Qualification of Suppliers of Cultivated and Wild Collected Medicinal Plants

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Abstract

The qualification of suppliers is part of the quality assurance system of manufacturers of medicinal products. Qualification of suppliers can be fulfilled by different tools, which may be chosen according to the particularities of the material, its use and its supply chain. Such tools, e. g. information from suppliers, on-site visits and ongoing supervision, serve to evaluate cultivation, collecting and primary processing practices in accordance with the Guidelines on Good Agricultural and Collection Practices (GACP) that are part of the European legal framework for the production of medicinal products of herbal origin. In order to assist companies and their suppliers of raw materials, the German Research Association of Medicines Manufacturers (FAH) provides a contribution for the qualification of suppliers with respect to cultivation and collection of medicinal plants and with a focus on the assessment of specific risks in this non-industrial environment. Since such requirements have to be adapted to the needs of the respective company and the supplier, this document is a recommendation and not a binding rule.

Zusammenfassung

Lieferantenqualifizierung bei Anbau und Sammlung von Arzneipflanzen

Die Lieferantenqualifizierung ist Bestandteil des Qualitätssicherungssystems der Hersteller pflanzlicher Arzneimittel. Die Lieferantenqualifizierung kann auf unterschiedlichen Wegen erfolgen, die entsprechend der Besonderheiten des Materials, seiner Verwendung und seiner Lieferkette gewählt werden können. Möglichkeiten wie Informationen vom Lieferanten, Besuche vor Ort und fortlaufende Beobachtung dienen dazu, Anbau, Sammlung und primäre Verarbeitung entsprechend der Leitlinien über die Gute Anbau- und Sammelpraxis (GACP) zu bewerten, die Teil des Europäischen Regelwerks zur Herstellung pflanzlicher Arzneimittel sind. Als Hilfestellung für Arzneimittelhersteller und Rohstofflieferanten stellt die Forschungsvereinigung der Arzneimittel-Hersteller e.V. (FAH) hier ein Konzept für die Lieferantenqualifizierung bei Anbau und Sammlung von Arzneipflanzen mit einem Fokus auf spezifische Risiken in diesem nicht industriellen Umfeld vor. Da diese Anforderungen auf die Gegebenheiten der jeweiligen Hersteller und seiner Zulieferer zugeschnitten werden müssen, ist diese Ausarbeitung als Empfehlung und nicht als bindende Regelung zu verstehen.

Pharm. Ind. 79, Nr. 1, 66–70 (2017)

Introduction

Each manufacturer of medicinal products has to establish a Quality Assurance (QA) system in order to guarantee a high and consistent quality of its products. This also applies to the manufacture of medicinal products of herbal origin (herbal products and homeopathic medicinal products). According to Chapter 5 of the EU Good Manufacturing Practices (GMP) Guideline [1, 2], qualification of suppliers is part of the QA system. Suppliers[1)] of cultivated and wild collected raw materials of natural origin have to be qualified as well. However, due to the natural origin and the particularities of the production of raw materials of plant origin, specific aspects have to be taken into account when the qualification of suppliers is performed in the field of medicinal products of herbal origin.

General Aspects of Qualification of Suppliers

Chapter 5 of the EU GMP Guideline [1, 2] points out the following: "*the selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product.*"

If active substances of herbal origin are used, there is a multitude of sources and steps involved which are usually highly diverse and adjusted to the specific environment, product and processes. Hence, the gathering of information and the specific approach to qualification, e. g. by audits, self-assessment or other appropriate means, is of utmost importance in order to establish sound knowledge about cultivation, collecting and primary processing practices as well as quality control procedures in place. Furthermore, like qualification of suppliers in general, these tools may contribute to proposals for procedural corrections and improvements.

The Relevance of GACP within the Quality Assurance System

Medicinal plants are the starting point in the production of herbal or homeopathic medicinal products. Thus, their origin, quality, processing and supply are part of the risk management approach of the medicinal product manufacturer and appropriate quality assurance measures have to be taken along the whole process chain. GMP rules are derived from pharmaceutical productions performed in laboratories and industrial productions sites with a primary focus on chemically defined active ingredients. The primary production steps performed under agricultural or wild collection conditions are different from those mentioned above. Therefore, quality requirements had to be adjusted to these conditions, resulting in the development of the European Medicines Agency (EMA) Guideline on Good Agricultural and Collection Practice (GACP) [3]. It represents a practicable tool to implement an appropriate quality assurance system in order to guarantee a high and consistent quality of herbal raw materials [4].

Annex 7 of the EU GMP Guideline [5] combines GACP and GMP and covers the whole range of medicinal products prepared from herbal raw materials along the process chain, e. g. solid forms such as (coated) tablets containing dry extracts, liquid preparations prepared from liquid extracts or tinctures, pressed juices, preparations containing essential oils as well as herbal teas. Guidance is given on how the different production steps of these preparations fall into the scope of GACP, GMP II (for active substances) or GMP I (for medicinal products). The allocation to the respective area can be interpreted in a manner that the closer the preparation is to the final product, the stricter the requirements are [6]. Thus, Annex 7 ensures a seamless quality assurance system from the natural origin of the herbal raw material to the finished herbal medicinal product including a clear definition of the interface between the two systems.

Particularities of Cultivation and Wild Collection of Medicinal Plants

The EMA GACP Guideline [3] and Annex 7 [5] take into account the particularities of medicinal plants and their cultivation or collection, respectively, as the first steps of the production of the raw materials. The GACP Guideline already points out that collection in wild habitats may present special issues and mentions the legal restrictions to protect endangered species [3]. Further particularities are generated by the complex supply chain which may include many different primary production entities (collectors, primary buyers, traders, final buyers). The complexity may vary case-by-case, depending, e. g. on the product and the geographic origin [7]. For cultivated medicinal plants, certain particularities also exist, e. g. the possible use of pesticides and its legal restrictions for use in minor crops like medicinal plants, the specific issues in organic farming, or the often small sizes of agricultural production businesses. Due to the complex and variable nature of plant material and its possible contamination with e. g. foreign matter, pesticides or heavy metals, adequate control as well as the storage and processing conditions gain

[1)] The producer is the entity that produces the raw material of herbal origin (e. g. farmer or collector). The supplier is the entity that delivers the raw material to the client (e. g. trader). The producer may also act as a supplier.

particular importance for the use of raw materials of herbal origin. Tests on potential contaminants are part of the incoming goods control, which is performed according to the requirements of the relevant national quality standards, the specifications and the pharmacopoeial references.

EUROPAM, the European Herb Growers' Association, has recently issued a document containing practical examples which serve as non-binding recommendations for different fields of agricultural production and wild collection [8]. It intends to assist European producers of raw materials in the interpretation and implementation of the principles of GACP in their daily practice. For the qualification of suppliers of herbal raw materials additional guidance is considered useful.

Recommendations for Appropriate Options of Suppliers' Qualification

To assist manufacturers in the qualification of their suppliers, the following recommendations have been elaborated by FAH, the German Research Association of Medicine Manufacturers. These recommendations are intended to enable cultivating and collecting companies and purchasing pharmaceutical companies to assure quality of the herbal raw materials by appropriate supplier's qualification. They are partly based on previous documents giving advice for the performance of audits [9, 10]. Due to extensive changes in the legal framework, an update is now presented outlining several options for performing a suppliers' qualification with regard to GACP compliance. These options can consist in documentation, visits or ongoing assessment of suppliers. They should take into account the particularities of herbal raw materials.

The following list gives examples of issues to be addressed which should result in recommendations for an appropriate tool of suppliers' qualification.

1. The Point of Use of the Herbal Raw Material in the Processing Chain

The closer the use of the herbal raw material is located to the final product, the more requirements have to be considered [5, 6]. Materials used as active substances in medicinal teas may present different focuses than materials used for extraction or purification processes.

2. The Supply Chain and the Production System of the Herbal Raw Material

Wild collection of herbal raw material presents different risks compared to cultivation. For example, in a wild collecting situation, a good traceability, a proper botanic identification and a possible contamination by foreign plant species may be more in focus. A cultivation situation may e. g. rather focus on potential contaminants from e. g. pesticide application or irrigation water.

A conventional (non-organic) cultivation system, which allows the application of chemical pesticides within the residue limits, needs to be evaluated differently compared to an organic cultivation system, in which application of chemical pesticides is restricted.

An agricultural production with many different crops and a potential cross contamination during processing and storage requires a different assessment than a farm that only produces one or very few crops.

3. Organizational, Geographical and Socioeconomic Setup of the Production Site

The geographical location of a cultivation or collection site including its surrounding should be considered in terms of possible sources of contamination, e. g. from nearby industrial sites, roads and neighbouring agricultural operations with uncontrolled drift during pesticide applications.

Furthermore, the setup of the plantation itself and the internal organization of the operations may need to be assessed as well. An operation with a good infrastructure and fields/collection sites close to the drying and processing facility requires a focus different from an operation where considerable delays between field or collection site and the drying facility may be an issue.

The socioeconomic environment and local habit for a specific production site might be relevant and should be taken into consideration in a risk evaluation. A region with a high rate of illiteracy requires a different approach compared to a sourcing situation with a high level of general and technical education.

Different levels of tradition or experience in the collection or cultivation of a certain herbal raw material within a local population or staff may need to be considered, as well as issues like the general local standards for personal hygiene, general local awareness for quality standards, or possible political or administrative issues in the location of production.

4. Plant Specific Parameters

Different plants may present different quality relevant particularities based on their specific biology, the required part of the plant or their method of cultivation or collection. Risk assessment may for instance need to emphasise a focus on possible contamination by foreign plant species in case the target plant grows to the same height at harvest time as important weeds.

Plants known to naturally accumulate heavy metals (e. g. cadmium) from the soil may require a different approach than other plants.

Evaluation of Potential Risks

As shown by the above-mentioned examples, it is important to understand the specific production situation of each supplier and of each plant in order to evaluate the specific risk correctly. Following the principles described in the ICH Q9/Q10 GMP rules [11, 12] will be helpful to decide about the appropriate level of

Pharm. Ind. 79, Nr. 1, 66–70 (2017)

supervision. A lower risk allows a lower level of supplier supervision.

In order to obtain the required information for risk assessment, the following tools may be used:

- Information about supplier, e.g.
  - Self-evaluation questionnaire including general information and supplier´s Quality Management System
  - Supplier´s documentation
- On-site visits may be feasible, e.g.
  - Technical visits
  - Audits
- Ongoing supervision of suppliers
  - Quality control results
  - Complaints
  - Batch-specific documentation

Based on information obtained, a systematic evaluation of the supplier should be performed identifying the specific risks. Thus, the supplier can be qualified and specific actions can be defined, e. g. specific training on site in technical, botanical or document-related matters. Support may also target the improvement in infrastructure, quality assurance systems, documentation and others. The decision for a specific support needs to be made individually. In this way, for an appropriate quality assurance based on the guidance given in GACP, a tailored risk-based qualification is possible and necessary. This will fit with the agricultural and collection conditions appropriately introducing in an adapted way the requirements for GMP in these environments.

In the following, several examples are given for the above-mentioned tools. They should be regarded as a flexible approach for manufacturers.

1. Information about supplier
   Information about the supplier which includes issues addressed in the EMA GACP Guideline [3] can be part of a self-evaluation questionnaire and/or the supplier´s documentation.
   As a minimum requirement of information, the supplier provides general information such as quality assurance, personnel and education, organizational structure, buildings and facilities, equipment and documentation including traceability. Product-specific items, e. g. seeds and propagation material, cultivation (e. g. growing area), collection, harvest, primary processing (production method, e. g. extraction process) and quality control procedures may be included or listed in a separate attachment or a batch-specific protocol.
   Based on the evaluation of the documentation, a decision is taken by the client whether the supplier meets the quality requirements. In this case, the supplier is qualified and undergoes an ongoing supervision. If additional information is needed, follow-up actions such as on-site visits have to be taken.

2. On-site visits
   Compared to the written exchange of information, a technical visit or an audit offers the option of direct verification at the production site, of traceability and of immediate suggestions of individual correcting measures.
   A technical visit focusses on specific aspects and risks, e. g. quality, storage or handling of the product.
   The main topics of an audit include – based on the EMA GACP Guideline [3] – systemic information such as quality assurance, personnel and education, buildings and facilities, equipment and documentation including traceability. Compared to other means of information exchange, the audit report contains additional information about the audited company, description of visited/checked local structures and processes as well as findings, assessment and measures.
   Based on the results of the on-site visit, the client decides whether the supplier meets the quality requirements and agrees with the supplier upon necessary measures. The supplier is then qualified and undergoes an ongoing supervision during which the implementation of these measures will be monitored.

3. Ongoing supervision of suppliers
   A continuous assessment of the quality of a supplier is essential for the assurance of the required level of quality in the manufacture of (herbal) medicinal products. Quality events in co-operation of supplier and client belong to the most important parameters. As examples, deviations in the supply (e. g. defective labelling, non-compliant containers, damages, contaminations) and observations during incoming goods control (e. g. OOS results) shall be evaluated. Depending on the individual raw material and the respective product, further specific quality requirements should be defined, e. g. re-evaluation of documentation provided or on-site visits.

Conclusion

Different raw materials of herbal origin often need to be produced in quite diverse production environments due to their specific growing requirements. The qualification of suppliers of such materials should be in line with GACP, respecting the individual risks of each supplier and each herbal raw material as well as its destined use. It can consist of different tools such as information about supplier or on-site visits or ongoing supervision of suppliers. This enables to define the specific risk of each supplying situation. By this risk-based approach, an appropriate level of quality assurance is achieved in an agricultural and wild collection environment.

Additional support of the supplier, e. g. through specific training or improvement in the infrastructure may

Figure 1

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also be very effective in certain sourcing situations in order to reduce the potential risk. Such a flexible approach takes into account the individual conditions of agricultural production and contributes to a high and consistent quality of herbal medicinal products. Insofar this approach is intended to complement the general GMP requirements of supplier's qualification for raw materials of herbal origin.

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