting should also be used for general discussions, exchanges of experience and for the update of KPIs and/or the quality agreement.

2.5 Re-audit

The decision for auditing/re-auditing contract laboratories with low risk activities should be based on the performance of the laboratory (classification).

High and medium risk quality control laboratories should be audited on a regular basis.

The GMP standard for the re-audit should be the same as the initial audit. Further developments in the regulatory guidelines should be considered.

The frequency of the re-audit should by dynamic and depending on criticality (for risk assessment see Annex 3) and on the rating.

Regulatory expectation are for companies with **high risk** contract quality control laboratories to assess the frequency of re-auditing the facility based on performance and a risk based evaluation. This evaluation should be documented.

The frequency should be maintained until the performance is on a higher level. If the laboratory shows a low performance for more than one year, the approval should be reconsidered.

In the case of stability testing problems, serious complaints, unsatisfactory response on remediation plans, bad results of authority audits or any doubts regarding GMP compliance an unscheduled audit can be performed.

2.6 Re-Evaluation

In parallel with the re-audit the contract laboratory should be re-evaluated. As a result of the outcome the Quality Agreement and other contracts should be reviewed and updated as necessary.

APPENDICES

Appendix 1: Contract Laboratories Potential ID Selection

Appendix 1_Contract
_lab_selection_checkl

Appendix 2: Contract Laboratories Questionnaires

CONTRACT
LABORATORY QUESTI

Appendix 3: Risk Assessments

Risk Assessment
matrix_annex3 - Mari