ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE

Best practices guide for managing suppliers of API manufacturers

Version 2, 18 March 2024

PREAMBLE

The first version of this document has been compiled by the APIC Supplier Management Task Force on behalf of the Active Pharmaceutical Ingredient Committee (APIC) of CEFIC. It replaces the 2009 APIC guide "Supplier Qualification & Management Guideline". Over time additional annexes will be made including templates (questionnaires, statements, agreements) as well as a Q&A document.

It should be noted that the following related APIC publications related to Supplier Management are still current at the moment of publication of this guideline and can also be found on the APIC website (www.apic.cefic.org/publication):

- APIC quick guide for API sourcing (2008)
- Guideline for Qualification & Management of Contract Quality Control Laboratories (2012)
- Quality Agreement for Laboratories – Guideline & Templates (2012)
- APIC Auditing Guide (2016)
- Quality Agreement Guideline and Template (2017)
- APIC guide for auditing registered starting materials manufacturers (2018)

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1. General Section

1.1 Introduction

Over the past decade, supply chains within the pharmaceutical industry have become increasingly complex. This is a result of a growing outsourcing trend, combined with a supplier base that is more and more spread from a global perspective.

This situation makes API manufacturers more dependent on their suppliers and also more vulnerable to supplier related risks. These risks are not only limited to quality or compliance issues, also business continuity or reputational risks can be a result of poor supplier management. To manage such risks, risk management (see also ICH Q9) is becoming an integral part of today's supplier management processes.

In addition, regulatory agencies nowadays focus more on how suppliers are managed, and pharmaceutical customers of API producers expect their API manufacturers to have adequate supplier qualification and evaluation programs in place.

This guide provides a framework for API manufacturers to implement an adequate, robust, risk-based supplier management process. Such a Supplier Management can be looked at from different angles, e. g. from a commercial, compliance, business continuity… perspective. This guideline looks at supplier management primarily from a quality perspective (i.e., materials or services potentially affecting quality). However, it also briefly touches, for the materials or services in scope, other non-quality related aspects (e. g. REACH, carbon footprint, CSR...). The reason is that in many cases different aspects cannot be seen independently when it comes to fulfilling the objective of having a reliable and stable supply base.

1.2 Objectives

This document's objective is to provide guidance and suggest a harmonized approach within the API industry on how to manage suppliers of materials and services in an adequate and compliant manner. The intention is to establish a supplier management framework that is not only compliant with the official requirements, but also covers other supplier management related aspects that play a role in real life, e. g. when dealing with suppliers that are reluctant to sign quality agreements or to accept physical audits. Although these other aspects are important, little detail is covered in official guidances, a gap which this 'best practices' guide is aiming to fill.

Throughout this document, the term "Supplier" will be used to refer both to material suppliers as well as service providers (service suppliers).

The guide is based on the experience and best practices of the authors while working in the API industry. It has no legal base nor is it endorsed by any official regulatory body. It is therefore not a replacement of any official guideline but reflects APIC's position on the topic.

In general, this guide focusses on supplier management of suppliers used for commercial production. The same approach can be applied also for suppliers used during earlier development stages, although (following the risk-based approach) the API manufacturer might define less strict requirements. It is the common expectation that the level of detail and requirements increase with the process development (e.g., preclinical, phase I, phase II, phase III), as such, not all the activities below mentioned may apply to all development stages.

Note: The principles of the guide can also be used in case materials or services are purchased on a contract manufacturing or contract development basis (CMO, CDMO). However, it is important to emphasize that in such a context supplier management becomes much more complex, and many other aspects need to be considered (e.g. protection of intellectual property, technology transfer, project management) which are not part of this guide.

1.3 Scope

In scope of this document are all third parties from which an API manufacturer purchases material or services that have a potential impact on the quality of the resulting API.

This includes suppliers of materials, such as e.g.: starting materials, intermediates, reagents, solvents, packaging materials, processing aids. The principles of the guide could also be used for other materials such as equipment, spare parts, certain product contact materials (e.g. equipment gaskets, seals), suppliers of quality-relevant software - even though this is not the primary focus of this guide.

It also includes providers of services, such as e.g.: contract laboratories, contract manufacturing, transportation, warehousing, calibration or critical IT services.

The above listing is just providing examples and not exhaustive. It needs to be defined individually, which suppliers are exactly in scope of the API manufacturer's supplier management program, based on the criticality of the material or service. The appropriate level of oversight required for the supplier management of these different types of suppliers is defined following a risk-based approach.

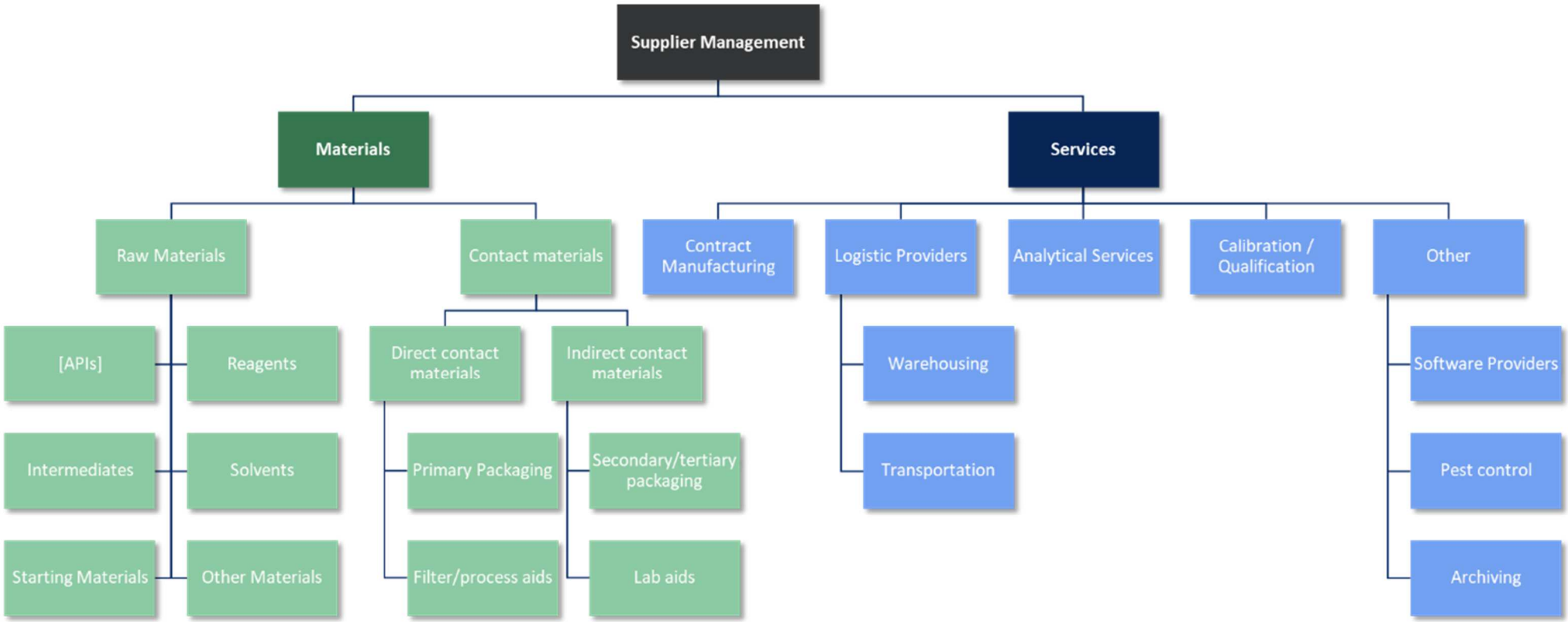

Figure 1: Scope of supplier qualification, non-exhaustive example, based on USP <1083>

1.4 Overall Process for Supplier Management

The flow scheme below is a graphical representation of the overall supplier / service provider qualification and management process. Details are described in the following chapters.

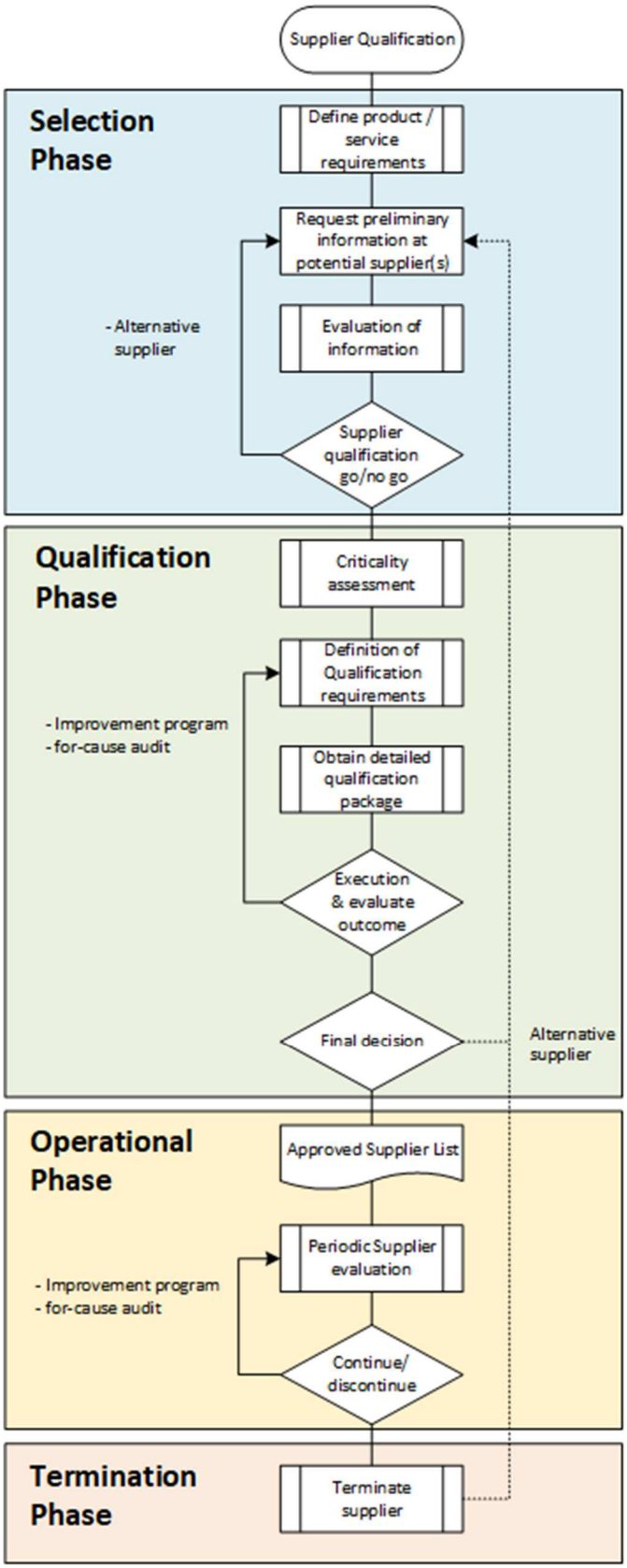

Figure 2 Supplier management process

The supplier management process typically involves input from different departments (e. g. R&D, Procurement, HSE). It is essential however that the Quality Unit oversees all quality and compliance related aspects and has the exclusive authority to approve or reject suppliers.

2. Supplier Management

During the Supplier Management Life Cycle, four stages can be defined:

- Selection Phase
- Qualification Phase
- Operational Phase
- Termination Phase

The **Selection** and **Qualification** phases apply to all new supplier (manufacturer)/material or service combinations. This means it also applies to *existing* (qualified) suppliers/manufacturers from which a *new* material or service is intended to be purchased. During these phases it is recommended to work with a multi-disciplinary team (i.e., typically Quality Assurance, Procurement, SHE, etc.) to ensure that required aspects are covered initially during the project.

The **Operational** phase applies to all suppliers of materials or services that are qualified.

The **Termination** phase can apply to either a specific supplier, or an individual material or service from a specific supplier.

From the qualification phase onwards, it is important that all activities are documented. In addition, change control is recommended to ensure proper management of the necessary steps. The level of detail of the change control depends on the criticality of the material / service / supplier / manufacturer and risk involved.

2.1 Selection Phase

Procurement (Sourcing) department usually is the department that is responsible for providing (a list of) potential suppliers, e. g by using their internal or external databases.

2.1.1 Define the product / service requirements

In order to allow Procurement to initiate the selection, the users of the material or service must provide the corresponding requirements (user requirements), these should contain:

- Material specifications (ideally fully finalized, alternatively R&D draft versions) and, as needed, corresponding methods or service (user) requirements
- Specific standards or specific constraints related to quality, safety, specific legislation related to the product or service (requirement for quality certifications, licences, permits, Reach, ….) or any other constraints (e.g., limitation to subcontracting cascade …)

2.1.2 Request for information – Request for proposal – Request for quotation (RfX)

During this stage typically standard documentation packages are requested, based on the defined product/service requirements. Besides pure commercial items (such as price, payment terms, minimum order quantity, price revisions, incoterms…) the requests will typically include one or more of the following items:

- Information related to Sustainability / CSR / EHS (as selection criterium, not necessarily for formal qualification).
- Legal compliance information
- Supply chain information (traders or intermediate parties involved?), if traders are involved, clarify their activities (do they have open product handling, e. g. repacking?). Request the identity of manufacturers and subcontractors that may be involved in the product or service
- Route of transport and transport related information: shipping risk assessments e. g. in case of temperature / humidity sensitive materials Supplier's core business, industries served
- Financial status of the supplier
- Capacity & capability, delivery performance
- Supplier's knowledge about the product of interest – manufacturing experience, quantities produced, batch size, importance of product within supplier's portfolio.
- REACH aspects
- Official or draft specifications, to confirm that the material complies with the requirements expected,
- Willingness to accept API manufacturer's qualification procedure (e. g. questionnaires, statements, spec agreements, cleaning certificates in case of deliveries in bulk, audits, quality agreements)
- High level info on Supplier's GMP compliance / Quality system / performance adequacy / regulatory status/track record (can be verified, e. g. via warning letters)

2.1.3 Evaluation of the information (Pre-qualification assessment)

The information received in the RfX package needs to be thoroughly evaluated by the relevant stakeholders (incl. quality department), in order to:

- Increase confidence that the new source will pass the next stages
- Identify any potential risks
- Decide on eventual additional actions, requirements or questions.
- Assess the necessity of an on-site visit, taking into account the answers of the RfX and the criticality of the product/service.

At the end of this stage a decision will be taken to initiate the formal qualification of a specific supplier. This decision is made involving all relevant stakeholders.

2.2 Qualification Phase

It is important to emphasize that a supplier is never qualified on its own, but always in combination with the material or service and their respective uses. This means, one must consider both material / service-related aspects as well as supplier specific related ones.

If the supplier is not the manufacturer, the basic aim should be to know and qualify the manufacturer. However, based on the criticality of the material it may be sufficient to limit the qualification to the level of the supplier. In that case an assessment of the supplier's own supplier management system would be expected.

In any case for materials or services that are highly critical (see table 1), the qualification should include the manufacturers, as required by ICH Q7. The same applies to most of the medium critical materials.

In any case for materials or services in the criticality category “High” (as defined in table 1), the qualification should include the manufacturers, as required by ICH Q7.

The outcome of the qualification phase will determine the suitability of the supplier for use by the API manufacturer (go/no go-decision). The qualification and its outcome should be formally documented.

The qualification phase should basically cover two aspects:

- Initial assessment of material or service to evaluate the quality of the material or service provided and the impact thereof on the quality of your API
- Evaluation of the suppliers' facilities and/or QMS to assess whether the supplier can consistently supply material or service with the required quality

Both aspects need to be considered in parallel during the qualification phase.

2.2.1 Criticality Assessment of the material or service

The criticality of the material or service to be provided will determine the level of qualification requirements. Therefore, the API manufacturer needs to determine the criticality of each material or service based on its intended use. Typically, this results in a categorisation of materials and services as first input for determining the level of qualification. Important aspects to consider are the GMP compliance and registration requirements. In contrast to non-registered materials, registered materials already have very clear guidelines that should be met (e. g. compliance to GMP, requirement to audit etc…).

Criticality	Materials	Services
High	Registered Starting materials Registered Intermediates API primary packing materials	Contract Labs for release or stability testing Contract manufacturers Transport of APIs External Warehouse for storage of API IT services (impacting release) 3rd party auditors
Medium	Building blocks Critical reagents Solvents used in the process API secondary packaging materials Product contact materials (i.e., filters, processing aids, etc) Utilities (e. g. Nitrogen) Primary Packaging for intermediates	Contract Labs (not release testing) Calibration Services Transport or storage of intermediates Storage of GMP documents Re-packing / re-drumming of non-APIs
Low	Basic Chemicals Non-Critical reagents Solvents for cleaning or cleaning agents Sec pack for intermediates	Transport or storage of “other” materials (e. g. chemicals) Pest Control IT services (other)

Table 1: examples of criticality levels

2.2.2 Detailed Definition of Qualification Requirements

The requirements to qualify a new supplier/material (or service) combination are determined based at minimum on the criticality of the materials or service (as indicated in Table 1). Additional factors that may impact the level of qualification can be:

- Complexity of material in terms of how it is produced
- Level of release testing (acceptance on CoA vs own release testing)
- Usage of the material (early or late in the synthesis) or service: increased level of control closer to the final API stage (cfr. ICH Q7 principle)

The requirements should be documented and approved by the Quality Unit. The qualification plan contains the actions to be completed, e. g. one or more of the following:

(1) Conduct a fit-for-use / fit-for-purpose (FFU/FFP) assessment:

- Documented evidence that the material or service intended to be purchased is suitable for the intended use. In case of materials the fit-for-use/fit for purpose typically involves a degree of testing of the material (see examples in Table 2)

High criticality	Medium Criticality	Low Criticality
For chemical materials: Analytical evaluation of samples including Use-testing For packaging materials: As required by the guidelines	Analytical evaluation of samples (and potentially use testing on a case-by-case basis, e. g; for building blocks)	Documentation (e. g. supplier data (CoAs)

Table 2: Examples of minimum Fit-for-use / fit-for-purpose requirements for materials.

For services the fit-for-purpose or fit-for-use assessment of services is in general based on auditing or evaluation of documentation (depending on the criticality).

(2) Request statements related to the attributes or compliance of the product or service e. g.:

- BSE/TSE
- GMO
- Residual solvents
- Metals (ICH Q3D)
- Potential genotoxic impurities (PGI)
- Nitrosamines statements or assessments
- other information: e.g., route of synthesis, pesticides, melamine, toxic compounds
- Training certificates or CVs of involved service providers
- Accreditation of a lab for a specific test
- Legal approval for handling/storage specific substances (e.g., narcotics)

(3) Assess the supplier's (manufacturer's) suitability, e.g.

- Questionnaires
- Audit

(4) Establishment of contracts or agreements, e.g.

- Specification Agreement
- Quality Agreements
- User requirements

It is recommended that the API manufacturer sets up a table (or a matrix, a flow or a diagram) of qualification requirements depending on the criticality level of the material / service that is purchased.

A basic example is given below:

Criticality of material or service / General Requirements	High	Medium	Low
FFU/FFP assessment	X	X	X
Applicable Statements	X	X	X
Questionnaire	X	X	(X)
Agreed specifications / User requirements (*)	n/a	X	X
Commitment declaration (*)	n/a	X	(X)
Audit	X	(X)	(X)
Quality Agreement (incl. Specification agreement)	X	(X)	n/a
Authorizations / Certificates	X (GMP, GDP, when applicable)	(X) ISO 9001 preferred	(X) ISO 9001 preferred

Table 3: Examples of qualification requirements, depending on the defined criticality level

(*) either as a standalone document or as part of the PO
(X) = case by case, based on risk related to individual material or service

Specific additional requirements can be added on a case-by-case basis: e.g., cleaning certificate or evidence of process validation.

In the specific case of outsourcing GMP activities, the qualification activities must include guarantees (and / or evidence) to keep complete oversight by the API manufacturer over the activities performed by the service or material supplier (see quality agreement chapter).

Once the qualification criteria specific to the material or service in scope have been defined, it is also important to consider certain additional aspects (both quality and non-quality) related to the supplier, as these aspects may alter (increase or decrease) the criticality. Examples can be:

- Reputation of the supplier
- Location of supplier
- Experience /maturity
- Complexity of the process used by the particular supplier (e.g., continuous single step vs multistep batch process, dedicated or multipurpose)
- Complexity of the supply chain (e.g., multiple intermediate parties involved)

For details on management of risk see also chapter 3.

2.2.3 Execution & outcome of the Qualification

Once all the required information has been collected and the qualification activities have been defined, these will be executed - in accordance with the plan -, evaluated and documented.

The results of the qualification activities should be documented and approved by the Quality Unit. This approval is the prerequisite to use the supplier and to place orders. Such an approval is often transferred into an ERP system to ensure appropriate ordering, release and use of material. In

addition, an overview of all qualified suppliers should be available, either as a list of approved suppliers or through a secured electronic system.

In case the supplier or service provider is going to be part of a regulatory filing, it is good practice to share this information with the respective supplier or service provider.

In exceptional cases, it may not always be possible to have all requirements finalized or signed prior to the ordering and /or using the material/service. It is important that these cases have to be treated with care and are justified with a written risk assessment, clearly identifying the missing items, typically approved by senior management. In any case, all required documents and actions must be completed before releasing the API.

2.3 Operational Phase

Once the supplier is qualified, the period of active use starts. During this Operational Phase, a Supplier Monitoring Program needs to be established in order to maintain the qualified status. A Supplier Monitoring Program consists of periodically re-evaluating

- the supplier risks, based on the performance of a supplier and supplier intrinsic risks (see paragraph 3.3)
- the validity of supplier related documentation (e.g. agreements) and / or audit status

The frequency at which the evaluation should be repeated is based on the criticality of the material or service (as defined in chapter 2.2.1), and the supplier risk that came out of the exercise (see table 4).

It is important to note that certain specific events (e.g. certain complaints, deviations, changes, audit observations) occurring between fixed re-evaluation moments can trigger an immediate evaluation of the supplier qualification status and/or risk level.

The supplier performance evaluation may consist of

- Quality aspects (e. g. material or service quality, audit outcome, compliance issues, deviation response, RFT%...)
- Other performance aspects (e. g. supply chain issues, on time deliveries)

Many companies translate the outcome of a supplier evaluation into a supplier (risk) score whereby the scoring system consists of a numerical evaluation of different parameters reflecting both supplier performance as supplier intrinsic risks The very first moment to define a risk score is immediately after qualification, whereby the score will in that case be based on the supplier intrinsic risk as there is in principle no real operating experience yet to evaluate the performance .

In case of negative performance within the assessment period, shorter review frequencies can be implemented as a risk mitigation measure. Severe negative performance will lead to termination (see chapter 2.4). In case the concerned source is the only qualified one and discontinuation would have severe effects on the availability of a medicine to patients, the API manufacturer needs to implement further measures for short-term mitigation of the risks. This could be e. g. additional controls of material or services, or intensified consulting to improve the quality systems of the supplier.

The Supplier Monitoring activities can be done separately by the Quality Unit or as a joint exercise together with other units, nevertheless it should be documented and approved by the quality function.

Potential activities resulting from the supplier evaluation or rating could include:

- Adapting the audit frequency (or other applicable assessment)
- Increase quality oversight (e. g. by (Q-)visits, meetings, person-in-plant)
- If reduced testing is applied, the frequency of full testing may be adapted
- In case of immediate risks, a specific risk mitigation plan should be established

Supplier evaluation can also trigger a temporary blocking of certain supplier. Examples may be:

- Dormant suppliers (e. g. no current purchase, price/competitiveness reasons, replaced by alternative suppliers, material or service no longer used): it should be decided if the supplier remains in a qualified state or should be inactivated to avoid unnecessary 'maintenance' activities (e. g. monitoring and re-qualifying). These suppliers may become active again after re-evaluation or re-qualification.
- Suppliers having issues that have not been resolved, e.g., implementation of an audit CAPA, general compliance issue (e. g. import alert, environmental issue).

In case of blocking due to quality issues, the potential impact on all related materials on stock, in transit, or already shipped to a customer should be assessed. It is a good practice to include possible criteria to reactivate the supplier or service provider. This assessment must be approved and documented by the Quality Unit. All concerned departments and sites need to be informed of the temporarily blocking of a supplier / service provider.

After the periodic re-assessment is completed, the qualified status is maintained / can be re-assigned.

Examples of re-assessment frequencies based on the Overall Supplier Risk Rating are given in Table 4:

Material or service criticality	**Supplier Risk (intrinsic and performance)**		
	High (e. g. poor quality performance)	Medium (e. g. supply chain risks)	Low (e. g. good performance)
High	1 years	3 years	3 years
Medium	2 years	5 years	review by exception (e.g., in case of complaints)
Low	3 years	5 years	review by exception (e.g., in case of complaints)

Table 4: Examples of re-assessment frequencies

2.4 Termination Phase

The active qualification status of a supplier / service provider may be terminated or not re-assigned for several reasons, e. g.:

- The supplier has discontinued the production of the material / provision of the service
- The API manufacturer has discontinued the use of the material, supplier or service
- The supplier has serious issues (e. g. quality related issues with no proper CAPA measures, negative audit output, supply chain issues, breach of agreed Quality requirements)

In case of disqualification due to quality issues, the potential impact on all related materials on stock, in transit, or already shipped to a customer should be assessed. This assessment must be approved and documented by the Quality Unit.

All concerned departments and sites need to be informed of the disqualification of a supplier / service provider.

Be aware that even in case of discontinuation of business it may be necessary to continue access to retain samples, manufacturers documentation or other information.

3. Risk Management applied to Supplier Management

The purpose of this chapter is to provide more detailed guidance that could be used for further development of risk management principles into supplier management, on top of those already described in previous chapters.

Risk management principles can be applied to any aspect of supplier management including qualification, monitoring/surveillance as well as for any ad hoc evaluations of potential risks and mitigating measures. Risk evaluation is ideally be done in a multidisciplinary team, including quality, procurement, SHE and other relevant functions.

3.1 Risk management process

Risk management processes are also described in other guidelines, e. g. ICH Q9 on quality risk management. The overall flow is illustrated in ICH Q9 as follows:

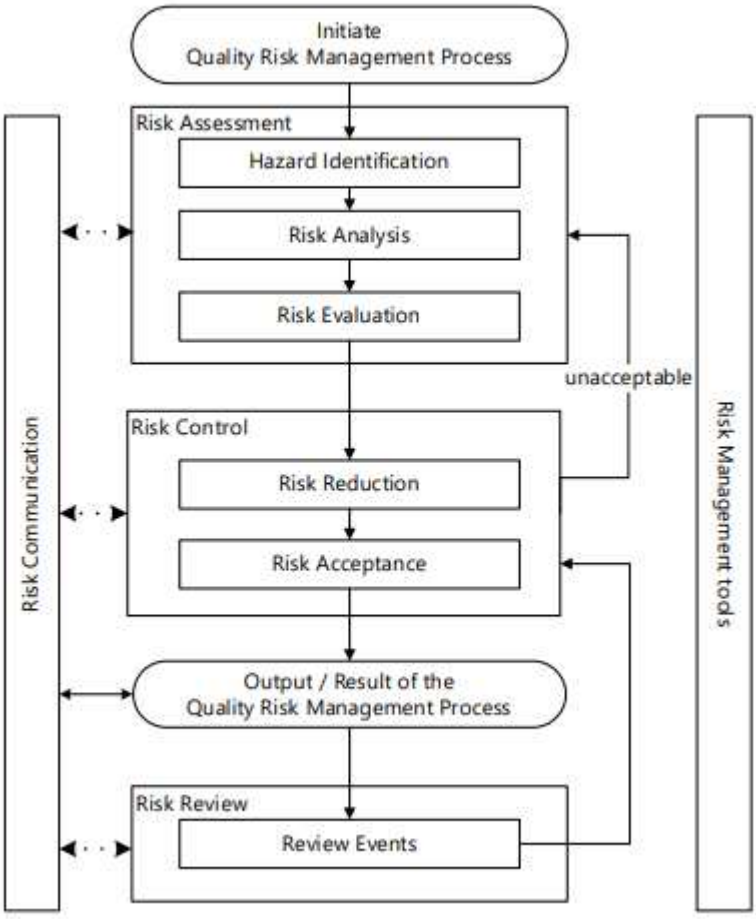

Figure 3: ICH Q9 Quality Risk Management Process

There are several methodologies for estimating / calculating risk, e. g. FMEA (Failure Mode Effects Analysis), FTA (Fault Tree Analysis), HACCP (Hazard Analysis and Critical Control Points). For the purpose of this guide, we use the 5x5 model (see section 3.4).

Risk = probability (of the event/failure mode occurring) * severity (or impact of the event)

3.2 Risk Identification and Analysis

Risks can arise from the following issues (events/failure modes), which can be categorized in four groups:

3.2.1 Delivery issues (supply interruption risk)

Supplier stops activities or cannot deliver due to e. g.:

- Bankruptcy
- Legal enforcement actions because of environmental or safety issues (e. g. accidents)
- Geopolitical situations, e. g. (trade) wars
- Pandemic

3.2.2 Ethical issues

Conflict with the API manufacturer's rules or ethical compliance standards, e. g.:

- Supplier involved in
    - Child labour
    - Corruption
    - Environmental pollution
- Supplier violates the API manufacturer's CSR standards
- Intellectual property violations

3.2.3 Regulatory / Compliance issues

Conflict with customers specification or quality compliance standards, e. g.:

- Supplier delivers material or service not in line with registration, e. g., different route of synthesis, deviating analytical method for release ("adulterated")
- Supplier violates cGMP (in case of registered materials)
- Supply chain integrity issues (e.g., supplier appears not to be the real manufacturer, usage of undisclosed third parties)
- Warning letters from health authorities

3.2.4 Quality issues

- OOS at supplier
- OOS upon QC acceptance testing
- Service complaints
- Hidden defects with delivered materials, e. g.:
    - New impurities not detected by QC incoming testing
    - Foreign matter / cross-contaminants
    - Identified issues after reduced testing or release based on supplier´s CoA only
    - Mix up of products/samples

3.3 Risk Evaluation and Risk Review

In order to evaluate an overall supplier related risk, the different parameters need to be transferred into a value / score.

★ For evaluation of the **probability** of an event or failure mode to happen, one has to look at the supplier ("intrinsic factors"):

For the qualification of NEW suppliers / service providers this could include the following factors:

- Supplier location (taking into account geopolitical stability, vulnerability to natural disasters, environmental policies, urban planning)
- Supplier strength (covering financial strength, company size)
- Supplier management systems (taking into account QM systems [e. g. GMP, ISO], change / deviation management, quality and regulatory history, inspection track record, quality culture, safety management, environmental care, social care)
- Supplier´s infrastructure (are production buildings / laboratories / warehouses built to modern standards?)
- Direct supply vs agents/ broker/ distributors
- Supplier know-how & experience
- Supplier´s production process (dedicated / non-dedicated equipment, continuous / batch process, closed / open equipment, manufacturing experience with a particular product

For the evaluation of EXISTING suppliers / service providers the following "performance related factors" could be used in addition:

- Supplier quality history and delivery performance
- Number of complaints and severity over a defined period
- Number and impact of deviations over a defined period
- Responsiveness and response quality to complaints, audit reports, questions, …
- Quality of CAPAs, investigations, reports, ...
- Adherence to established agreements
- Assessment of changes at the supplier in the assessment period
- Quality performance (e. g. OOS, Nonconformities, Rejected batches, re-occurrence issues, complaint follow-up)
- Regulatory / GMP compliance issues (e. g. warning letters, license)
- Audit outcomes: e. g. periodical audit results, critical observations, missing observation response

★ For evaluating the **severity** of the event or failure mode**,** one has to look at the impact to the API manufacturer ("criticality"):

Nature/category of the delivered materials:

- Impact to API quality - distance from API step
- From regulatory perspective: registered material / not registered material
- From process perspective:
    - High critical (e. g. regulatory starting materials or intermediates, building blocks, certain critical reagents, late-stage solvents, primary packaging materials)

- Low critical (e. g. solvents, acids/bases, organic/inorganic salts, other non-critical reagents)

Importance of the resulting product using the material or service:

- For your own business: contribution to turnover / margin
- For your customer (e. g. strategic customers)
- For the patients (e. g. life-saving drugs)

Sourcing status:

- Single source material or service
- Supply contracts and agreements

Probability and severity can be rated according to the following model which also provides the resulting risk.

Risk Matrix

			Severity of the effect				
			1	2	3	4	5
			Insignificant	Minor	Significant	Major	Severe
Probability of the risk to happen	5	Almost Certain	5 Medium	10 High	15 Very High	20 Extreme	25 Extreme
	4	Likely	4 Medium	8 Medium	12 High	16 Very High	20 Extreme
	3	Moderate	3 Low	6 Medium	9 Medium	12 High	15 Very High
	2	Unlikely	2 Very low	4 Low	6 Medium	8 Medium	10 High
	1	Rare	1 Very low	2 Very Low	3 Low	4 Medium	5 Medium

Table 5: Examples of a 5x5 matrix

Based on the magnitude of the calculated risk (from very low to extreme) it can be decided which mitigating actions need to be undertaken and by which priority. It can also be decided to accept the risk.

In case any changes to the risk factors are observed during supplier monitoring, the risk evaluation has to be checked or repeated.

3.4 Risk control

The result of the risk evaluation is the basis for determining mitigation actions that will control the risk such as:

- Increase quality control by:
  - Increasing the number of drums to be sampled
  - Increasing testing of incoming material
  - Increasing testing of finished product
  - No reduced testing
- Supervision of the executed service
- Person in plant
- Establish a quality agreement (in case it was originally not foreseen)
- Execute an additional Q visit

- Increase audit / re-assessment frequency
- Add polishing filters to remove potential mechanical contaminations
- request more documents (e. g. cleaning certificates)
- Build / increase safety stock
- Quality alternative sources (Business continuity plan)
- Consider back-integration (make or buy)

4. Auditing

4.1 General

Auditing is one of the most powerful tools to assess whether the supplier effectively meets the API Manufacturer's needs. However, auditing of all suppliers of materials and services is not mandatory per GMP.

This is particularly important during the initial qualification but can also be of use during the subsequent supplier monitoring.

When preparing for an audit, it is important to identify the scope of the audit and the standards (e. g. GMP, ISO, IPEC, API manufacturers standards, quality agreements) against which the audit will be performed.

Audits related to quality should be performed and led by qualified auditors, in general members of the Quality Unit or other persons qualified by the Quality Unit. Depending on the case, members from other departments may join the audit as subject matter experts.

For more detailed information on auditing please refer to the respective APIC auditing guides. At the time of release of this document the current versions are:

- APIC Auditing Guide (2016)
- APIC guide for auditing registered starting materials manufacturers (2018)

4.2 Audit organisation

In order to successfully manage audits an audit plan must be made. Based on the regular audit frequencies and other aspects (new suppliers, changes, risk-based considerations) the audit program is defined, typically on a yearly basis. Changes to or deviations from the plan should be justified. If the regular supplier monitoring shows problems with quality, performance or compliance at the supplier, the audit is typically performed earlier than the default audit frequency. In case of critical issues, also for-cause audits or CAPA follow-up audits should be planned outside of the regular frequencies.

Together with an audit program the API manufacturer needs to have qualified auditors available - either internal or external (a qualified third party) and their qualification should be documented.

It is a good practice to distribute a tentative agenda upfront to define the scope of the audit and to ensure good preparation on the auditor´s and the auditee´s side.

4.3 Audit Types

Audits can be done in different ways, depending on the qualification requirements, organisational or even official restrictions.

- From supplier lifecycle perspective => audit type
  - Initial qualification audit
  - Follow-up audit
  - For cause
  - Routine audits (monitoring audit)
- From an audit format perspective => audit mode
  - On-site
  - Remote
- From auditor perspective
  - Own audit
  - 3rd Party audit
  - Joint audits

4.3.1 Initial Qualification Audit

The initial qualification audit is the very first audit of the company that supplies the material or service. It is the most important event to evaluate the suitability of the external partner.

For this reason, it is highly recommended that the API manufacturer performs the initial audit with its own qualified auditors (accompanied with SME) and not to replace this with remote, paper-based or 3rd party audits (unless the company has previously been audited for a different material or service). If such a replacement has to be done because of certain circumstances (e. g. travel restrictions), an on-site audit should be planned as soon as possible.

4.3.2 Follow-up audits

Audits outside the regular scheme intended to do an on-site verification of the progress of actions identified in an earlier audit and considered as covering serious concerns.

4.3.3 For-cause

For cause audits may be conducted as an immediate action to serious concerns related to a supplier quality performance.

4.3.4 Routine audits

Performed according to the API manufacturer´s annual program as part of the requalification of the supplier.

4.3.5 On-Site Audit

An on-site audit is the default choice for auditing suppliers, especially for initial qualification audits. Such an on-site audit provides live interaction between the auditor and the auditees. A qualified auditor will verify the quality system, on-site activities (be it manufacturing or service), compliance etc. by visiting the location of the supplier / manufacturer.

4.3.6 Remote Audit

A risk assessment should determine for which suppliers it can be acceptable to perform a remote audit instead of an on-site audit (e. g., well known suppliers with good audit history, no manufacturing activities).

If an on-site audit would be the preferred audit mode but there is no possibility to perform it, the risk of replacing it with a remote audit should be assessed. The impact on the annual audit program and adequate audit frequency also has to be considered.

A remote audit can be executed as a desktop audit or a paper/documentation audit:

4.3.6.1 Desktop audit

A desktop audit does not take place at the location of the supplier, instead the auditor is located at a different location and the communication takes place via telecommunication tools (e. g. teleconferencing or video conferencing). It is highly recommended not to use this type of audit for the initial qualification audits of entirely new partners.

4.3.6.2 Paper audit

During a paper audit, questions are being raised purely on documentation (questionnaires, procedures, …), without live interaction with the auditees. A paper audit is not limited to a questionnaire but includes requesting detailed documentation from the supplier to be reviewed by an auditor (e. g. SOPs, form sheets, drawings). It is highly recommended not to use this type of audit for the initial qualification audits of entirely new partners.

4.3.7 3rd party Audit

3rd party audit service providers can be contracted to perform dedicated audits or provide existing audit reports from a database. When audits are outsourced to 3rd party auditors, it has to be ensured that the auditors and the auditing company are qualified according to acceptable standards. Aspects to be considered in this qualification are their auditor qualification program, regular auditor trainings, experience / CVs of their auditors for the specific audit reports. Usage of 3rd parties for initial qualification audits should be considered with care and depend on the level of confidence the API manufacturer has built with the 3rd party. Joint audits in an initial stage of collaboration can help to gain trust on the 3rd party's way of auditing.

4.3.8 Joint Audits

Some suppliers will only allow joint audits, where several of their customers perform an audit together on a fixed date. In those cases, every company will create their own audit report. If necessary, adequate confidentiality measures should be in place. In general, joint audits can be considered as equivalent to other on-site audits, if the required information can be received.

4.4 Audit rating

Typically, the outcome of an audit can be translated into a classification, e.g.:

- Acceptable

- Conditionally acceptable
- Unacceptable

This classification will also affect the overall supplier rating or status and can - in case of a negative outcome - trigger specific actions such as risk mitigation plans (see the chapter on risk management) or even disqualifying the supplier permanently or temporarily. In the latter case an escalation to higher management and all relevant stakeholders should take place.

Re-audit frequency:

While the re-audit frequency for APIs is usually recommended to be 2 - 3 years (as defined in the EMEA document "Compilation of Union Procedures on Inspections and Exchange of Information"), for other materials and services these frequencies have to be defined following a risk-based approach. This could be based on the following timelines:

Material or service criticality	**Supplier Risk (intrinsic and performance)**		
	High (e. g. poor quality performance)	Medium (e. g. supply chain risks)	Low (e. g. good performance)
High	1 years	3 years	5 years
Medium	2 years	5 years	review by exception (e.g., in case of complaints)
Low	For cause if defined in risk mitigation plan	No audit	No audit

Table 5: Example audit frequencies

4.5 Refusal of audits

If a routine audit is refused to be performed on-site, it should be assessed if it can be replaced by other audit types, like remote, 3rd party or joint audits.

If no adequate audit can be performed at the supplier, the use of alternative suppliers should be considered. Only in rare cases where there is no alternative, the risk of using the suppliers has to be assessed and internal mitigation measures (e. g. increased monitoring or incoming testing) have to be in place.

5. Quality agreements

5.1 General

Quality Agreements are mandatory for highly critical materials and services. The purpose of a Quality Agreement is to define clear (quality) rules and responsibilities of the parties involved towards the material to be supplied/produced or the service to be provided. It must be assured that the (quality) requirements are clearly communicated to the supplier and maintained throughout the product lifecycle. Based on the risks of the specific material or service the number of parties required to sign-off may vary (i.e., in case of traders involved).

If a Quality Agreement is required due to the risk level of material or service, it should ideally be signed before ordering the material or using the service. In case the agreement is not (yet) finished, a risk assessment should be done, with approval by higher management, including at least Quality.

Different templates covering the specific requirements are available:

- API intermediates: APIC publication “Quality Agreement Guideline & Template”
- Contract labs: APIC publication “Quality Agreement for Laboratories Guideline & Templates”
- RSMs and critical materials: “Quality Agreement Template for Registered Starting Materials and Critical Materials”, see annex 1[1]
- Other materials/services: “Commitment declaration”, see annex 2

If a Quality Agreement has been agreed upon, it is highly recommended to avoid quality provisions in Supply Agreements, the preferred way is to include a simple reference to the Quality Agreement.

It is important to bear in mind that - in order to be legally binding - the Quality Agreement should be connected (referring to or annex to) to the supply agreement or referenced by the purchase order. In case there is no supply agreement, the quality agreement should contain a legal section. In case there is a Supply Agreement, care should be taken not to have conflicting requirements.

Verification of compliance to the established Quality Agreement is important. This can be done e. g. during audits.

Existing Quality Agreements should be periodically reviewed to confirm they are still up to date. This verification could coincide with the periodic re-assessment of the supplier or service provider (see chapter 2.3).

5.2 Refusal or partial acceptance of agreements

In case a supplier is reluctant in signing a Quality Agreement or only partly accepts it, the risk assessment for the supplier should be re-evaluated, mitigation measures should be discussed and implemented. Eventual mitigation measures can be reducing the audit interval, increase analytical testing, include conditions into the contract or PO, and other.

[1] this annex will be issued shortly after the publication of version 1 of this guide

6. Definitions and abbreviations

6.1.1 Abbreviations

API	Active Pharmaceutical Ingredient
BSE/TSE	Bovine / Transmissible Spongiform Encephalopathy
CAPA	Corrective Action / Preventive Action
CMO CDMO	Contract manufacturing organisation Contract development and manufacturing organisation
CoA	Certificate of Analysis
CSR	Corporate Social Responsibility
FFU/FFP	Fit for Use / Fit for Purpose
FMEA	Failure Mode and Effect Analysis
FTA	Fault Tree Analysis
GDP	Good Distribution Practice
GMO	Genetically modified organism
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis Critical Control Point
IPEC	International Pharmaceutical Excipients Council
MSDS	Material Safety Data Sheet
OOS	Out Of Specification
OTIF	on-time in-full (Delivery)
PGI	Potential Genotoxic Impurity
QC	Quality Control
QMS	Quality Management System
REACH	Registration, Evaluation, Authorisation and Restriction (of Chemicals)
RFT	Right First Time
RfX	Request for X (I: Information, P: Proposal, Q: Quote)
RSM	Registered Starting Material
SHE / EHS	Safety Health & Environment

6.1.2 Definitions

(Registered) Intermediate	A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this Guide only addresses those intermediates produced after the point that the API manufacturer has defined as the point at which the production of the API begins.) (EU GMP Guide, Part 2)
Agreement	Arrangement undertaken by and legally binding on parties.
API	Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. (EU GMP Guide, Part 2)
API Starting Material	A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house. API Starting Materials are normally of defined chemical properties and structure. (EU GMP Guide)
Audit	An audit is a formal, independent, disciplined and objective review activity designed to assess the performance of an operation, a set of operations, a process or a system with regards to established standards or regulations
Basic Chemicals	Commodity products, largely available with many suppliers and commonly used in many industries.
Broker / trader / distributor / agent	An external party that is selling goods of which it is not the original manufacturer, but can be involved in repacking and/or relabelling
Building Blocks	A chemical compound that forms a substantial structural fragment of the final API.
CAPA	System for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. (ICH Q10)

Commitment Declaration	Low level quality agreement to assure the supplier commits to basic things such as notifying the API manufacturer of changes to relevant aspects (e.g., specifications, production location, etc.)
Contract	Business agreement for supply of goods or performance of work at a specified price.
Contract Manufacturing Organisation (CMO) Contract Development and Manufacturing Organisation (CDMO)	A contractor (supplier) performing some aspect of manufacturing and/or development on behalf of the customer (e. g outsourced activities) owning the product
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. (EU GMP Guide, Part 2)
Manufacturer	A company that carries out at least one step of manufacture. (WHO GMP)
Material	A general term used to denote Raw Materials, Process Aids, Intermediates, Active Ingredients and Packing Materials. (EU GMP Guide)
Packaging Material	Any material intended to protect an intermediate or API during storage and transport. (EU GMP Guide, Part 2)
Process Aids	Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon, etc). (EU GMP Guide)
Product Contact Materials	Disposable materials used during processing that come into contact (directly or indirectly) with the API or its intermediates (i.e., filters, process aids, gaskets)
Quality Agreement	A legally binding agreement that is mutually negotiated and concluded between (the Quality Departments of) API/intermediate manufacturers and a supplier or service provider. It is intended to define, in a formalised manner, mutual expectations/responsibilities concerning quality matters relative to the supplied goods or services. It typically also includes commitments between the parties regarding (a) the provision of information, documents, or samples, and (b) communication and notification rules, including contact details.
Quality Unit	An organisational unit independent of production which fulfils both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organisation. (EU GMP Guide, Part 2)
Registered Starting Material (RSM)	The material where the registered part of the synthesis starts. A registered starting material is a raw material, an intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. A registered starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house. Registered starting

	materials normally have defined chemical properties and structure. Regulatory files typically include details of the RSMs process and origin (manufacturer names and addresses).
Risk	The combination of the probability of occurrence of a harm and the severity of that harm.
Service Provider	An external party that takes over outsourced activities (e.g., manufacturing steps, analysis, storage, transportation, calibration etc.). For the purpose of this guideline, Service Providers are considered a sub-category of suppliers (service suppliers).
Specification	A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. “Conformance to specification” means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. (EU GMP Guide, Part 2)
Statements	Statements are documents providing evidence regarding specific attributes or compliance of the product/service; e. g., BSE/TSE, GMO, residual solvents, metals ICHQ3D, PGI, nitrosamines etc.
Subcontractor	A third-party contractor engaged and qualified by the supplier or original contract acceptor to perform any part of the supplier’s or original contract acceptor’s obligations under the License, Supply or Quality Agreements.
Suppliers	External parties from which goods or services are purchased. A supplier is not necessarily the (original) manufacturer of the product.
Supply Chain	For the purpose of this guide the term “supply chain” refers to both the supply of raw materials to the API manufacturer and the transport of the API manufacturer’s products to the customers.
Utilities	Utilities are neither reactants nor products but are essential for enabling manufacture of products. Compressed air, nitrogen, water, steam, cooling/refrigeration, heating, etc., are the common utilities used in chemical plants.

7. References

- ICHQ7 Good Manufacturing Practices for Active Pharmaceutical Ingredients (2000)
- ICH Q9 Quality Risk Management (2023)
- ICH Q10 Pharmaceutical Quality System (2008)
- ICH Q11 Development and Manufacture of Drug Substances (20212)
- APIC Guideline for Qualification & Management of Contract Quality Control Laboratories (2012)
- APIC Quality Agreement for Laboratories – Guideline & Templates (2012)
- APIC Auditing Guide (2016)
- APIC Quality Agreement Guideline and Template (2017)
- APIC guide for auditing registered starting materials manufacturers (2018)
- USP-NF <1083> Supplier Qualification

8. Annexes

Refer to Annex area of APIC publications website, subtopic “Supplier Management”

9. Version History

1	2009	New document (“Supplier Qualification and Management Guideline” plus 5 appendices and 6 questionnaires)
2	2024	Full revision: - Complete rework of the 2009 version, which this guide is replacing - This guide includes annexes of which the most current versions can be found on the APIC publications page subtopic “Supplier Management”