Guidance for Industry: Material Supplier Management

Version 2.0
(Draft for information)

Drug Office
Department of Health

Contents

1. Introduction

This guideline is intended to provide general guidance on the interpretation of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* ("the GMP Guide") and the relevant Annexes, in particular Annex 2, with respect to managing suppliers of starting materials and raw materials where applicable. These documents may be downloaded from the PIC/S website and should be consulted for detailed information.

This document is developed on the basis of current knowledge of the subject matter and should be regarded as for guidance only. It is not mandatory under law. It is not intended to create additional requirements or to form the basis for GMP inspection.

There may be other acceptable approaches in providing a good level of quality assurance that materials used to manufacture pharmaceutical products are procured from a reliable source and are of appropriate quality.

2. Purpose

To provide guidance to industry on how to manage suppliers of starting materials and raw materials.

3. Scope

This guidance is applicable to managing all suppliers who provide starting materials (active pharmaceutical ingredients (APIs) and excipients) to manufacturers for the manufacture of pharmaceutical products, including investigational pharmaceutical products. It is also applicable for suppliers providing raw materials used in the manufacture of advanced therapy products ("ATPs").

Important: The term 'supplier' in this document refers to any entity supplying starting materials and raw materials to manufacturers of pharmaceutical products, such as:

- distributor;
- broker;
- agent;
- actual manufacturer of materials; or
- blood or tissue establishment for cell or tissues used as starting materials or raw materials for ATPs.

4. Background

It is a requirement of GMP that material should be purchased from approved suppliers and manufacturer has a particular and thorough knowledge of the suppliers. Supplier qualification should include an evaluation on the reliability of the suppliers to supply materials of consistent quality with adequate evidences. An integrated supplier qualification program should also identify and mitigate the risks associated with material in question. Therefore, it is the responsibility of GMP manufacturer to establish a robust supplier qualification program. Assessment of suppliers with supporting evidence should be formally documented and should be available during GMP inspection.

5. Material Supplier Qualification

5.1. Selecting and evaluating a supplier

A new supplier evaluation is typically initiated using the change control process to formally document the selection process.

Pharmaceutical manufacturers should identify the use and function of each material and risks presented to its quality and safety from its source. For example:

- type of material – API, excipients, raw materials;
- function of the materials in the formulation;
- country of origin;
- sources – human, animal, mineral, vegetable, synthetic, etc
- compliance with any international standards, e.g. British Pharmacopoeia (BP), U.S. Pharmacopoeia-National Formulary (USP) and European Pharmacopoeia (EP);
- potential of contamination with adventitious agents;
- potential risks during supply chain and on-site storage; and
- pharmaceutical form and use of the subsequent pharmaceutical product.

The potential supplier should be evaluated by gathering information, including (but not limited to):

- type of supplier – manufacturer, broker, distributor, agent, etc;
- any relevant audits/inspections conducted in the last 3 years and available reports, responses and close-out;
- history of the supplier (if known) – additional controls may be required for suppliers with questionable track records;
- GMP agreement, if available;
- supplier's current GMP certificates, if applicable;
- certification of quality systems e.g. ISO 9001, if available or the quality systems which the supplier has in place;
- evidence of accreditation of relevant good practice guides e.g. the Foundation for the Accreditation of Cellular Therapy (FACT) and the American Association of Blood banks (AABB) for cell or tissues starting materials and raw materials used in used in ATPs;
- Site Master File, if available;
- any technical information, such as information received from Regulatory Affairs in the API Drug Master File;
- any testing history for related materials from the supplier already delivered on site;
- any testing results for materials provided by the potential supplier; and
- changes, deviations or investigations communicated by the supplier.

Representative samples (e.g. from 3 different batches) may be requested from the supplier and tested as part of the evaluation of a new supplier. Approval of the supplier should not continue if the material does not meet specifications.

5.2. Risk classification of suppliers

Once a potential new supplier has been selected, the supplier should be classified according to risk, based on the types of considerations described in Section 5.1 above. Similarly, existing suppliers that have not yet been formally approved should also be classified.

The classification of suppliers may change over time. For example, adverse information about a supplier or out of specification (OOS) test results may increase the risk and result in a supplier being moved to a higher risk category.

The following table is for illustrative purposes only – the number and variety of risk factors to be considered for supplier/starting material combination mean that it is not possible to provide a definitive set of criteria.

Supplier Classification	Examples of suppliers
Category 1 (Highest Risk)	Manufacturers of materials used in sterile preparations or with known stability issue. Manufacturers of APIs in a country with poor or unknown GMP regulation. Brokers, distributors or agents where the supply chain from the manufacturer is complex, not fully known, or there is an increased possibility of counterfeit.
Category 2 (Moderate Risk)	Manufacturers of materials used in non-sterile pharmaceutical products. Brokers, distributors or agents handling APIs requiring cold chain management.
Category 3 (Lowest Risk)	Manufacturers of excipients produced at a dedicated site (e.g. sugar).

5.3. Questionnaires

To determine if a supplier is capable of meeting the GMP quality requirements to supply the material, a questionnaire can be used as a way to gain information about the quality standards at the supplier's site. However, it does not provide the same level of assurance as on-site audit, but it has a part to play in a risk-based strategy.

Questionnaires should contain questions that are applicable to the approval of a particular supplier. Sufficient information should be provided in order to determine that the supplier has an appropriate quality management system and there is satisfactory assurance that the material supplied will be of appropriate quality.

The completed questionnaire and available documentation (as requested from the supplier) should be critically reviewed to determine the acceptability of the supplier.

5.4. Supplier audits

Pharmaceutical manufacturers are responsible for auditing all Category 1 (highest risk) suppliers of materials initially and on a follow-up basis.

The need for an audit of Category 2 (moderate risk) suppliers should be determined on a case by case basis. Where an audit is not deemed to be necessary, this should be properly justified, including a formal risk assessment.

Audits of Category 3 (lowest risk) suppliers are not required.

When a supplier audit is indicated, it should be conducted by staff with adequate knowledge and training. A written plan for the audit should be prepared before the audit. After the audit, an audit report should be prepared to briefly record what was audited and any observations identified. A written response to any deficiencies should be expected from the supplier, and be reviewed before they are closed-out.

An on-site audit by the manufacturer may be avoided if objective evidence (e.g. GMP certificate, copy of audit report, response and close-out) of a recent audit by a reputable organisation (e.g. regulatory agency, European Directorate for the Quality of Medicines (EDQM)) is provided, the scope of the audit included the specific material(s) and a review thereof indicates acceptable compliance. Audits by other organisations may be considered on an exceptional case by case risk basis if it can demonstrate an equivalent level of quality assurance with documented justification.

Manufacturers may individually or collectively arrange for an on-site audit of a supplier to be undertaken on their behalf by a suitable (e.g. technically competent and free from conflict of interest) third party. The arrangements should be addressed in the technical agreement. There should also be evidence that the manufacturers have evaluated the technical competency of the third party. Reasonable steps to ensure the validity of the report should be taken.

The resulting audit report can form the basis for approval of the supplier.

Where audits are indicated, the supplier should be re-audited at a specified frequency to verify on-going performance. A rationale for the minimum audit frequencies for each supplier should be documented. As examples only, the re-audit frequency for Category 1 suppliers may typically be 1 – 3 years and for Category 2 suppliers, 3 – 5 years. Even if the initial audit was on-site, a desktop and/or questionnaire audit may be acceptable for re-audits if there have been no quality issues and the supplier has a good history of supply.

5.5. Approving suppliers

The objective of evaluating and approving suppliers is to provide a reasonable level of assurance of the supplier's capability to consistently provide material of the required quality.

The completed questionnaire (with any other evidence requested) may be used to approve Category 3 (lowest risk) suppliers. If it is used to approve Category 2 (moderate risk) suppliers, the justification should be based on risk and be documented.

For Category 1 and Category 2 suppliers requiring an audit, the audit report and supplier response to the report should be evaluated. All corrective actions arising from an on-site audit must be either closed or at a satisfactory stage of completion for the supplier to be approved. Where evidence of an audit by a third party has been accepted (e.g. GMP certificate, copy of audit report, response and close-out), this documentary evidence should be evaluated.

Based on the outcome of the evaluation, the supplier may be approved or not approved. In some circumstances it may be appropriate to assign a conditional approval status (e.g. the first 10 batches from a new supplier to be fully tested).

5.6. Periodic review

A program for periodic review should be established to monitor the performance of approved suppliers and to determine subsequent action taken if quality issues are encountered. Based on the criticality of the quality issues, appropriate actions e.g. removing the qualified status of supplier, request for investigation and CAPA for the quality issues from the supplier, should be taken.

Items that may be considered during periodic review:

- update of supplier quality systems including validity of certification;
- quality warning from competent authorities;
- supply history including quality of batches of material received, physical conditions of the containers received and complaints;
- information obtained from supplier questionnaires and/or on-site audits.

5.7. Using distributors, brokers or agents

Often a manufacturer may procure a material from a distributor, broker or agent instead of the material manufacturer/producer. In this situation, all the parties involved in the supply chain of the material from leaving the manufacturer's control to the final delivery to the pharmaceutical product manufacturer should be identified. The following should be taken into consideration:

- a distributor, broker or agent is a type of supplier requiring evaluation and approval;
- approval of a distributor, broker or agent does not replace the need to approve the manufacturer/producer of the material;
- the supply chain for each material procured through a distributor, broker or agent should be traceable to the actual manufacturer of the material;
- if a material has been repackaged or relabelled and not supplied in the original actual manufacturer packaging, the repackaging operation must be fully compliant with Section 17, Part II of the GMP Guide and Hong Kong Guide to Good Manufacturing Practice for the Secondary Packaging of Pharmaceutical Product; and
- the origin of the Certificate of Analysis for the material.

  Note: It is unacceptable for results from a material manufacturer's Certificate of Analysis to be transcribed from the original to another supplier's letter head.

Where supply is through a distributor, broker or agent, the actual manufacturer/producer of the material should be included in the material specification and included in the supplier approval process.

6. Preparing GMP Agreements for Suppliers of Materials

Manufacturers should discuss all quality requirements and expectations for materials with the supplier. A GMP agreement formalises any discussions and clarifies expectations of both parties. For example:

- specified materials, services or situations (e.g. in the event of a quality failure in material);
- access to the supplier's manufacturing site for audit with respect to GMP and quality expectations;
- requirements to ensure traceability;
- expectations for storing reference/retention samples;
- access to manufacturing and/or laboratory records (records must meet GMP requirements – legible, traceable, etc.);
- rules concerning sub-contracting;
- requirements to minimise cross-contamination or other quality-related issues;
- rules concerning implementation of corrective actions by the supplier; and
- notification of changes to the manufacturing process, site, equipment, testing methods, specifications, supplier/third party, any other quality-related parameter that could impact the quality of the starting material. Any change must be approved by the manufacturer before accepting supply.

Changes to a GMP agreement may occur at the time a supplier notifies the manufacturer of a change (e.g. change in process or testing) or at the next scheduled update to the agreement. Critical amendments to the agreement should be completed at the time of notification.

7. Special Considerations for Investigational Pharmaceutical Product

The extent of supplier qualification for investigational pharmaceutical product depends both upon the phase of development and upon criticality of the material. In the early stages of product development, safety concerns should be the primary focus of material supplier qualification. Material and suppliers are classified through a risk-based approach based on the understanding of materials and knowledge of products and process acquired during product development. In the later stages, material qualification activities should be completely developed.

8. Special Considerations for Advanced Therapy Products

The quality of starting materials (e.g. cell or tissues incorporated as an integral part of the finished product) and raw materials (e.g. reagents, culture media, buffers, sera, enzymes, cytokines, growth factors, feeder cells) is a key factor to consider in the production of ATPs. Particular attention should be paid to avoiding contamination and to minimizing as much as possible the variability of the starting and raw materials. During process of material supplier qualification and prior to introduction in the manufacturing process, the nature and specific characteristics of starting materials and raw materials used in manufacture of ATPs should be considered.

8.1. Starting materials

8.1.1. For the donation, procurement and testing of human cells and tissues, including blood-derived cells, used as starting materials for ATPs, the accreditation, designation, authorization or licensing of the related suppliers under the relevant legislation in the country of origin if applicable should be verified.

8.1.2. When the cells or tissues are obtained in a country or region where there is no requirement for accreditation, designation, authorization or licensing by competent authority, the ATP manufacturer should take appropriate steps to ensure the quality, safety and traceability thereof, in accordance with the terms of the marketing authorization/ clinical trial authorisation. Evidence on compliance with relevant good practice guides or accreditation by a competent third party should be sought.

8.1.3. The ATP manufacturer should establish quality requirements for the starting materials (specifications) which should be agreed with the supplier(s). These agreed specifications should cover aspects of the production, testing and control, storage, and other aspects of handling and distribution as appropriate.

8.2. Raw materials

8.2.1 From a risk perspective, the use of raw materials free from human or animal substances is preferred.

8.2.2 Raw materials used in the manufacturing of ATPs should take into consideration the recommendations in relevant chapters of pharmacopoeia e.g. *EP <5.2.12> Raw Materials of Biological Origin for the Production of Cell-Based and Gene Therapy Medicinal Products*, and *USP <1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products*. While raw materials should be of pharmaceutical grade, it is acknowledged that, in some cases, only materials of research grade are available. The risks of using research grade materials should be understood (including the risks to the continuity of supply when larger amounts of product are manufactured). Additionally, the suitability of such raw materials for the intended use should be ensured, including – where appropriate– by means of testing (e.g. functional test, safety test).

8.2.3 Where available, the use of raw materials that are authorized as pharmaceutical products by competent authority (e.g. human albumin), is encouraged.

8.2.3 The ATP manufacturer (or, as appropriate, the sponsor or marketing authorization holder) should assess whether a specific raw material is critical having regard to the specific risks. For authorised ATPs, quality requirements included in the specifications of critical raw materials (e.g. cytokines, growth factors, enzymes, sera) should be agreed with the supplier(s) ("agreed specifications"). For investigational ATPS, the technical specifications for the critical raw materials should be agreed with the suppliers whenever possible.

8.3. Risk of contamination with adventitious agents

8.3.1. The risk of contamination of starting and raw materials of biological origin during their passage along the supply chain should be assessed, with particular emphasis on viral and microbial safety and Transmissible Spongiform Encephalopathy ("TSE"). Compliance with the latest version of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Product is required.

8.3.2 When starting or raw materials of animal origin are used, there are additional risks of transmitting known and unknown pathogens to humans, including the potential risk of introducing new infectious diseases. These animals should fulfil specific health requirements and should be fit for human consumption and reared under controlled conditions, when applicable. Please refers to Annex 2 of the GMP Guide and other reputable recommendations for details.

8.4. Material traceability

8.4.1. The ATP manufacturer should verify the full traceability of human cell or tissues contained in ATPs from the point of donation. Traceability information is also required for raw materials and all substances coming into contact with the cells or tissues.

8.5. Quality agreement for suppliers of starting materials

8.5.1. A technical agreement should be in place between the ATP manufacturer (or, as appropriate, the sponsor or marketing authorization holder) and the supplier of starting materials. In addition to the specifications for the starting materials, the agreement should contain clear provisions about the transfer of information regarding the starting materials, in particular, on tests results performed by the supplier, traceability data and retention period, and transmission of donor health information that may become available after the supply of the staring material and which may have an impact on the quality or safety of the ATPs manufactured therefrom.

Document Information

Version	Date	Description of Change
1.0	27 Dec 2013	First version
2.0	02 Jul 2019	Second version (draft for information) ● Changed in title and scope to address the special considerations for advanced therapy products and investigational pharmaceutical products ● Restructured and updated to be consistent with PIC/S Guide to GMP and relevant annexes.

References

Document Title
1. Council of Europe. (2016). European Pharmacopoeia. Ninth Edition. Volume I. [5.2.12] Raw Materials for the Production of Cell-Based and Gene Therapy Medicinal Products.
2. European Commission. (2017). Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products.
3. European Medicines Agency. Guidance on Good Manufacturing Practice and Good Distribution Practice: Questions and Answers. [Cited 29 March 2019]. URL https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers#section16
4. Parenteral Drug Association. Technical Report No.56 (Revised 2016) Application of Phase-Appropriate Quality System and cGMP to the Development of Therapeutic Protein Drug Substance (API or Biological Active Substance).
5. Pharmaceutical Inspection Co-operation Scheme. (2014). Guide to Good Manufacturing Practice for Medicinal Products (PE 009-11): Part I
6. Pharmaceutical Inspection Co-operation Scheme. (2018). Guide to Good Manufacturing Practice for Medicinal Products (PE 009-14): Part I
7. Pharmaceutical Inspection Co-operation Scheme. (2018). Guide to Good Manufacturing Practice for Medicinal Products (PE 009-14): Part II
8. Pharmaceutical Inspection Co-operation Scheme. (2018). Guide to Good Manufacturing Practice for Medicinal Products (PE 009-14): Annexes
9. Pharmaceutical Inspection Co-operation Scheme. (2018). Guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice for excipients of medicinal products for human use (PI 045-1).
10. Therapeutic Goods Administration. (2013). Technical Guidance on the interpretation of manufacturing standards. Supplier qualification. Technical Working Groups (TWG) on non-sterile medicines & complementary medicines. Version 1.1.
11. United States Pharmacopoeial Convention, Inc. (2019). U.S. Pharmacopeia-National Formulary [USP 42 NF 37] Volume 1. <1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products.
12. United States Pharmacopoeial Convention, Inc. (2019). U.S. Pharmacopeia-National Formulary [USP 42 NF 37] Volume 1. <1046> Cellular and Tissue-Based Products.

DOCUMENT END