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MINIMISATION OF RISKS ASSOCIATED WITH THE USE OF POLLEN-BASED MEDICINES, AT THE STAGE OF POLLEN COLLECTION

A.A. Taube[1], T.A. Buyanova[2], E.I. Sakanyan[3]

[1] Scientific Centre for Expert Evaluation of Medicinal Products
Bld. 2, 8, Petrovsky Blvd, Moscow, Russia, 127051
[2] St. Petersburg Chemical and Pharmaceutical University
Bld. A, 14, Prof. Popov Str., St. Petersburg, Russia, 197376
[3] Joint-Stock Company "Scientific and Production Association "Microgen"
Bld. 2, 15, 1st Dubovskaya Str., Moscow, Russia, 115088

E-mail: Aleksandra.taube@pharminnotech.com

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The aim of the study is the elaboration of Rules for Harvesting/Collecting of Pollen to minimize the risks associated with the use of pollen-based medicinal products.

Materials and methods. The following electronic resources were used in the study: PubMed, Medline, ScienceDirect, Web of Science, Scopus, Google Scholar, eLibrary, World Allergy Organization, Cochrane Database, Stallergenesgreer, Allergen-scienceandconsulting, Pharmacopoeia, Fda.gov, fs.usda.gov, Ema.europa.eu. The analysis covered the period from January 1, 2010 until December 31, 2021.

Results. Currently, there are some general requirements for the quality of pollen in Russia, but there are no controls or standardised procedures for harvesting, drying, and purification of pollen. The USA and EU also lack established qualification programmes for pollen-collecting companies and/or individual pollen collectors. Regulatory authorities establish requirements only for visual control of raw materials or delegate responsibility to the manufacturer. The analysis of the existing regulatory documentation revealed lack of requirements for collection, storage, and processing of pollen used as the raw material for the production of allergen products. This calls for the elaboration of appropriate regulatory documents. The authors have compiled the Rules for Harvesting/Collection of Pollen, which include 6 parts. The Rules are intended for individuals directly involved in harvesting/collection of pollen, and contain requirements for pollen collectors, the process of pollen collection, documentation, storage, and transportation.

Conclusion. The authors have prepared the Rules for Harvesting/Collecting of Pollen, which include 6 parts. The Rules cover the whole process of pollen collection and all related processes. The implementation of this document will improve the process of pollen collection, thus reducing the risks associated with the use of pollen-based medicines. Further studies will assess the impact of the pollen quality on the safety of medicinal products.

Keywords: allergen-specific immunotherapy; herbal substances; safe use of medicinal products; good collection practice; adverse drug reactions; pollen; allergen extract

Abbreviations: ASI – allergen-specific immunotherapy; GM – general monograph; EU – European Union; USA – the United States of America; SP Rus. XIV ed. – State Pharmacopeia (Russia) XIV edition; PPE – personal protective equipment.

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МИНИМИЗАЦИЯ РИСКОВ ПРИМЕНЕНИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ НА ОСНОВЕ ПЫЛЬЦЫ НА СТАДИИ ЗАГОТОВКИ СЫРЬЯ

А.А. Таубэ[1], Т.А. Буянова[2], Е.И. Саканян[3]

[1] Федеральное государственное бюджетное учреждение «Научный центр экспертизы средств медицинского применения» Министерства здравоохранения Российской Федерации
127051, Россия, Москва, Петровский б-р, д. 8, стр. 2
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования Санкт-Петербургский химико-фармацевтический университет» Министерства здравоохранения Российской Федерации
197376, Россия, Санкт-Петербург, ул. Профессора Попова, д. 14, лит. А
[3] Акционерное общество «Научно-производственное объединение «Микроген»
115088, Россия, Москва, 1-я Дубовская ул., д. 15, стр. 2

E-mail: Aleksandra.taube@pharminnotech.com

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Цель. Подготовка проекта Правил заготовки (сбора) растительной пыльцы для минимизации рисков при применении лекарственных препаратов на основе пыльцы.

Материалы и методы. В исследовании использовали следующие электронные ресурсы: PubMed, Medline, ScienceDirect, Web of Science, Scopus, Google Scholar, eLibrary, World Allergy Organization, Cochrane Database, Stallergenesgreer, Allergenscienceandconsulting, Pharmacopoeia, Fda.gov, fs.usda.gov, Ema.europa.eu. Поиск осуществляли за период с 1 января 201 по 31 декабря 2021.

Результаты. В настоящее время в России существуют общие требования к качеству пыльцевого материала, однако какой-либо контроль и стандартизация процесса заготовки, сушки и очистки отсутствует. В США и ЕС также отсутствуют установленные программы квалификации организаций по сбору пыльцы и/или индивидуальных сборщиков. Регуляторные органы ограничиваются визуальными требованиями к исходному сырью или возлагают ответственность на усмотрение производителя. В ходе анализа действующих нормативных документов было выявлено отсутствие требований в отношении сбора, хранения и обработки пыльцы, используемой в качестве сырья для производства лекарственных препаратов аллергенов. В связи с этим существует необходимость разработки нормативных документов. Составлены «Правила заготовки (сбора) пыльцы», в которых выделены 6 разделов. Правила предназначены для лиц, непосредственно осуществляющих заготовку (сбор) пыльцы, и содержат требования к заготовителям, к процессу сбора пыльцы, документации, хранению и транспортированию пыльцы.

Заключение. Составлены «Правила заготовки (сбора) пыльцы», в которых выделены 6 разделов. Составленные Правила полностью регламентируют процесс сбора пыльцы и все сопутствующие ему процессы. Внедрение документа позволит повысить качество сбора пыльцы, тем самым уменьшить риски применения лекарственных препаратов на ее основе. Планируется изучение влияния качества пыльцевого сырья на безопасность применения лекарственных препаратов.

Ключевые слова: аллергенспецифическая иммунотерапия; лекарственное растительное сырье; безопасность применения лекарственных препаратов; надлежащая практика сбора; нежелательные реакции; пыльца; экстракт аллергена

Список сокращений: АСИТ – аллерген специфическая иммунтерапия; ЛП- лекарственный препарат; ОФС – общая фармакопейная статья; ЕС – Европейский Союз; США – Соединенные Штаты Америки; ЛРС – лекарственное растительное сырье; ГФ РФ XIV издания – Государственная фармакопея XIV издания; СИЗ – средства индивидуальной защиты.

INTRODUCTION

A significant part of the population is affected by allergic diseases [1, 2]. According to some estimates, about 20–30% of the world's population [3] suffer from allergies, including 1 to 5% of the ones who suffer from pollen-associated food allergies, which may not necessarily include allergic rhinitis symptoms [4].

The study of the allergic diseases mechanism and pathogenesis resulted in the development of a modern treatment method—allergen-specific immunotherapy (ASI) [5–7]. The ASI principle consists in the administration of gradually increasing doses of pollen-based allergen extract which induces an allergic response, to a patient [8, 9]. The ASI method is the only evidence-based etiotropic therapy for allergic diseases [10–13]. However, there are still topical problems regarding clinical efficacy and tolerability of the therapy [14–16]. Different dosage forms of allergens and allergoids are manufac-

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tured for the ASI method that uses pollen's ability to induce an allergic response [17]. Pollen is a herbal substance used for the production of allergen extracts, i.e. active pharmaceutical ingredients (herbal preparations) which, in their turn, are used for the production of allergen and allergoid products [15]. Herbal substances are highly diverse and variable in terms of bioactive substance composition [18–20], which depends not only on the geographical range and weather conditions, but also on the period and procedure of collecting/harvesting [21, 22], and this makes it difficult to establish uniform standards [23, 24].

Pollen, as a morphological group, has a number of specific features that are not taken into account in current regulatory documents. Pollen is a delicate material that is rather difficult to collect. The main difference between pollen and other herbal preparations is that much of pollen is harvested in the natural habitat, which has a significant impact on the quality and uniformity of the final product [25]. Pollen composition is affected by genetic and environmental factors, such as the harvested plants, weather conditions, air and soil pollution during the plant growth [26,27], which makes it difficult to assess the products' safety profile [28]. A potential development of adverse events, as well as a medicinal product efficacy in ASI, depend not only on the administered dose, but also on the biochemical characteristics of the administered allergen product [29-33]. The first stage of the study included the elaboration of a controlled physicochemical parameters list, qualitative and quantitative characteristics (including macro- and microscopic species-specific characteristics) to be included in the regulatory documentation for pollen [34].

The efficacy and safety of medicinal products are affected by pollen harvesting and storage conditions. To prevent pollen contamination, including the one with pollen from other plants, the harvesting/collecting of raw materials should be regulated by relevant documents. In this area, the following regulations are in force in the Russian Federation: Rules of Good Manufacturing Practice of the Eurasian Economic Union adopted by Resolution No. 77 of the Council of the Eurasian Economic Commission dated November 3, 2016 (hereinafter Resolution No. 77)[1]; Resolution No. 15 of the Council of the Eurasian Economic Commission On Adoption of the Rules of Good Practice of Cultivation, Collection, Processing, and Storage of Starting Materials of Herbal Origin (hereinafter Resolution No. 15)[2]; Recommendations of the Board of the Eurasian Economic Commission dated May 10, 2018, No. 6[3].

Pollen collectors must follow the Rules of Good Practice of Cultivation, Collection, Processing, and Storage of Starting Materials of Herbal Origin adopted by Resolution No. 15 of the Council of the Eurasian Economic Commission dated January 26, 2018[4]. Chapter 3 "Personnel" of Resolution No. 15 states: "If the harvesters/collectors do not have knowledge of the harvested medicinal plants, they should receive training, their work should be supervised, and appropriate records should be kept". At the same time, there are no established criteria and requirements for pollen harvesting/collecting. The environmental issues should also be given consideration[5]. All of the above listed factors support the need for the elaboration of rules for harvesting/collecting of pollen as a morphological group of herbal substances.

THE AIM of the study is the elaboration of Rules for Harvesting/Collecting of Pollen to minimize the risks associated with the use of pollen-based medicinal products.

MATERIALS AND METHODS

The following electronic resources were used in the study: PubMed, Medline, ScienceDirect, Web of Science, Scopus, Google Scholar, eLibrary, World Allergy Organization, Cochrane Database, Stallergenesgreer, Allergenscienceandconsulting, Pharmacopoeia, Fda.gov, fs.usda.gov, Ema.europa.eu. The queries were made using the following English and Russian keywords combinations: allergen specific immunotherapy; pollen; pollen collection; major and minor, Allergy, grass allergens; molecular diagnosis; safety; Allergen extract; Allergen standardisation. The analysis covered the period from January 1, 2010 until December 31, 2021.

Russian and foreign laws and regulations were used as study materials. The rules were elaborated based on the following documents: State Pharmacopoeia of the Russian Federation, XIV edition (SP Rus., XIV ed.)[6]; Rules of Good Practice of Cultivation, Collection, Processing, and Storage of Starting Materials of Herbal Origin[7]; Russian National Standard GOST 24027.0-80 Herbal Sub-

[1] Rules of Good Manufacturing Practice of the Eurasian Economic Union adopted by Resolution No. 77 of the Council of the Eurasian Economic Commission of November 3, 2016 (as amended on July 14, 2021)

[2] Rules of Good Practice of Cultivation, Collection, Processing, and Storage of Starting Materials of Herbal Origin adopted by Resolution No.15 of the Council of the Eurasian Economic Commission of January 26, 2018

[3] Recommendations of the Board of the Eurasian Economic Commission On the Guideline for the Quality of Herbal Medicinal Products of May 10, 2018, No.6.

[4] Order of the Ministry of Natural Resources of Russia of July 28, 2020 No. 494 On Adoption of the Rules for Harvesting Forest Plants for the Food Industry, and Medicinal Plants (Registered in the Ministry of Justice of Russia on December 14, 2020, registration No.61428).

[5] Forestry Code of the Russian Federation of December 4, 2006 No.200-FZ (as amended on July 31, 2020). Available from: http://www.consultant.ru/document/cons_doc_LAW_64299/.

[6] State Pharmacopeia of the Russian Federation XIV edition. Vol. I–IV; M., 2018. available from: https://femb.ru/record/pharmacopea14.

[7] Rules of Good Practice of Cultivation, Collection, Processing, and Storage of Starting Materials of Herbal Origin adopted by Resolution No.15 of the Council of the Eurasian Economic Commission of January 26, 2018.

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stances. Rules for Acceptance, and Sampling Methods[8]; Russian National Standard GOST 24027.1-80 Herbal Substances. Identification, Detection of Pest Contamination, Testing of Impurities and Degree of Fineness[9]; Russian National Standard GOST 24027.2-80 Herbal Substances. Determination of Water Content, Ash, Extractives, Tannins, and Essential Oil[10]; Committee for Medicinal Products for Human Use. Guideline on Allergen Products: Production and Quality Issues. European Medicines Agency. –London. 2008[11]; European Pharmacopoeia. 10th ed. European Department for the Quality of Medicines[12]; US Food and Drug Administration. Compliance Program Guidance Manual, Chapter 45, Biological Drug Products, Inspection of Biological Drug Products (CBER) 7345.848[13]; Code of Federal Regulations Food and Drug Administration (21 680.1). Allergenic Products. V.7[14].

RESULTS AND DISCUSSION

Like other herbal substances, pollen is usually harvested from wild and cultivated plants. General Pharmacopoeia Monograph (GPM).1.7.1.0001.15 "Allergens"[15] states that in the case of cultivated plants, the maturation of pollen has to take place in pollinaria – specially equipped facilities with continuous indoor climate monitoring. Such methods of obtaining raw materials are used in the EU and the USA. Several large manufacturers, such as Stallergenes (France), have their own pollinaria[16]. This is a new and fairly uncommon strategy that allows obtaining homogeneous materials and minimizing man-caused impacts [26].

There are several methods of pollen collection: manual, vacuum-assisted, and water-assisted. Any of these methods may be used for pollen collection from a wide variety of plants. The choice of the method will depend on the experience of a particular collector, available resources, an area size, and the required amount of raw materials[17]. Each method has its benefits and drawbacks. The most common method in Russia is a manual collection by an open method, which is very laborious, but not very efficient. The water method is more efficient. It consists in placing the plant parts with mature anthers in trays filled with water. The anthers open up, and the pollen grains stick to the tray surface. The main advantage of this method is that it helps to obtain high-purity materials. However, this method is also very laborious, and the collected pollen is exposed to moisture, which subsequently stimulates the growth of microorganisms, including pathogenic ones [26].

The vacuum method is recommended for pollen collection from the plants that grow as a ground cover, like most weeds. Before starting the collection process, the area is carefully inspected for any related or unrelated plants that could by collected by mistake. The collection is carried out with the help of special devices in the form of reservoirs fitted with air tubes working similar to a vacuum cleaner. The main advantage of this method is that it is relatively simple. The main disadvantage of the method is that it is impossible to remove all unwanted plants from the collection area, and the final product may contain a lot of pollen grains from other plants, which cannot be isolated. Mechanical sieving is the easiest and most popular method of pollen purification, as sieving through different micronic mesh sizes helps to remove biological contaminants that are different in size from pollen grains. The purification by air allows removal of those impurities that are also different in mass. However, the air-assisted purification equipment is expensive and often results in the damage to pollen, which makes it difficult to assess its allergenic properties [26].

Based on the above, it is recommended to include three main manual collection methods into the Rules[18]. The first collection method uses cyclone dust collectors and is the most effective of all the three methods. Raw materials are collected into special bags and can be processed immediately after the collection. The second method is more problematic, because pollen is collected together with flowers. The collected flowers have to be dried in special convection dryers. Next, the flowers are cut to separate the pollen, and the pollen is sieved. The advantage of this method is that it produces dried materials, already ready for storage. However, a major disadvantage of the method is the likelihood of finding parts of the cut flowers in the harvested materials. The third method is the least effective of all. Inflorescences are placed in a plastic bag, without cutting them from the

[8] Russian National Standard GOST 24027.0-80 Herbal substances. Rules for Acceptance, and Sampling Methods. Available from: https://docs.cntd.ru/document/1200022938.

[9] Russian National Standard GOST 24027.1-80 Herbal Substances. Identification, Detection of Pest Contamination, Testing of Impurities and Degree of Fineness. Available from: https://rags.ru/gosts/gost/14034/.

[10] Russian National Standard GOST 24027.2-80 Herbal Substances. Determination of Water Content, Ash, Extractives, Tannins, and Essential Oil. Available from: https://rags.ru/gosts/gost/30604/.

[11] Guideline on Allergen Products: Production and Quality Issues. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-allergen-products-production-quality-issues_en.pdf.

[12] European Pharmacopoeia. 10th ed. Available from: https://www.edqm.eu/en/web/edqm/european-pharmacopoeia-ph-eur-10th-edition.

[13] US Food and Drug Administration. Compliance Program Guidance Manual, Chapter 45, Biological Drug Products. Available from: https://www.fda.gov/media/73834/download.

[14] Code of Federal Regulations Food and Drug Administration (21 680.1). Allergenic Products. V.7. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-680/section-680.1.

[15] State Pharmacopeia of Russian Federation XIV ed. GMP.1.7.1.0001.15 Allergens. M.; 2018. Available from: http://pharmacopoeia.ru/ofs-1-7-1-0001-15-allergeny. Russian

[16] Stallergenes Greer. Allergen Extracts: Derived from Natural Sources. Available from: https://www.stallergenesgreer.com/manufacturing.

[17] Copes DL, Vance NC, Randall WK, Jasumback A, Hallman R. Vacuum collection of Douglas-fir pollen for supplemental mass pollinations. Res. Note PNW-RN-503. Portland, OR: U.S. Department of Agriculture, Forest Service, Pacific Northwest Research Station. 1991: 9 p.

[18] Encyclopaedia of Beekeeping. Collection and Storage of Pollen. Available from: http://paseka.pp.ru/pchela-i-zdorove-cheloveka/614-sbor-i-xranenie-pylczy-i-pergi.html. Russian

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plant, and are shaken vigorously. This method is more appropriate for large inflorescences, as it is less likely to damage the flowers.

The choice of the method should be governed by the type of the harvested plant. The composition and quality of pollen depend on a variety of factors, therefore, no major biologically active components have been determined yet that could be used for pollen qualification or standardisation.

General Pharmacopoeia Monograph.1.7.1.0001.15 "Allergens"[19] (SP Rus., XIV ed.); provides the general requirements for the quality of pollen: a harvesting period; a residual moisture; morphological characteristics; impurities; heavy metals (sulfated ash); pest contamination. Nevertheless, the general monograph does not contain requirements for the methods of pollen collection.

The most relevant current regulations include the following ones: Russian National Standards GOST 24027.0-80, GOST 24027.1-80, and GOST 24027.2-80, Rules of Good Manufacturing Practice of the Eurasian Economic Union adopted by Resolution No. 77. The analysis of the regulatory documents has revealed no mention of pollen in them. Resolution No.15 applies to the production of herbal substances by the agricultural industry and covers the organic material production and obtaining herbal substances from wild-growing plants. However, the collection rules do not cover specific aspects of pollen collection from wild-growing and cultivated plants. At the same time, Resolution No. 77 states that the requirements for raw materials also apply to pollen.

Thus, there are some general requirements for the pollen quality ~~of~~ in Russia, but there are no controls or standardized procedures for harvesting, drying, and purification of pollen. The USA and EU also lack specific qualification programmes for pollen-collecting companies and/or individual pollen collectors[20]. Regulatory authorities have established requirements for the allergen extract quality, but when it comes to the raw materials, they mainly rely on the requirements for visual control of raw materials or suggest delegating the responsibility to the manufacturer. Therefore, allergen extract manufacturers usually provide a list of their own requirements for the companies supplying pollen and/or for individual collectors [36]. Table 1 summarizes quality control parameters for some medicinal products by different manufacturers, which are authorized in Russia [37]. The standardisation performed is based on the major protein [38-40].

The pollen composition has an effect on both efficacy and safety of ~~the~~ pollen-based herbal medicinal products. The allergenic composition of pollen depends on genetic factors, weather and climate conditions, man-made factors, a period and methods of pollen collection, its procession, and storage [35]. For instance, rains damage the exine of pollen grains, and that affects the allergenicity of the obtained pollen [41]. Therefore, collection of pollen during rains may affect the allergen profile of pollen. The qualitative and quantitative composition of allergens contained in pollen, is determined not only by specific weather or soil conditions, but also by intrinsic genetic properties of different varieties of plants [42]. If the raw material contains pollen from different plant genera and species, this may result in the presence of cross-reacting allergens and, consequently, increase the risks of adverse drug reactions due to the changes in the dosages of allergens in herbal medicinal products [43], or reduce the treatment efficacy due to the allergen incompatibility [44]. The risks of adverse reactions to immunotherapy depend on each patient's individual model of sensitization to plant allergens [45]. In general, ASI is regarded a safe kind of therapy. The studies suggest that the most frequent adverse reactions are of a local type (64%) [45]. No systemic adverse reactions have been observed in pre-clinical [46] and clinical [47] studies.

A proper pollen storage is critical for ensuring the quality of raw materials and preserving their protein composition[21]. Harvesting, processing, storage, and a quality control of pollen are performed with due regard to anatomical and diagnostic properties of plants.

Elaboration of regulatory document setting requirements for pollen collection as raw material for medicines production

The authors of this paper suggest an approach to the elaboration of a document on harvesting/collecting, storage, and processing of pollen (hereinafter referred to as the Rules) (Fig. 1). These Rules apply to harvesting/collecting of pollen from wild and cultivated plants, to be used as a raw material for the industrial-scale production of medicinal products.

The Rules are intended for the individuals who are directly involved in harvesting/collecting of pollen, i.e. individual collectors and self-employed businessmen who have an appropriate certificate of training.

Personnel – pollen collectors

1. In order to be admitted to pollen harvesting/collecting, a Collector must be checked for infectious diseases, and if any infection is detected, the Collector must be suspended.

2. The Collector must meet all the requirements set forth in the Rules of Good Practice of Cultivation, Collection, Processing, and Storage of Starting Materials of Herbal Origin.

[19] State Pharmacopeia of Russian Federation XIV ed. GMP.1.7.1.0001.15 Allergens. M.; 2018.

[20] US Food and Drug Administration. Compliance Program Guidance Manual, Chapter 45, Biological Drug Products. Inspection of Biological Drug Products (CBER) 7345.848. Available from: https://www.fda.gov/media/73834/download.

[21] Allergen Science and Consulting. Storage of Allergenic Raw Materials. Available from: http://allergenscienceandconsulting.com/allergenic-raw-materials-storage/.

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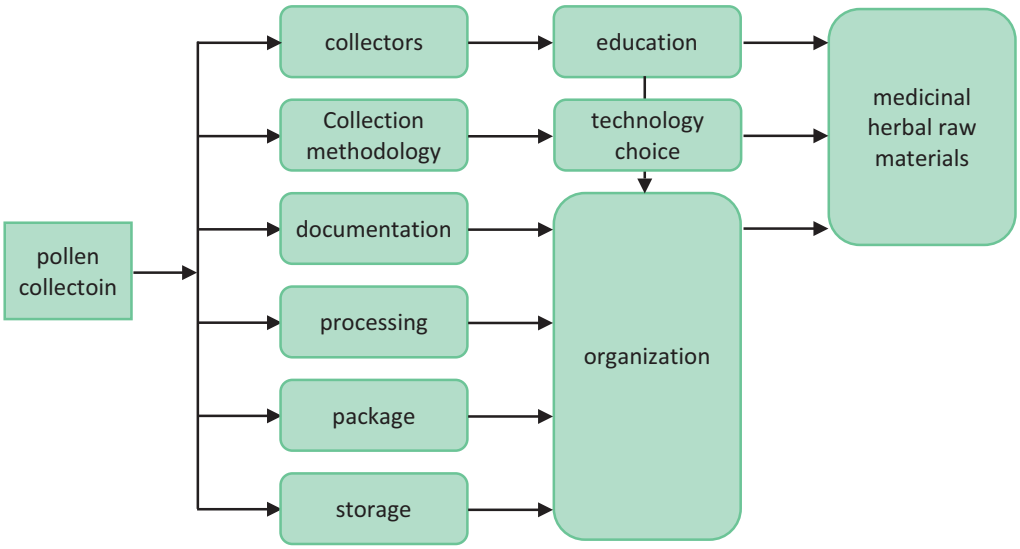

Figure 1 – Diagram of proper pollen harvesting for medicines production (A.A. Taube, 2021)

Table 1—Principles of standardization of medicinal products for ASI

Parameter	Allergens ("Seva Pharma", Czech Republic)	Staloral, Oralair (Stellergen, France)	LAIS (Lofarma, Italy)
Molecular structure	Polymer	Polymer	Monomer (allergoid)
Standardization	Protein nitrogen content	Reactivity index (characterises the major antigen)	Allergenic unit (characterises the antigenic determinant)
Administration route	Sublingual (drops, tablets)	Sublingual (drops, tablets)	Sublingual (tablets)

3. Prior to harvesting, the Collector must be informed about the principles of handling rare and protected medicinal plants, and a sustainable use of natural resources in accordance with the Forestry Code of the Russian Federation[22].

4. The Collector must have sufficient knowledge of the harvested wild and cultivated plants.

5. Pollen is a highly allergenic product; therefore the Collector must be protected from its harmful effect.

6. Collectors must be provided with adequate sanitary-hygienic labour conditions, working clothes, and appropriate personal protective equipment (PPE).

Technical requirements for pollen harvesting/collecting

The next stage of the study involved the elaboration of technical requirements for pollen collection methods.

The authors have carefully studied the process of pollen collection and formulated the following requirements.

1. To minimize the content of heavy metals and other ecotoxicants in pollen, it is forbidden to carry out harvesting near roads and manufacturing facilities.

2. Harvested medicinal plants should not be damaged by bacteria or insects, only healthy plants should be harvested.

3. A harvesting period should coincide with the flowering period of the plant, which may vary depending on the type of the plant and its vegetation area. For example, flowering of birch takes place from the end of April till the end of May, while flowering of cereals takes place much later – from the end of May till the end of July.

4. Pollen collection should not be carried out during or after the rain and in the morning, if there is dew. Damp or wet plants/trees should not be harvested. A high humidity increases the risk of mould and bacteria that are damaging for the pollen allergen. Pollen collection should take place in the daytime or in the evening A more specific time of pollen collection depends on the genus and species of the harvested plant. The collection time may also be influenced by the region where the collection is taking place.

5. Pollen collection should be carried out in such a way as to minimize particulate contaminations (e.g., from the soil).

6. Contact of raw materials with other types of pollen must be avoided in order to prevent cross-contaminations.

7. Pollen collection may be carried out by manual

[22] Forestry Code of the Russian Federation of December 4, 2006 No. 200-FZ (as amended on July 31, 2020). Available from: http://www.consultant.ru/document/cons_doc_LAW_64299/. Russian

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or vacuum methods. The choice of the method must be justified for each type of the plant. A proper collection helps to increase the efficiency of the process and avoid contaminations of raw materials.

8. The equipment should be made from high-quality materials preventing cross-contaminations. The machine parts that are in direct contact with the raw materials, must be carefully cleaned to avoid contaminations from previously collected pollen and from residual amounts of detergents.

9. During harvesting, raw material must be protected from the exposure to the substances used in the equipment operation, such as lubricants and fuel.

10. In order to obtain pollen of good quality, the processing time should be stuck to. The Collector must deliver the harvested raw materials to the customer within 2–3 hours after the collection. If this is not feasible, the raw materials must be dried. Drying is carried out in convection dryers at 35–40°C [48]. Before drying, the pollen is spread out in a thin layer on greaseproof paper. This helps to prevent mould formation during storage. After drying, plant parts, fungal spores, and insect fragments are removed from the pollen. The two main purification methods are mechanical sieving and air purification.

11. The storage of pollen until its delivery to the manufacturer is carried out according to the Rules of Good Practice of Cultivation, Collection, Processing, and Storage of Starting Materials of Herbal Origin.

12. Accompanying documentation is prepared according to the Rules of Good Practice of Cultivation, Collection, Processing, and Storage of Starting Materials of Herbal Origin.

13. It is prohibited to harvest endangered plant species (Article 85 of the Administrative Offence Code of the Russian Federation dated December 30, 2001 No.195-FZ[23]).

14. Repeated harvesting of medicinal plants in the same area is carried out in accordance with the Order of the Ministry of Natural Resources of Russia dated July 28, 2020 No.494[24]. Pollen is an above-ground organ of the plant, therefore the collection interval is once in 2 years for annual plants and once in 4–6 years for perennial plants. This is an essential requirement for prevention of medicinal plant extinction.

15. The harvesting/collection method is developed for each species on a case-by-case basis.

16. Values of organoleptic properties should be determined by dedicated experts for each individual type of a herbal substance. However, there are some visual control parameters, which are common for all types of herbal substances: evident impurities, such as soil or parts of plants; contaminations with pathogenic microorganisms, mould, larvae, etc. These problems may arise when pollen is collected from unhealthy plants, or when the conditions of raw materials storage are not observed [49].

[23] Administrative Offence Code of the Russian Federation of December 30, 2001 No. 195-FZ (as amended on April 20, 2021).

[24] Order of the Ministry of Natural Resources of Russia of July 28, 2020 No. 494 On Adoption of the Rules for Harvesting Forest Plants for the Food Industry, and Medicinal Plants (Registered in the Ministry of Justice of Russia on December 14, 2020, registration No. 61428). Russian

Documentation

At the next stage of the study, the authors elaborated the Documentation part of the Good Practice. All activities performed with raw materials must be documented. The authors elaborated a Pollen Collection standard form, which is given in the annex to the Rules.

The Pollen Collection form was compiled, based on the form for harvesting herbal substances given in the Rules of Good Practice of Cultivation, Collection, Processing, and Storage of Starting Materials of Herbal Origin. The form contains the following fields to be filled:

1. Latin name of the harvested plant (genus, species, subspecies, variety);
2. Russian name of the plant;
3. Place of collection (district / region / country / geographical bearings if possible);
4. Date and time of the collection to make sure that the collection time is chosen correctly;
5. Collector's data, i.e. his/her full name;
6. Collector's location. For legal entities—the address of the company, for the individuals registered as self-employed businessmen – residential addresses, to enable a communication with the supplier, if necessary;
7. Collection/weather conditions, since collection is forbidden in rainy weather;
8. Nearby plants – to know which pollen impurities may be present in the harvested material;
9. Insects that may be found on nearby plants—to perform tests for potential contaminations of pollen;
10. Collection method – in order to know which impurities should be tested and which tests should be performed;
11. The amount of collected pollen;
12. Additional information which may include the growing conditions if known, and the fertilizers used;
13. Whether the harvested material was dried after the collection, and if so, which equipment and conditions were used;
14. The circumstances that can affect the quality.

The delivery of the harvested material by the Collector to the customer must be based on a commercial contract, which stipulates the provision of accompanying documents confirming that the collection of pollen was performed in accordance with the applicable requirements.

Storage and transportation

Pollen must be stored under well-defined conditions. Requirements for storage and transportation are

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established in the SP Rus., XIV ed. and in the Rules of Good Practice of Cultivation, Collection, Processing, and Storage of Starting Materials of Herbal Origin. Individual storage conditions may be considered for pollen of some particular plants.

The main requirements are:

1. Pollen and packaging materials must be stored in dry, well-aerated facilities, protected from rodents, birds, and insects.

2. Pollen must be packaged in dry, clean, thick bags.

3. Each package must be labelled in accordance with the Decision of the Council of the Eurasian Economic Commission dated November 3, 2016 No. 76[25]. The following has to be specified:

– raw materials names;
– names of suppliers/collectors;
– lot/batch number;
– year and month of harvesting/collecting;
– delivery dates;
– shelf life.

4. Different types of raw materials must be stored in tight packages to prevent contamination.

5. Packaged raw materials must be stored on trays to avoid wetting.

6. Pollen herbal substances must be stored and transported frozen (at a relative humidity of 3±0.5%);

7. Frozen herbal substances should be stored at temperatures below –18°C, and below –20°C in case of long-term storage.

CONCLUSION

Based on the results of the performed analysis, the authors prepared the Rules for Harvesting/Collecting of Pollen, which include 6 parts. The Rules cover the whole process of pollen collection and all related processes. The implementation of this document as an independent part of the Rules of Good Practice of Cultivation, Collection, Processing, and Storage of Starting Materials of Herbal Origin will make it possible to collect pollen of wild and cultivated plants and obtain high-quality raw materials (with minimum impurities/heavy metals/contaminations with pathogenic microorganisms/mould, etc.), without detriment to the plant population.

The availability of a regulatory document establishing requirements for the process of harvesting, storage, and processing of pollen herbal substances will make it possible to improve the process of pollen collection, thus reducing risks associated with the use of pollen-based medicines. The focus of further studies could be on establishing the correlation between the quality of pollen and development of adverse drug reactions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS’ CONTRIBUTIONS

Aleksandra A. Taube – formulation of the study concept, choice of the study methods, analysis and interpretation of the obtained results, direct involvement in the study, carrying responsibility for all aspects of the study; Tatyana A. Buyanova – analysis of scientific literature and guidelines, carrying responsibility for all aspects of the study related to data reliability; Elena I. Sakanyan – editing and revision of the text, final approval of the paper, carrying responsibility for all aspects of the study.

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[25] Decision of the Council of the Eurasian Economic Commission of November 3, 2016 No.76 On Adoption of the Requirements for Labelling of Medicinal Products for Human Use and Veterinary Medicinal Products.

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AUTHORS

Aleksandra A. Taube – Candidate of Sciences (Pharmacy), Leading Researcher at the Center for Planning and Coordination of Research Works of the Scientific Centre for Expert Evaluation of Medicinal Products. ORCID ID: 0000-0001-5594-4859. E-mail: Aleksandra.taube@pharminnotech.com

Tatyana A. Buyanova – master's student of the Department of Economics and Management of St. Petersburg Chemical and Pharmaceutical University. ORCID ID: 0000-0001-7033-424X. E-mail: buyanovatanya1@gmail.com

Elena I. Sakanyan – Doctor of Sciences (Pharmacy), Director of Research, Joint-Stock Company "Scientific and Production Association "Microgen". ORCID ID: 0000-0001-8536-4804. E-mail: sakanjan@mail.ru