**ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE (APIC)**

# SUPPLIER QUALIFICATION & MANAGEMENT GUIDELINE

**December 2009**

# Content

# INTRODUCTION

Manufacture of Medicinal Products and the Active Pharmaceutical Ingredients (APIs) used as starting materials in the production of these products is subject to strict good manufacturing practice regulations that are designed to ensure their quality, safety and efficacy. This 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.

While in the vast majority of cases, the pharmaceutical industry, under the oversight of the Regulatory Authorities and inspectorates consistently applies appropriate cGMP practices, there are many cases known where the standards expected from manufacturing companies have not been maintained. Some of these cases had very serious consequences e.g.:-

- The heparin case in 2008, causing around 150 fatalities in the U.S. due to deliberate contamination of the API with a bogus substance (oversulphated chondroitin sulphate)
- The many scandals involving the contamination of glycerine with diethylene glycol that led amongst others to 107 deaths in the USA (1937), around 300 deaths in Bangladesh (1990), 88 deaths (young children) in Haiti (1996), and 138 deaths in Panama (2006), due to lack of controls in the distribution networks of glycerine and in the medicinal product manufacturing sites involved
- The gentamicin sulphate case in which unknown contaminants caused in total around 65 deaths in the USA in 1994 and 1999 respectively
- Other cases of counterfeit medicines, falsified APIs and medicinal product recalls due to adulteration of medicines or APIs released to the market underline the potential magnitude of the risk to patients if the supply chain for medicines is not properly qualified.

In some cases business pressures to reduce costs results in sourcing APIs and the raw materials used in their manufacturing process at the lowest cost. While this practice, in and of itself, does not create non-compliance, it does create an opportunity for unscrupulous suppliers to insert themselves into the supply chain and introduce substandard materials. This situation also highlights the need for clarity regarding expectations and requirements for supplier quality and assurance of the full supply chain.

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

- **Supplier Selection Process** based on definition of the User's Requirements for a material with as a minimum a specification
    - Sample evaluation including where necessary laboratory and /or production trials

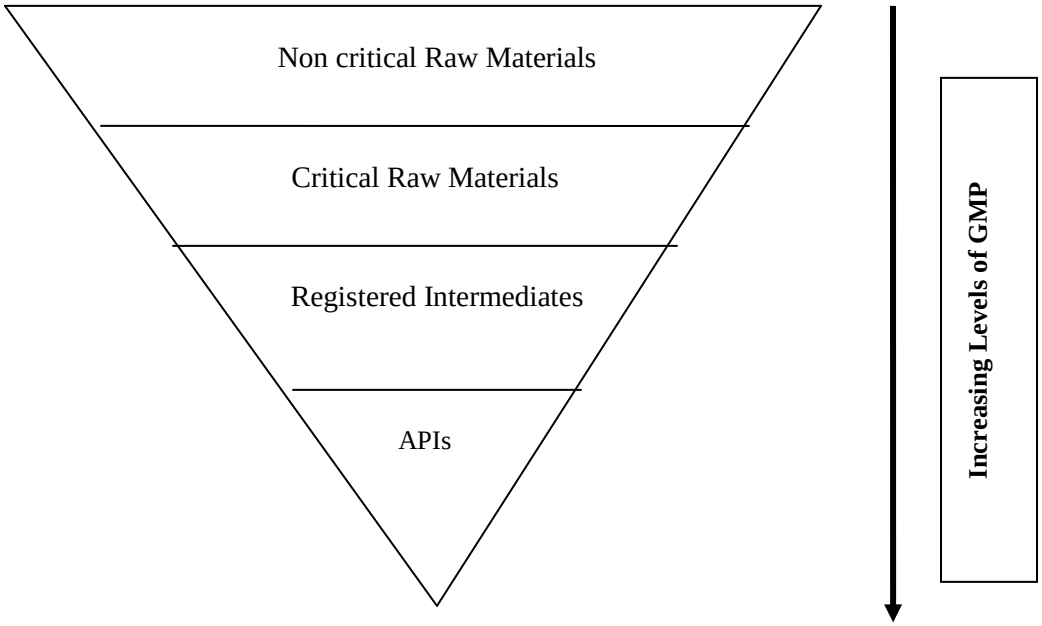
- **Due Diligence process** of potential suppliers of critical raw materials, registered intermediates and APIs
- **Quality Assessment of all suppliers**
- **Change control and production assessment** as necessary
- **Supply chain security**
- **Ongoing monitoring and evaluation**

The target audience for the guidance document is primarily API Manufacturers while it may also be used by medicinal product manufacturers who are primarily responsible to qualify their suppliers / manufacturers of APIs used as Starting Materials in the manufacture of medicinal products.

We have classified the materials into the following four categories based on quality criticality to the API manufacturing process and on risk related to potential for harm to the patients:-

- Non-critical raw materials
- Critical raw materials (including API Starting Materials)
- Registered intermediates
- APIs

The quantity of materials in each category is likely to decrease as the criticality increases as indicated in the following triangle:




In terms of defining the categories of materials we recommend that companies review the use of the material based on the ICH Q7 definition of *Critical*:-
"*Critical describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification*".

For an API manufacturing process involving multiple-step synthesis, raw materials used in the early steps are likely to be less critical than those used in the final API step given that accurate specifications will be defined for all raw materials.

To assess the risk to patients related to the material 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*".

For example the risk of particulate or microbiological contamination from a reagent, solvent, water system, utility or primary packaging material that are in direct contact with an API will or greater than materials used earlier in the process.

We recommend that suppliers of all the materials should be approved using the Company's Change Control Procedures and / or Supplier Approval Procedures. Change

control requirements would also be more stringent for critical raw materials (including API Starting Materials), registered Intermediates and API and should include a Regulatory Assessment.

**Definitions:**

- **Raw materials** can be sub-categorised into three different classes:

a. Those that are widely commercially available and are used in multiple industries, for example acids, bases, solvents, filter aids, petroleum based raw materials, naturally occurring raw materials, packaging materials, water systems or utilities in contact with the API such as nitrogen or compressed air.

b. Those that are commercially available for use in the API Industry such as catalysts, enzymes, chemical (including chiral) building blocks.

c. API Starting Materials. These may be generally available or involve custom synthesis or specific process development by the supplier before becoming available on an industrial scale.

- **Registered intermediates** usually involve custom synthesis or process development by the supplier.

- **APIs** will be manufactured under custom synthesis or contract manufacture or will be generally available if used in the manufacture of off-patent medicinal products.

- Further examples of types of materials covered by the scope of this guidance document and guidance on criticality are given in *Appendix 1*.

**Guidance:**

The quality system requirements to identify, select, approve and qualify suppliers of all materials used in the manufacture of APIs and medicinal products are clearly defined in the GMP Guidelines.

Manufacturers of medicinal products, APIs and registered intermediates for APIs are responsible for approving and qualifying their suppliers and to monitor on an ongoing basis the performance of their critical suppliers.

The Regulatory Agencies will and do inspect the supplier qualification procedures used by medicinal product manufacturers and expect that they periodically audit their API supplier / manufacturer. As part of this audit, the medicinal product manufacturer should ensure that the API supplier / manufacturer also has supplier qualification procedures in place for their suppliers of critical and non-critical raw materials, API Starting Materials, Registered Intermediates and APIs (in the case of contract manufacturers). In relation to critical raw materials the Authorities will also expect a monitoring programme to be in

place and for the manufacture to have clear oversight of the changes with possible quality impact made by their suppliers.

Inspectors will also expect that the distribution and supply chains have also been evaluated and that controls are in place to ensure there is adequate Supply Chain Security, to avoid possible fraudulent practices and to ensure that appropriate transportation conditions (i.e. temperature and humidity) are applied during distribution where this is required based on the properties of the materials.

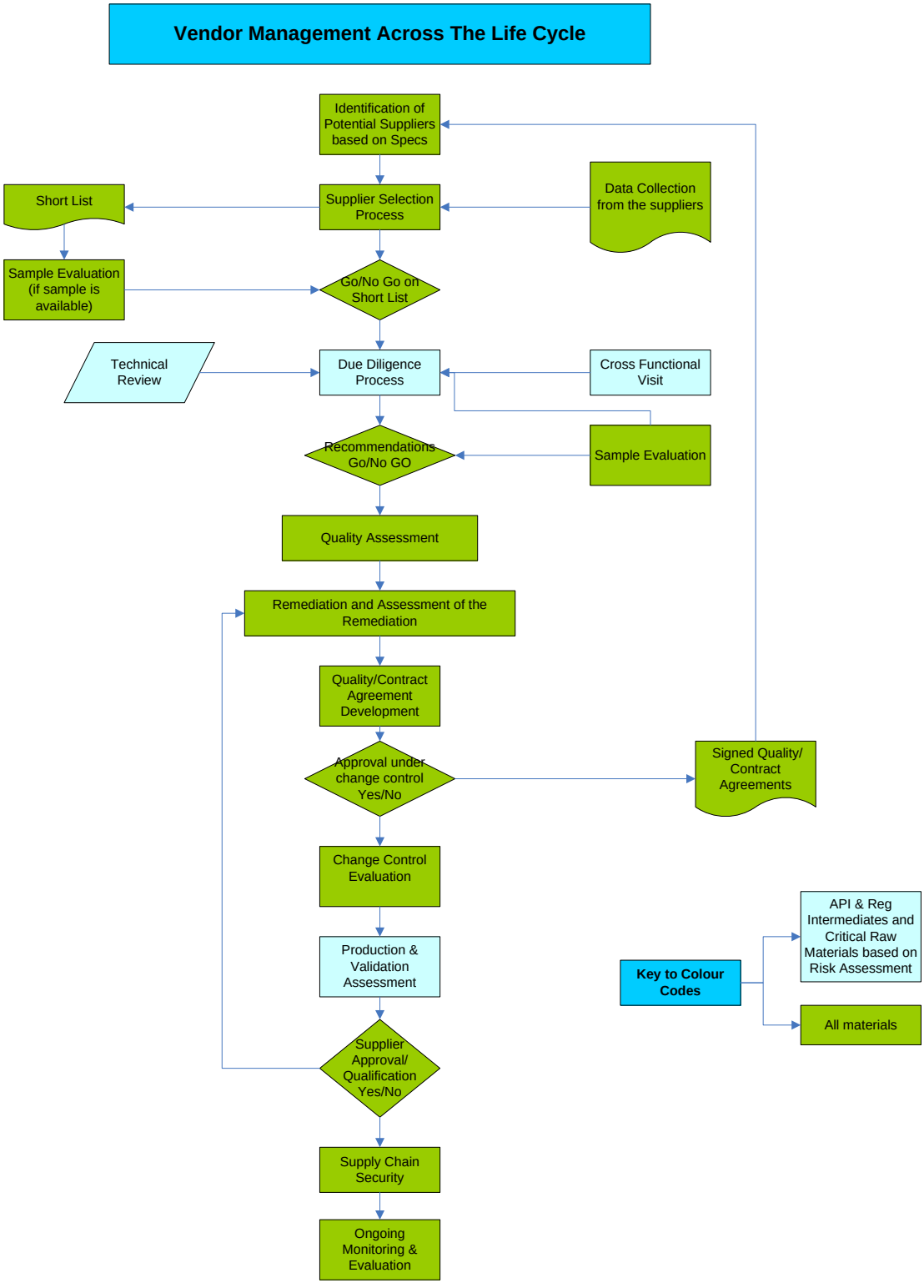
The pre-requisites for approval of suppliers of all materials including non critical raw materials are that the material meets the specification defined by the customer confirmed by 1) sample evaluation (QC testing) and that 2) there is an evaluation of the quality system in place designed to assure and control the manufacture, testing, release and distribution of the material.

The expected Product Quality Standard and the depth of the quality assessment will vary depending on the type of material but these two pre-requisites should always be there and would be considered as the basic requirement for approval of a non-critical raw material supplier.

For critical raw materials, intermediates and API's, it is recommended there should be a due diligence assessment, a more detailed assessment of the quality system and material evaluation should involve laboratory or plant trials prior to full production assessment.
A purchasing contract that defines quality requirements should be in place for suppliers of all materials and a Quality Agreement should be in place for suppliers of registered intermediates and APIs.

Any changes to the material specification, analytical methods and/or manufacturing process that may affect the quality of the material supplied and/or the down stream products should be informed in advance (and prior to implementation) to evaluate the impact on down stream production/product.

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


Vendor Management Across The Life Cycle
Identification of Potential Suppliers based on Specs
Supplier Selection Process
Short List
Data Collection from the suppliers
Sample Evaluation (if sample is available)
Go/No Go on Short List
Technical Review
Due Diligence Process
Cross Functional Visit
Recommendations Go/No GO
Sample Evaluation
Quality Assessment
Remediation and Assessment of the Remediation
Quality/Contract Agreement Development
Approval under change control Yes/No
Signed Quality/ Contract Agreements
Change Control Evaluation
Production & Validation Assessment
Supplier Approval/ Qualification Yes/No
Supply Chain Security
Ongoing Monitoring & Evaluation
Key to Colour Codes
API & Reg Intermediates and Critical Raw Materials based on Risk Assessment
All materials

The main steps of Supplier Management are described in each chapter including the elements relevant for non critical or critical raw materials, registered intermediates or API's.

We are also referring to existing APIC guidance documents whenever 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

Those 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:

- Bryson Lynn (JOHNSON MATTHEY MACFARLAN SMITH)
- Buggy Tom (DSM ANTI-INFECTIVES)
- Stilgenbauer-Voigt Ingrid (BASF)
- Chekatt Habiba (DSM NUTRITIONAL PRODUCTS)
- Hamrin Pia (DSM NUTRITIONAL PRODUCTS)
- Vandeweyer François (JANSSEN PHARMACEUTICA)
- Stampfli Claudia (LONZA)
- Cox Robert (LONZA)
- Counihan Eileen, **Chair** (MERCK SHARP & DOHME)
- Vandenbossche Claude (AJINOMOTO OMNICHEM)
- Storey Anthony (PFIZER)

We have had a lot of fun and enjoyed working together and sharing best practice in the creation of this document. We hope you will find it useful in the serious business of supplier management and the assurance of 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:

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

## CHAPTER 1. SUPPLIER SELECTION

The purpose of this step is to define a set of criteria that can be taken into consideration in the selection process of a supplier. If a supply need is identified purchasing is contacted for the identification of (a) potential supplier(s). The supplier selection process starts with the definition of the user requirements for the materials(s) within scope.
The user requirement specifications provided to purchasing should contain as a minimum the following information:
• Name of the product (including formulae and CAS number when available)
• Material specifications
• Quantity required

The materials within scope of this guidance have been classified as follows:
• Non-critical raw materials,
• Critical raw materials (including API starting materials);
• Registered intermediates;
• APIs

For the raw material group a sub-categorisation into three different classes is proposed.
• Those that are widely commercially available and are used in multiple industries, for example acids, bases, solvents, filter aids, petroleum based raw materials, naturally occurring raw materials, packaging materials, water systems or utilities in contact with the API such as nitrogen or compressed air.
• Those that are commercially available but are for use in the API Industry such as catalysts, enzymes, chemical (including chiral) building blocks.
• API Starting Materials. These may be generally available or involve custom synthesis or specific process development by the supplier before becoming available on an industrial scale.

The quality system evaluation may be less or more elaborate in function of the identified material classes and follows a documented process. The following information from the supplier should be requested as part of the Suppliers Questionnaire *(As per Appendix 4)* :
- Specifications
- Manufacturing/packaging/labelling details
- Materials Safety Data Sheets
- Logistic information (lead time to produce, delivery time, etc)
- Certificates regarding Quality system, residual solvents, etc...
- BSE/TSE evaluation
-Analytical test method

It is a pre-requisite to demonstrate that the material provided by the potential supplier meets the specification as defined, and compliance to the specifications should be verified by analytical testing of a sample. The sample (representative of commercial production) can be pre-shipment sample(s) (with appropriate controls) or the release sample of the first delivery.

For critical raw materials, intermediates and APIs it is likely that the data to be requested and collected from the potential suppliers will be more elaborate comprehensive than for raw materials.

For critical raw materials, registered intermediates and APIs key selection criteria have been identified and categorised.

Following different dimensions could be assessed:

- Assurance of Supply,
- Quality & Regulatory compliance;
- Cost/Procurement aspects;
- Technical/Innovation;
- Communication capabilities & responsiveness

The Supplier Selection Checklist (*Appendix 2*) contains a non-exhaustive list of areas to address which must be requested from the supplier. The Supplier selection checklist should be seen as an example and should be adopted in function of the company's need. Some of the identified criteria can also be considered in the selection process for non-critical raw materials. A suggestion of topics to be checked for non critical raw materials is provided in *Appendix 2*.

Each different criteria is discussed in more detail below:

### 1. Assurance of Supply

Assurance of supply is an essential element in order to guarantee appropriate supply chain management in the organisation. To obtain a picture as complete as possible following aspects should be taken into consideration:

- Capacity (Scale equipment, batch size, chemistry experience, etc.…)
- Safety/Health/Environmental Risk
- Inventory management
- Financial solvency/business stability
- REACH requirements
- Delivery performance
- Supply chain management of the material in question

### 2. Quality & Regulatory Compliance

In the selection process it is essential to take the quality and regulatory track record history into account. To obtain a comprehensive picture of the supplier's compliance status, the following aspects should be taken into consideration:

- cGMP Compliance & regulatory track record
- Recalls & Complaints
- Change/Deviation Management
- Materials management controls

- Quality Management Systems
- Quality Agreement
- Quality Culture
- Production Facilities & Equipment
- Product Quality Review
- Process Validation approach:
- QOTIF % (On time in Full)
- Documentation standard

### 3. Procurement/Cost

Next to the price of the material within scope there are other aspects related to cost and procurement that should be taken into consideration:

- Cost Management (Cost visibility)
- Presence in Low Cost Countries (Emerging markets)
- Ability to achieve the target price

### 4. Innovation/Technical

In order to generate a better understanding of the technical competences and innovative profile of the supplier, following aspects should be taken into consideration:

Technology specialism

- Plant capabilities
- Laboratory capabilities
- Business problems resolving capabilities
- Technical skills/ Staff Qualifications
- Control systems
- Development capability
- Process development expertise
- Project management
- Willingness to innovate
- Intellectual property

### 5. Responsiveness & Communication

In order to generate a better view on the responsiveness and communication capabilities, following aspects should be taken into consideration:

- Rapidity project assessment
- Resource availability
- Flexibility (Attitude)
- Functional contacts definition
- Openness
- Ease of communication (understanding of English)
- Pro-activeness

For critical raw materials, registered intermediates and APIs all data collated from the potential suppliers is assessed thoroughly ideally by a multidisciplinary team. This assessment should result in a shortlist of potential suppliers. In case material samples were received the analytical test results generated are used to support the GO/NO GO decision to pursue the supplier qualification process of the identified supplier. The next step is to initiate the due diligence procedure. This will allow the company to compile documented evidence of the supplier's suitability. Further guidance on the due diligence procedure is provided in *Chapter 2*.

For non critical raw materials meeting the defined user requirements a quality assessment is started to determine the suitability of the supplier. A positive outcome of the quality assessment is required to continue progressing with the supplier. Further guidance on how to conduct the Quality Assessment is provided in Chapter 3.

## CHAPTER 2. DUE DILIGENCE

**Purpose:**

- This chapter is not applicable for non-critical raw materials.
- For Critical Raw Materials including API Starting Materials the necessity to perform a due diligence can be based on a risk assessment according to ICH Q9.
- This chapter will define and provide detail to assure that the appropriate due diligence is conducted prior to contracting with the supplier. Documented evidence will be assembled to support the Go/No Go decision process.
- The possibility of establishing a long term business relationship with the supplier will be evaluated.
- The implemented systems and existing facility will be assessed and challenged in order to evaluate the capability of the supplier to comply with the customer's requirements.
- The potential to supply where process is not yet established and samples / production batches are not available/ produced will also be assessed based on capabilities for example:
    - process equipment ,
    - facility containment,
    - quality of utilities,
    - analytical equipment availability including stability chambers
    - potential for process and analytical method development and validation
    - ability / demonstrated performance of preparing regulatory submissions

### 1. Selection of cross functional team:

Depending on a criticality evaluation a cross functional team will be formed. Representatives of the Project Management, Procurement and the Quality Unit will always be part of the due diligence team. Resulting from the criticality evaluation the team can be extended with representatives from other areas such as:

- Engineering,
- Regulatory,
- Environmental/ Health / Safety,
- Technical Experts e.g. Chemical/Biological Process Engineer(s) and QBD experts,
- Procurement,

Each member of the due diligence team documents the collected information and formulates a decision and/or action proposal related to his/her expertise field. The combined information is presented to the Senior Management in the form of a recommendation.

## 2. Areas to be challenged:

### 2.1. General Material Information:

The general material information to be challenged can be based on sample evaluation results where available, possible impurity profile issues, quality system pre-assessment and/or supply chain assurance. Examples to verify are:

- Sufficient capacity to assure supply chain,
- Anti Counterfeiting measurements,
- Audit sustainability (qualification of the total supply chain),

The most important items to challenge related to the general material information are listed in *Appendix 3* Due Diligence Check List.

### 2.2. Quality Systems:

ICH Q7 must be used as basis to evaluate the implemented quality systems for Registered Intermediates and API's.
If for Critical Raw Materials including API Starting Materials, the outcome of a risk assessment according to ICH Q9 indicates the necessity to perform a due diligence, the focus of the evaluation of the quality systems implemented can be reduced according to the requirements indicated by the risk assessment.
If ICH Q7 is not applicable the General Quality System in place (example ISO 9001) should be challenged.
Additional to compliance to ICH Q7 other topics can be challenged. Examples are:

- Use of Quality By Design,
- Implementation of systems to assure Continuous Quality Improvement,
- Implementation and use of Risk Management

### 2. 3. Plant Tour / Organization

A plant tour contributes to the evaluation of the ability and willingness of the management to support facility and equipment maintenance and contamination prevention.
Examples of items to be challenged during the plant tour are:

- Contamination prevention,
- Utilities: Water system, HVAC, Nitrogen, Steam, Cool media,
- Equipment calibration and maintenance (production and QC),
- Laboratory controls and product release procedures
- Warehouse controls

### 2.4. Documentation / Organization

The documentation review contributes to the evaluation of capability of the organization to demonstrate traceability, compliance to the manufacturing process and compliance to ICH Q7 and/or the General Quality System in place.
Examples of documentation that can be challenged during review are:

- master records, batch production records, laboratory records
- Training and personnel qualification,
- Quality systems (product release, change control, deviation handling, failure investigations, stability program, etc.).

### 2.5. Process

Evaluation of the process and equipment availability contributes to the evaluation of the capability of the company to manufacture material of consistent quality and compliant to ICH Q7 if applicable (examples: API and registered intermediates) or compliant to the General Quality System in place.

#### 2.5.1. Chemical Synthesis.

Examples of items that can be assessed are:

- Critical process parameters and their associated critical quality attributes identified,
- Chemical development history/report,

#### 2.5.2. Bio Chemical Synthesis.

Examples of items that can be assessed are:

- Cultivation Process,
- Purification Process,
- Cell bank maintenance,

#### 2.5.3. Manufacturing process (Chemical and Biological):

Examples of items that can be assessed are:

- Process trending (Yield, Quality, etc.),
- Rework / Reprocess
- Validation protocols and reports,

### 2. 6. Physical Properties of the material

Evaluation of the consistency of the Physical Chemistry of the material contributes to the evaluation of the manufacturability of the material in next process steps.

Examples of Physical properties can be assessed are:

- Solubility profile,
- Polymorphism, documentation on most stable polymorph,
- Particle size
- Degradates

### 2. 7. Analytics & Stability

Evaluation of the analytical and stability results contributes to the evaluation of the consistency of the quality of the material, its quality profile and accuracy of implemented storage conditions.
Examples of items that can be assessed are:

- Stability indicating methods,
- Analytical methods validated
- Pharmacopeia methods are verified,
- Specifications and technical justification,
- Product Quality Reviews

### 2. 8. Regulatory:

Evaluation of the regulatory status and documentation contributes to the evaluation of the compliance status of the material for all intended countries.

### 2.9. Economics:

Evaluation of the economic contribution to the decision process related to the location of the manufacturing site, supply chain, and business continuity assurance:

### 2.10. Intellectual Property

Evaluation of the patent situation, as well for the production process as the manufacturing technologies used contributes to the decision process.

### 2.11. Safety, Environment & Health

Evaluation of the safety, environment & health systems implemented contributes to the evaluation of the ability and willingness of the management to assure compliance to local authorities' requirements and people health protection as part of the decision process.
Examples of items that can be challenged are:

- Industrial Hygiene aspects,
- Child labour
- Synthesis steps with extreme conditions (temperature, pressure, reagents),
- Waste Management Licences and SHE Quality Systems such as ISO 14001

### 3. Conclusion/Outcome:

An overall report will be issued by the team. The combined information must be used to formulate a final recommendation to Senior Management.

If critical issues (Quality, Safety, Health, Environment, Regulatory, Business continuity) 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 Audit will be executed.
Senior Management is responsible for the final Go/No-Go decision.

## CHAPTER 3. QUALITY ASSESSMENT

A summary of the quality assessment procedure is outlined in table 1 for the three categories of materials.

**Table 1: Summary of Quality Assessment Procedure**

| Requirement | Non Critical Raw material | Critical Raw material | Registered Intermediate/ API |
|---|---|---|---|
| TSE/BSE Assessment | √ | √ | √ |
| Tanker Cleaning Assessment | √ | √ | √ |
| Supplier/Manufactures Questionnaire | √ | √ | √ |
| Manufacturer Audit | | **√ | √ |
| Historical Performance* | **√ | √ | √ |
| cGMP Compliance History | | **√ | √ |
| 3rd party certification* | **√ | **√ | √ |
| Contract Agreement | √ | √ | √ |
| Quality Agreement | | **√ | √ |

*(if available)

√- Required

**√ - Dependant on risk assessment performed on material being purchased.

### 1. Format of the Quality Assessment

The format of the quality assessment is dependant on the criticality of the raw material being purchased and the outcome of risk assessment being performed on the material.

Non critical Raw Materials

For non-critical materials the quality assessment may be limited to a core section of the supplier questionnaire as outlined in *Appendix 4* and/or the provision of an ISO 9001:2008 or equivalent certificate and/or satisfactory past performance by the supplier. The level of assessment is ultimately a decision based on a documented risk assessment.

Critical Raw Materials

The level of quality assessment is based on risk assessment which will take into account the level of in house analysis the customer intends to perform.

In some circumstances, depending on the supply relationship, the customer can use the suppliers evaluation procedures for the manufacturer, as long as this is documented as part of their (the customers) supplier evaluation procedure.

If the customer intends to implement reduced testing of the material it is recommended that the quality assessment takes the form of a manufacturer questionnaire or for "critical" raw materials a manufacturer audit. This decision is again risk based. An example of a full scope of a manufacturer questionnaire is outlined in *Appendix 4.*

Registered Intermediates and API's

For registered intermediates and API's a quality audit of the manufacturer is recommended as a key part of the quality assessment.

## 2. General Considerations

The following must be addressed in the quality assessment of all raw materials/ registered intermediates and API's:

TSE/BSE Assessment

The supplier must be able to certify that all raw materials/ source materials and any other materials (i.e. cleaning agents) used at any stage of the production process comply with the "Note for guidance on minimising the risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products"- EMEA/410/01 (TSE Guideline).

Materials delivered in tankers

When dealing with material which is to be delivered in tankers the quality assessment must address if the tanker is dedicated to one material and if not, cleaning verification procedures must be considered as part of the assessment. This may be in the form of cleaning certificates, testing for trace impurities or if necessary an audit of the tanker cleaning procedure.

## 3. Timeline

Non critical Raw Materials

The quality assessment for non-critical raw materials can be concurrent with the production assessment as long as TSE and tanker cleaning certification are in place before the material is accepted for use in production, following usual raw material acceptance criteria i.e. testing to specification.

Critical raw materials

The quality assessments for critical raw materials should be initiated as early as possible in the procurement process, refer to flow chart. It may not always be possible to have a manufacturer questionnaire response or manufacturer audit performed prior to the production assessment process. The requirement for theses being in place prior to production assessment should be considered as part of the risk assessment for the raw material. At a minimum TSE and tanker cleaning certification must be in place and full testing to specification must be performed prior to the production assessment going ahead, with the manufacturer questionnaire having been sent ( if previously deemed necessary). In some cases the risk may be such that the production assessment does not go ahead until the manufacturer questionnaire / audit have been performed and satisfactory responses have been obtained.

The customer cannot implement reduced testing until the manufacturer evaluation has been completed as per in house SOPs and the requirements of ICHQ7 section 7.3 have been met.

Registered Intermediates and API's

It is to be remembered that the quality assessment must be completed, with satisfactory outcomes before any production can be scheduled. Therefore planning is vital, ensuring data can be gathered, assessments made and remediation performed, if necessary, without risking the integrity of the assessment or project due to time constraints.

The time line should cover items such as:

- The preparation and sending of a pre-audit questionnaire, allowing suitable time for response.
- The development of the agenda with the company and allowance of time to obtain any up front information.
- The actual scheduling of the audit and its performance, at a time convenient to not only the project but also when the supplier has an available slot in their schedule.
- Submission of the audit report/ receipt of response.
- Remediation- if necessary.
- Close out of the audit, once remediation is successful and if necessary re-audit/ assessment.
- Agreeing and signing the quality agreement by both parties

It should also be noted that flexibility has to be built into the time line as all supplier quality assessments will be different, dependant on the scope of the project and the level of compliance of the supplier.

## 4. Roles and Responsibilities

The quality assessment is under the complete control of the Quality unit. The Quality Unit can ask for assistance from other departments which may be able to provide specialist knowledge however ownership cannot be delegated. The Quality unit is responsible for carrying out the assessment and making the Go/No Go decision based on the quality assessment independently.

When an audit is being performed, the lead auditor should be a certified/ experienced auditor who is either internal to the company purchasing the material or from a 3rd party, with relevant experience in the field being audited.

## 5. Manufacturer Questionnaire

Each manufacturer questionnaire should be tailored to the raw material being purchased. The format of the questionnaire can mimic that of a pre-audit questionnaire, as outlined in the APIC auditing guide or refer to an example questionnaire, *Appendix 4*. It should be remembered that manufacturers of critical raw materials do not always work to cGMP and as such an appropriate standard suitable for the manufacture of the material should be applied where available.

## 6. Audit Standard

The audit should be tailored to the particular type of material being manufactured and it's mode of manufacture i.e. critical raw materials, API's derived from plant sources, sterile liquids, and biotechnological processes.

Critical raw materials

Critical raw materials are not always manufactured to cGMP. The manufacturer may be registered to an alternative quality standard or no quality standard at all. Therefore the audit must be performed taking into account the manufacturers quality system and the customers requirements from the manufacturer i.e. does the manufacturer have full traceability from raw material to final product, final product testing etc.

Registered Intermediates and API's

ICHQ7 will be the preferred standard for auditing however depending on the market source consideration should be given to other standards. The audit must be performed with consideration to the potential sales region of the finished goods and potential expansion of sales in the future. Is the market for the finished goods world wide or local? Is particular regulatory approval to be sought? Will the finished material be BP, USP etc? Knowledge of where the finished goods are to be sold will define the audit standard i.e. ICH Q7 guidelines and it will also aid in determining the predefined audit acceptance criteria. The acceptance criteria must be defined prior to the audit taking place.

## 7. Performance of Audit

For guidance on how to perform a supplier audit refer to *APIC Auditing Guide*. When auditing the following should also be considered:

Depending on the country being audited and the written and spoken language of the supplier/ manufacturer, an interpreter may be a vital member of the audit team. The interpreter will aid in an overview of documentation and communicating questions and answers. The preferred option is that the interpreter is independent of the company being audited and is employed by auditing company.

The performance of this audit would be for the proposed manufacture of the intended drug / material but should also facilitate expansion of scope. Does the manufacturer being audited have the potential to supply to a different regulatory standard, if it is required in the future? Does this supplier have the potential to be a long term partner?

Depending on the complexity of the supply chain the scope of the audit may need to be expanded and the decision should be risk based.

## 8. Audit Report

The audit report should be issued in a timely manner and a response, with timelines for remediation, should be requested from the supplier. Personnel with the authority to action the remediation must be identified in the report response by the manufacturer.

The report should state whether the pre-determined acceptance criteria have been met and if not, what points require remediation. The levels of deficiencies should be assessed as per the APIC auditing guide as the criticality of the deficiencies will define the next stage in the process.

Critical raw materials

If *critical* or *major* deficiencies have been identified in the audit, then a risk assessment must be performed on whether the deficiencies are such that the customer's product may be at risk from the raw material supplied. At this stage the customer must maintain full

testing of the raw material. The manufacturer must agree that a need for remediation has been identified and a commitment made to remediate with a time line. A re-audit may be performed if the deficiencies warrant it.

If there is a deficiency that is deemed *other* then the assessment can proceed as long as remediation has been identified and a commitment made to remediate.

If remediation is not required then the quality assessment can be completed.

Registered Intermediates and API's

If *critical* or *major* deficiencies have been identified in the audit, then the assessment process cannot be completed until these have been satisfactorily addressed in the view of the auditor.

If there is a deficiency that is deemed *other* then the assessment can proceed as long as remediation has been identified and a commitment made to remediate.

If remediation is not required then the quality assessment can be completed along with Quality Agreement being signed (if the assessment outcome is GO).

Registered Intermediates and API's Remediation

If remediation is required, then it must be agreed between the Quality unit of the auditing company and supplier in advance, with a timeline for completion (taking into account the project schedule, as no manufacturing can occur until all critical/ major points have been addressed).

The auditor should also decide in advance what level of checks are required post remediation i.e. re-audit or supply of documented evidence. This will be dependant on the criticality of the deficiencies previously identified and this should be scheduled into the project timeline.

The cycle of remediation and re-check is continued until the auditor is satisfied with the remediation outcome and the pre-determined audit acceptance criteria have either been met or only *other* actions are outstanding.

If satisfactory remediation cannot be agreed and the deficiencies are critical/ major to the project then the quality assessment is ended as a NO GO.

## 9. Completion of Quality Assessment

All the data of the quality assessment should be collated and reviewed; this will vary depending on the category of raw material however may include satisfactory QC testing of the material to specification, tanker cleaning certification, TSE certification, historical performance, response to the questionnaire , manufacturer questionnaire, audit data and completion, compliance history, reputation, 3rd party certification and successful

authority inspections. Much of this data will have been previously collated and reviewed earlier in the supplier assessment i.e. during due diligence; however it still forms part of the quality assessment. This review is independent and the final decision is the Quality Units alone. If the review of all 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.

Non critical Raw Materials
If the quality assessment is satisfactory then the decision is GO

Critical raw materials
If the quality assessment is satisfactory then the decision is GO. If the customer wishes to consider reduced testing then the criteria outlined in ICHQ7 section 7.3 must also be met

Registered Intermediates and API's
If the quality assessment is satisfactory then the decision is GO, on the signing of the Quality Agreement.

## 10. Quality Contract/ Agreement

Non critical Raw Materials
A purchasing contract will suffice for non-critical raw materials, this may include any specific quality issues that need to be addressed i.e. compliance to pre-agreed specification etc.

Critical raw materials
A quality/ purchasing contract is required for critical raw materials. This can be supplemented with a quality agreement, if the customer feels the quality of the material supplied is at risk by not having one.

Registered Intermediates and API's
A quality agreement should be drawn up- e.g. refer to the APIC Quality Agreement Template. This should be forwarded to the supplier, when the rest of the quality assessment process is ongoing. The Quality agreement must be approved and signed by both parties before any manufacturing takes place. The Quality Agreement should address the need for 1) notification of any potential changes that may impact the quality of the product and 2) no changes to be made without prior approval.

## CHAPTER 4. CHANGE CONTROL AND PRODUCTION ASSESSMENT

The change control and production assessment process follows five main steps, Initiation of Change, Execution of Change, Evaluation of Change, Closure of the Temporary Change Control Package and Preparation for Ongoing Monitoring as follows.

### 1. Initiation of Change

The execution of changes to the process are managed by a cross functional team according to the following principles

- All changes that have the potential to impact product quality (identity, strength, purity, bioavailability, regulatory filings) must be evaluated. The types of changes requiring notification should be defined and agreed to by both the firm and the supplier.
- The system for Change Control is overseen by the Quality organisation, but may be managed by another function
- All changes are assessed from a Technical, Quality, Regulatory, Stability, Safety, Environmental and business standpoint with the appropriate personnel involved in the review.
- The impact of the change to the affected areas, processes and systems is evaluated and communicated
- All changes requiring a change to the filed process will be communicated to the appropriate agencies
- For non critical raw materials the process may be streamlined to assess the change as there is no regulatory impact and the impact may be minor to the process.

### 2. Mechanism for Review of Change

### 2.1 Non Critical Raw Materials:

2.1.1. The mechanism for review is as follows. A temporary change request (this can also be covered under the Vendor Approval Process) is issued by the assigned coordinating function (usually technical) to all appropriate other functions together with the supporting justification. This request should consider the following points,

- Tracking number
- Detailed description of change
- Specification for the material based on User Requirements
- Defined number of batches that will be impacted if known
- Products impacted (name and identification code)
- The reason for the change
- Acceptance Criteria
- Supporting documentation – if required by the evaluation of the change
    - Outline of changes to master batch records
    - Financial impact
    - Impact on current testing

- Analytical test results of samples preferably from typical industrial scale batches
- Results of use test of material and the follow on product evaluation (if applicable)

2.1.3. The resulting temporary change request must be approved, at a minimum by the Technical function and Quality units.

For changes to non critical raw materials the change control may be approved and closed at this point depending on the assessment outcome. This process must be documented in an SOP and at a minimum the approval must be completed by the Technical function and Quality unit.

**2.2 For Critical Raw Materials and API Intermediates**

2.2.1. The mechanism for review is as follows. A temporary change request is issued by the assigned coordinating function (usually technical) to all appropriate other functions together with the supporting justification. This request may include, but is not limited to,

- Tracking number
- Detailed description of change
- Specification for the material based on User Requirements
- Defined number of batch that will be impacted
- Products impacted (name and identification code)
- The reason for the change
- Acceptance Criteria
- Supporting documentation
    - Outline of changes to master batch records
    - Financial impact
    - Impact on current testing
    - Validation impact
    - Results of use test of material and the follow on product evaluation

2.2.2. Each of the supporting functions (Quality, Regulatory, Stability, Safety, Environmental and business) then reviews the package and the change is again assessed as per *Appendix 5*

The reviews may take place in parallel by all functions for additional impact. The results of the assessment are communicated to the coordinating function and the findings are consolidated and the final package is complied approval.

2.2.3. The resulting temporary change request must be approved, at a minimum by the Technical function and Quality unit. All prior to release and prior to implementation requirements must be consolidated and placed in the appropriate sites system.

2.2.4. Amendments to the temporary change is allowed, but only if the original intent is not changed. This can be managed through the addition of an amendment to the change request and this must be approved by the original approvers (Technical and Quality unit).

2.2.5. The material to be used is assessed on delivery. This assessment may include, but is not limited to, the following

- For each batch, routine testing is assigned to this material (sampling level may be tightened)
- Extra testing that may be appropriate to the evaluation
- Use test of the material

2.2.6. If there is a process validation impact this is documented using the site system and a Process Validation Protocol is developed and approved.

**3. Execution of Change:**

Following approval of the temporary change request by the appropriate functions and the completion of all actions required for the change the process is executed using the new material. Depending on the regulatory impact assessment the resulting material may need to be segregated and controlled to ensure compliance.

**4. Evaluation of Change:**

The evaluation of the change is performed at a number of levels as follows

4.1. The resulting material produced as part of the temporary change is then evaluated by

- Routine testing of the material for all materials
- Use tests to produce the final product for critical materials and API Intermediates
- Extra testing to evaluate the material produced and ensure that it is within expectations for critical materials and API Intermediates

4.2. The validation completion report is drafted and approved as per the normal site procedure.

4.3. All prior to release and prior to implementation requirements are assessed and tracked to closure as per the site systems.

**5. Closure of the Temporary Change Control Package:**

5.1. A closure memo is prepared by the assigned coordinating function that verified and shows evidence that all requirements of the temporary change request have been met. This may include but is not limited to the following

- Evaluation of the material received
- Evaluation of the product by testing (routine and extra)
- Approval of the validation completion report

- Confirmation that all prior to release and prior to implementation requirements are fulfilled. If there are some requirements that will remain pending after closure then this will be highlighted and are managed by other site systems.

The final document is approved by the original approvers of the change Technical, Quality unit and Business areas.

5.2. Material may be released following approval of the change.

For any regulatory requirement that remain pending, the appropriate control of the material and documentation should be maintained.

5.3. If the change does not perform as expected then the temporary change request will be discontinued and cancelled and the resulting material destroyed.

5.4. The change request remains temporary until all the appropriate regulatory agencies approval is received. The change then progresses through the site system and the change can be made permanent.

**6. Preparation for Ongoing Monitoring**:

To assist ongoing monitoring and evaluation of the material and the supplier, the company must identify KPIs (Key Performance Indicators) at this stage in the process.

Examples of KPIs are chosen based on the criticality of the material and the following examples could be included

- No agency observation leading to supply impact
- Number of observations from agency inspections
- No significant investigations
- Number of atypical investigations and OOSs on the material
- No market action as a result of an investigation or customer complaint
- Number of Customer complaints
- Response time to customer complaints and atypical investigations
- No of rejected batches in the year
- On time delivery performance in full
- Percentage on time completion of audit observations
- Percentage on time completion of Corrective Action

## CHAPTER 5. SUPPLY CHAIN SECURITY

The previous chapters preliminarily focused on the supplier qualification and management activities in a direct interaction between the customer and the manufacturer of the material. However, this is not always the case as agents, brokers, distributors, repackers, relabelers may be involved (in addition) apart from transport companies. As a general principle it should always be considered that the shorter the supply chain, the more secure it will be.

In the light of an increasing presence of counterfeit and sub-standard products this aspect gains even more importance. This development is also reflected by the fact that various initiatives have been taken such as the founding of the FDA Counterfeit Drug Task Force, the European Commission's "Public consultation in preparation of a legal proposal to combat counterfeit medicines for human use" (adaptation of directive 2001/83 EC) and the WHO Program "IMPACT" (International Medical Products Anti-Counterfeiting Taskforce). The "APIC Quick Guide for API Sourcing" provides some specific guidance on this topic especially related to the interaction between the API manufacturer and the medicinal product manufacturer and provides possible measures that may be taken by both partners in order to ensure only non-rogue APIs are used in the manufacture of medicinal products

The entire supply chain from the manufacturer of an API, registered intermediates or critical raw material to the customer should be assessed and qualified from a quality perspective by applying the same principles as described in the previous sections of this guide, mainly related quality system, transportation, storage and related conditions as well as traceability of the material.

For temperature/ humidity sensitive materials, the use of data loggers should be considered in order to have documented evidence that the product was stored at the required conditions during transportation.

As any changes on the original container – e.g. by repackaging, relabeling – are considered as an additional risk for alteration or contamination, these should, whenever possible, be avoided.

Apart from the supplier qualification and management activities the following measures related to packaging can be considered and may increase the supply chain security for APIs, registered intermediates and critical raw materials:

- Use of tamper-resistant packaging closure by the manufacturer, a manufacturer-specific design of the seal is recommended to be used; the use of unique seals may be considered. The communication of the type of seal, by the manufacturer to the customer, is needed.
- Evaluation of the label by the customer: the label on the material matches the reference label provided by the manufacturer. The labels need to be in line with ICH Q7, 9.42/43 for APIs & registered intermediates hence also need to indicate

the name, address of the manufacturer and special storage/transport conditions apart from the name or identification code of the product, batch number, quantity of contents and the expiry date. In case of a retest date, this may be indicated on the CoA.

- Assessment of the CoA against an authentic manufacturers CoA.

For non critical raw materials, the activities as described in chapter 1, 3, 4 and 6 of this guide are applied to qualify and manage the supplier.

## CHAPTER 6. ONGOING MONITORING AND EVALUATION

After the approval of a new supplier, 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 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 muti-displinary team evaluating all aspects of supply. The Quality Unit is responsible for the ongoing evaluation and the re-approval 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

#### *Ongoing monitoring*

Each supplied batch should be assessed according to defined criteria. These criteria should be a result of the risk assessment. At least the following aspects should be taken into consideration:

- Specification (results on certificate of analysis and own results)
- Statistical Evaluation of Quality Control data for critical parameters (if applicable) to identify any adverse trends
- Packaging, sealing
- Labelling
- Delivery dates and quantities
- Certificates and other documents
- Other aspects

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

#### *Periodic evaluation*

Regular, typically on an annual basis, the supplier's performance should be assessed. For non-critical raw materials a periodical evaluation may not be required.
Depending on the type of material the following data should be evaluated:

- Periodic full testing of material
- Quality – for example number of not right first-time deliveries
- Complaint situation
- Product Quality Review (registered intermediates and APIs)
- Results of SQC/SPC analysis (if applicable)
- Assessment of changes (critical materials, registered intermediates and APIs)
- Reaction on audit and remediation plan (if audit had taken place)
- Response times for complaints and questions
- Reaction time if e.g. regulatory requirements change (critical materials, registered intermediates and APIs)

- Regulatory or cGMP/compliance issues (critical materials, registered intermediates and APIs)
- Predefined KPIs with examples in Chapter 4 (registered intermediates and APIs)

The result of the evaluation should be summarised in a report which is the basis for the rating and the Review.

***Rating (classification of supplier)***

After the periodic evaluation the supplier should be classified 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 supply)
- Partially satisfactory: conditional approval (no supply until corrective actions are in place)
- Not satisfactory: Supplier 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.

***Review with supplier***

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 critical materials, registered intermediates and APIs.
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 and exchanges of experience.

***Re-audit***

The decision for auditing/re-auditing suppliers of critical raw materials should be risk based. In this regular risk assessment the performance of the supplier, regulatory requirements and criticality of the material should be considered. The result of the assessment should be documented.

The supplier of registered intermediates and APIs 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 guidelines should be considered.
The frequency of the re-audit should by dynamic and depending on the rating.
Example:

- Completely satisfactory: 5 years
- Mainly satisfactory: 3 years.
- Partially satisfactory: 1 year

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

For APIs the recommended period for re-audit is 2 to 3 years as defined in the EMEA document "Compilation of Community Procedures on Inspections and Exchange of Information"

In the case of serious complaints, unsatisfactory response on remediation plans or any doubts regarding GMP compliance an unscheduled audit can be performed.

***Re-Evaluation***

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

**3. Reduced testing**

Testing of non critical, critical raw materials and registered intermediates may be reduced depending on the rating and the performance of the supplier over a period of time and the criticality of the material. The approach also needs to be in line with ICHQ7 chapter 7.3.

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