review

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Good manufacturing practice- and good distribution practice-compliant cold storage and refrigerated transport of allergen products: what is important?

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Abstract
Background All currently available products for diagnosis and therapy of type I allergies are protein extracts from allergenic source material. The extracted proteins have different properties and their structure is differently labile to temperature variations. Despite various pharmaceutical formulations to increase product stability, with few exceptions, allergen products must be refrigerated to ensure that their quality and native protein structure do not change during storage and transport. Maintaining quality is a challenge in complex distribution chains.
Methods Regulatory requirements and guidelines that apply to cold storage and transport of allergen products are summarized and the responsibilities of the stakeholders are explained.
Results The storage conditions determined in stability studies correspond to the transport conditions. These stability data can also be used to assess tolerable conditions during transport. According to a good distribution practice (GDP) contracts must be concluded between the responsible pharmaceutical entrepreneur and the qualified distribution service provider that regulate storage and transport in accordance with the product requirements.
Conclusion Monitoring of storage and transport conditions is achieved by transport in qualified means of transport (e.g. truck). Alternatively, qualified transport packaging with active or passive cooling (e.g. cold packs) and qualified "data loggers" that record the transport temperatures can be used. Regardless of the system used, it must be demonstrated—by validating the transport conditions, routes and packaging at different times of the year and over the entire duration of transport—that regulatory requirements are met and that the quality of the products is maintained during shipment.

Keywords Quality of allergen products · Regulatory requirements · Stability of allergens · Good Distribution Practice (GDP) · Good Manufacturing Practice (GMP)

Abbreviations

AMG	German Medicinal Products Act
AMK	Drug Commission of the German Pharmacists
AMWHV	Ordinance on the Manufacture of Medicinal Products and Active Substances
CAPA	Corrective Action and Preventive Action
GDP	Good distribution practice
GMP	Good manufacturing practice
ICH	International Committee of Harmonization
PCM	Phase change material
QP	Qualified person

Introduction

Test and therapy allergens are obtained from various allergenic sources by protein extraction. For this purpose, a variety of efforts are made in the process chain during production in order to achieve a high, consis-

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tent quality of the allergen products [1]. To ensure quality also after manufacturing, transport and storage, most allergen products must be refrigerated. Due to increasing complexity of supply chains, the responsibilities and measures that need to be defined and taken to ensure and monitor transportation and storage are challenging. Here, we provide an overview of the most common procedures and regulatory background for good transport and storage practices of allergen products.

Stability of allergens to heat and cold

Allergen extracts consist of a range of proteins that will respond differently to defined temperatures with regard to their stability [2]. The thermostability of allergens varies depending on their molecular structure. Influencing structural features include the protein sequence, glycosylation pattern, possible ligand binding, degree of oligomerization or matrix effects of excipients [3].

Changes in the quaternary, tertiary and secondary structure of allergens are accompanied by changes in allergenic activity. On the one hand, thermal unfolding may decrease allergenic activity due to reduced binding of IgE antibodies; on the other hand, previously hidden epitopes can become freely accessible, which in turn can increase activity [4]. To ensure the stability of allergen products, various measures are therefore required on the part of the manufacturers.

In the galenics of allergen products, excipients such as glycerol, human serum albumin, phenol, and mannitol are used to improve stability compared to aqueous extracts without excipients. The appropriate composition is allergen-specific. For example, when extracts from different allergen sources are combined, stability can be negatively affected if they contain proteolytic enzymes—as in the case of mold extracts [5].

For pollen extracts, a glycerol concentration of 50%, also in combination with human serum albumin, and storage at 2–8 °C in a qualified refrigerator (see below) has been shown to preserve the original activity of the allergenic proteins [6, 7]. At the same time, glycerol protects the proteinaceous active materials from solution freezing. A common storage error, possibly also in doctors' offices, is storing allergen preparations near the evaporator in the refrigerator or in the refrigerator door. Temperatures there are often below the freezing point or above 8 °C respectively, even if the refrigerator is set to a usual 2–8 °C. Ideally, the requirements for medicinal products which must be refrigerated (for definition, see following section "Labeling") of DIN 58345 "Refrigerators for drugs—Definitions, requirements, testing" [8] are also met for allergen products requiring refrigerated storage. This includes, among other things, the requirement for a safety device against temperatures below 0 °C and daily monitoring on workdays, including corresponding documentation of the refrigerator temperature with a min–max thermometer. Temperatures below the freezing point can lead to a reduction in allergenic activity in birch pollen extracts, for example [9]. In the case of house dust mite extracts, this effect is intensified by repeated freezing and thawing [10]. However, high concentrations of glycerol are only suitable for test allergens, as increasing glycerol concentrations (more than 12%) of solutions for injection may cause pain in the patient [11].

Furthermore, it is possible to achieve greater stability to temperature fluctuations by the appropriate storage form (e.g. by lyophilization, spray drying) of extracts. Lyophilizates nevertheless require specific storage temperatures. The lyophilization process also alters proteins by removing the hydration shell. Therefore, drying aids (e.g., mannitol, sorbitol or glycine) are added to preserve their activity.

Finally, temperature fluctuations during transport must be reduced by using suitable packaging materials [12]. By using reusable insulated containers, precooled packaging materials and temperature monitoring by means of electronic loggers, very cost-intensive cold transport can be circumvented, especially for products that can be stored above freezing point. The cost situation is strongly dependent on the quantity of product transported. For small quantities, the passively cooled transport box is an alternative. Since the transport box can only hold a few drug packages due to the insulation and number of gel coldpacks, this is generally not economically feasible for the transport of larger quantities.

The greatest influence on the storage quality of allergen products is the storage temperature [13]. However, there are only few published data on this [14].

Regulatory framework for storage and transport of allergen products

Labeling

The EU Guideline on Declaration of Storage Conditions [15] contains requirements for the labeling "Store and transport refrigerated/Store and transport frozen". This labeling corresponds to the German terms "Kühlkettenpflicht" and "kühlpflichtig". This describes a complete compliance with the prescribed temperatures from production to use. The labeling should only be used for products that do not tolerate temperature deviations. Examples are live vaccines, certain antibody preparations, blood products or first generation erythropoeitin preparations. Allergen products are not among these extremely temperature-sensitive drugs. This means for allergen products with the indication of "storage between 2–8 °C" on the packaging that a short-term exceeding of the temperature up to 25 °C can be tolerated [16]. However, this tolerable time window is not defined more precisely and must be determined on a product-specific basis. The manufacturer of a medicinal product

substantiates this requirement with corresponding stability data, which are detailed in the marketing authorization documents. Nevertheless, manufacturing, storage and transport must be organized by the pharmaceutical entrepreneur, the manufacturing companies and the service providers commissioned in the logistics chain in such a way that the temperature of 2–8 °C is guaranteed over the entire period of the logistics chain and thus the product quality is maintained.

According to the Guideline on Good Distribution Practice of Medicinal Products for Human Use 2013/C 343/01 [17], the storage conditions listed on the packaging also correspond to the transport conditions if no separate information on transport is provided. Likewise, according to the Guidelines for Good Distribution Practice of Medicinal Products for Human Use [17], it must be ensured in principle "that temperature conditions are maintained within acceptable limits during transport". This acceptable temperature range is further specified in Chap. 9.2 as "the defined limits as described by the manufacturers or on the outer packaging". Transport thus is mobile storage or storage with a change of location.

Stakeholders in storage and transport of allergen products

Today's retail chains for pharmaceuticals involve many players who transport the product from the manufacturer to the patient. In order to ensure that quality is maintained during distribution, the principle of good distribution practice (GDP) is implemented by all actors. According to the WHO Guideline Good Distribution Practices for Pharmaceutical Products [18] GDP is the part of quality assurance that monitors and ensures the quality of pharmaceuticals during logistics by means of appropriate controls.

The German Medicinal Products Act (AMG) distinguishes between the pharmaceutical entrepreneur, the manufacturer and the pharmaceutical wholesaler. All three and, if applicable, commissioned external storage and transport service providers are involved in the storage and transport of medicinal products. The pharmaceutical entrepreneur (Sect. 4 (18) AMG [19]) usually holds the marketing authorization and places the drug on the market under his name. The law describes this as "keeping in stock for sale or for other forms of supply, the exhibiting and offering for sale and the distribution to others" (Sect. 4 (17) AMG). The manufacturer of the drug as the holder of the manufacturing authorization according to Sect. 13 AMG is responsible, among other things, for the entire manufacturing process including packaging, labeling and storage and the final release (Sect. 4 (14) AMG, and Sect. 16 AMWHV). The wholesaler, on the other hand, is the one who performs any "professional or commercial activity for trading purposes that consists of procuring, storing, selling or exporting medicinal products" (Sect. 4 (22) AMG) and requires a wholesale distribution authorization in accordance with Sect. 52a AMG. In Germany, a wholesale authorization is applied for at the competent authority of the respective federal Land and requires, in addition to evidence of suitable premises, facilities, equipment and a quality assurance system in accordance with Sect. 1a of the Ordinance on the Trade with Medicinal Products (Arzneimittelhandelsverordnung—AM-HandelsV [20]), also the appointment of a responsible person for wholesale trade who has the necessary expertise and reliability (Sect. 52a AMG).

A further distinction is made between the storage service provider and the transportation provider. The storage service provider must notify the local competent authority of the federal Land of his activities in accordance with Sect. 67 AMG and he is subject to official supervision in accordance with Sect. 64 AMG. The transportation provider does not require a license under pharmaceutical law, but must nevertheless comply with the regulations under pharmaceutical law by means of a delimitation of responsibility agreement with a pharmaceutical manufacturer and/or a pharmaceutical entrepreneur or a pharmaceutical wholesaler. The contract giver must ensure this.

The monitoring according to Sect. 64 AMG of "Enterprises and establishments in which medicinal products are manufactured, tested, stored, packaged or placed on the market, in which they are otherwise traded, or that import medicinal products ..." is the task of the competent authority responsible for them locally. The monitoring tasks of the competent Land authorities also include the performance of GDP inspections. Upon their successful completion, a GDP certificate is issued, which is valid for five years. The monitoring of the transport of medicinal products is not named in Sect. 64 AMG as an official monitoring task, which is why the transportation providers themselves are not inspected by the competent authorities. The responsibility for the qualification and the necessary auditing of the transport companies, for the validation of the transport processes as well as the warehousing, lies, depending on the contract design, regularly and ultimately with the pharmaceutical entrepreneur. Since the pharmaceutical entrepreneur is supervised by the authorities, contracts can be examined in the course of an inspection. It is therefore of particular interest for the pharmaceutical entrepreneur to record the fulfillment of the GDP requirements in detail in corresponding contracts (AMWHV Sects. 7 and 9, EU-GDP Chap. 7).

The responsibilities for the transport of a medicinal product are to be defined in a written contractual agreement (also called quality assurance agreement, logistical agreement or delimitation of responsibility agreement) between the pharmaceutical entrepreneur placing the product on the market and the companies involved in the logistics chain. Companies involved in the logistics chain may include, for example, trans-

port companies, pharmaceutical wholesalers, storage companies or other pharmaceutical manufacturers. The responsibilities for checking the transport conditions and, if applicable, the storage conditions at contracted storage companies, as well as for carrying out transport validation, must be clearly defined. According to Chap. 7.2 of the GDP Guideline, the contract giver is responsible for evaluating the contract acceptor with regard to the implementation of the processes and for ensuring, by means of contract design and audits, that the principles and guidelines of GDP are complied with. Clear instructions for action or standard operating procedures (SOPs) are also required in the event of deviations from defined parameters (Chap. 9.2 in [17]).

If a pharmaceutical entrepreneur and manufacturer delivers the medicinal products he produces directly to pharmacies or hospital pharmacies, this is covered by his manufacturing authorization according to Sect. 13 AMG. In such cases, no separate wholesale authorization is required. Nevertheless, the competent authority of the federal Land where the factory site of the manufacturer is situated also monitors compliance with the storage conditions and transport in accordance with the GDP Guideline during regular inspections and issues a GDP certificate if compliance is established.

In the case of transports to the end user, for example in the case of drug transports directly to the trial centre as part of a clinical trial, deviations from the specified transport conditions are to be expected more frequently. As a rule, smaller vehicles not equipped with active cooling are used. However, these vehicles should at least comply with DIN SPEC 91323 "Temperature conditioned transport equipment used for distribution of pharmaceutical products (for human beings or veterinary use)—Guidelines for qualification" [21]. Deviations from the GDP guideline applicable to the "last mile" with regard to orderly and controlled transport are not tolerable and must be prevented by suitable packaging, by means of active or passive cooling, temperature monitoring or refrigerated transport.

If the transport takes place as a package with parcel service providers, validation of the transport conditions is probably not feasible without an additional agreement. Critical temperature deviations, especially in the summer and winter months, may not be detected during storage or transport. This can be remedied by data loggers that can provide accurate information on the temperatures of critical goods at any point in the distribution chain. Package service providers without suitable qualification for the transport of medicinal products may not be used in accordance with Chap. 9 of the GDP Guideline. Only qualified transport service providers who guarantee temperature monitoring and the use of suitable packaging can be commissioned (Chap. 9 GDP Guideline).

A short-term increase in temperature can, in addition to changes in the single allergen content and changes in the band pattern in a gel electrophoresis for identity detection, also lead to a decrease in allergenic activity [22]. However, these modifications do not necessarily represent an "out of specification" event, i.e. a critical product change that lies outside the quality parameter limits laid down in the marketing authorization [23]. Whether a product can still be used after a temperature deviation should be decided for each individual case based on the marketing authorization-related specifications of the pharmaceutical entrepreneur and after consultation with the pharmaceutical entrepreneur.

However, if no data from a temperature logger is available because it was not available or was not put into operation, a risk-based assessment must be made by the pharmaceutical entrepreneur, taking many factors into account. These include the time of year, outside temperatures, heat capacities of the packaging and outer packaging, weather, vehicle type, storage rooms, potential loading processes and the duration of transport. Decision support is provided by the transport validation data and stability studies in the marketing authorization documents (dossier). A justification that a delivery of goods can be used despite temperature deviations during transport or storage must be able to demonstrate conclusively and comprehensibly, under the responsibility of the qualified person (QP) as well as the pharmaceutical entrepreneur's graduated plan officer, that the quality of the allergen product is maintained and that the specifications are met.

If a deviation from the specified temperature conditions is noticed in a pharmacy, this must be documented and reported in accordance with Sect. 21 of the Pharmacy Practice Order [24] to the authority responsible for the pharmacy. For this purpose, reporting forms of the Drug Commission of the German Pharmacists (AMK) are usually used, which are forwarded by the pharmacy via the AMK to the competent authority and also to the responsible pharmaceutical entrepreneur, who initiates an evaluation of the reported deviation. In order to ensure patient care through a replacement delivery, the supplied pharmacy directly contacts the pharmaceutical entrepreneur in parallel to the reporting procedure regarding the usability of the delivery. The competent authority hears the pharmaceutical entrepreneur on the facts of the case and coordinates the further procedure with him. If such deviations are already noticed by the pharmaceutical entrepreneur, he must, according to his quality management system (Chap. 1.2 in [17]), initiate a CAPA case (Corrective Action and Preventive Action) and follow it up accordingly. The examination of the necessary measures takes place within the scope of the inspections by the competent authority, if necessary accompanied by the competent higher federal authority.

Regulatory requirement for stability data in the dossier

For all drugs, stability data must be submitted with the dossier when applying for marketing authorization [25]. In order to have data collections that are as meaningful as possible at the time of approval, corresponding studies are already started in the development phase of the drug.

The requirements for stability data collection are detailed in the ICH (International Committee of Harmonization) Guideline ICH Q1A (R2) "Stability testing of new drug substances and drug products" [26]. The Guideline ICH Q5C "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products" is also helpful [27]. Although this guideline excludes allergen extracts, the basic requirements and general concepts are still applicable. If a shelf life of more than 6 months is desired, stability data from three independently produced batches over a storage period of at least 6 months must be provided. Storage conditions (refrigerated, ambient temperature, relative humidity, or similar) should be selected in the stability studies to ensure that pharmaceutical quality requirements can be met at all times during the storage period.

If not all the required data are available at the time of submission of the marketing authorization application, they could also be submitted subsequently by means of declarations of commitment on an exceptional basis after individual assessment of the respective case—provided that the available data already permit a meaningful assessment. In addition to real-time stability studies, studies after the opening of a multidose container and under more stringent so-called accelerated conditions (increased temperatures, higher humidity) are also common.

In mixtures of nonhomologous allergens, stability must be proven for each active substance individually. If allergens in mixtures all originate from a single homologous group according to the concept of Lorenz et al. [28] (e.g. the birch group, which includes alder, hazel, hornbeam and oak in addition to birch), the main allergens are considered to have similar physicochemical properties or are cross-reactive. In these cases, it is possible to use stability data of a representative allergen to extrapolate the shelf life and storage conditions for the mixed drug. However, in mixtures, the important parameter for determining the quality of the allergen product, the allergenic activity, can rarely be determined individually for the representative allergen due to cross-reactivities [29]. The choice of the lead allergen and a suitable method to follow degradation processes though is crucial for the validity of generated data [10].

Also for allergens that are crosslinked by chemical modification and/or adsorbed to adjuvants, the determination of activity is usually not possible directly. In order to be able to measure the activity at the beginning and at the end of the shelf life of the product according to the specifications, many manufacturers use validated in vivo or in vitro binding assays on an IgE or IgG basis [30].

In addition to real-time data from long-term storage studies, data from storage tests under stress conditions or under accelerated conditions can provide valuable information regarding the stability of products. These data primarily provide information about the change processes with regard to quality during storage under defined conditions. Degradation processes can be provoked by elevated storage temperatures to reveal undesirable product changes. These data can be helpful to assess the influence of short-term temperature deviations, as they can occur during transport [26].

Refrigerated transport according to GDP requirements

In Germany, GDP is legally anchored in the German Medicinal Products Act (Sect. 55), in the Ordinance on the Manufacture of Medicinal Products and Active Substances (AMWHV) and in the EU (European Union) GMP (good manufacturing practice) Guide Part 1 and its annexes. Sect. 7 of the AMWHV stipulates that the suitability of storage and transport procedures must be demonstrated, especially if they may have an influence on the quality of the medicinal product. For the EU, such suitable procedures are described in detail in the GDP Guideline [17]. This guideline is binding together with the respective national law. The GDP certificates issued throughout the EU by the competent authorities of the member states can be viewed on the website http://eudragmdp.ema.europa.eu/inspections/displayHome.do. Any deviations are also listed at this website. Worldwide, GDP aspects are monitored in the context of GMP inspections by the respective authorities of the importing country or through mutual recognition agreements.

According to the GDP Guideline, operating rooms should be "designed or adapted to ensure that the required storage conditions are maintained". The same applies to transport: "The required storage conditions for medicinal products should be maintained during transport within the defined limits as described by the manufacturer or on the outer packaging", whereby the transport route is considered risk-based in order to be able to carry out necessary temperature controls at the appropriate point. Since the GDP guideline came into force in 2013, regular temperature-monitored transport is carried out for products that have to be transported at 2–8 °C. For this purpose, either qualified packaging capable of safely maintaining the temperature range is used or qualified refrigerated transport is organized.

For temperature control, Chap. 3.2.1 of the GDP Guideline deals with the qualification of storage rooms. Already in the run-up to commissioning,

refrigerators, cooling chambers or cold storages used must be qualified with regard to temperature distribution by means of a temperature mapping exercise using calibrated temperature sensors placed at defined locations. These mapping studies are intended to show at which points in the room temperature sensors must be optimally positioned. The size of the warehouse, average occupancy, doors, windows, the orientation of the room ventilation system, loading and unloading processes all play a decisive role. However, serious temperature fluctuations are more likely to occur during transportation. Similar to storage rooms, the GDP guideline therefore also provides for a temperature distribution study in refrigerated vehicles. The temperature monitoring instruments must be calibrated annually (Chap. 9.2 Guideline 2013/C 343/01 [17]). In order to be able to prove compliance with the specified temperature conditions, this data should be made available to the transport client.

If no systems with active cooling are used, care must be taken when using coldpacks or "phase change material" (PCM) that they are arranged in such a way that direct contact with the drug is prevented. The coldpacks are stored at the correct temperature for reuse until they are sufficiently cooled again (Chap. 9.4 in [17]).

Conclusion

A great amount of effort is put into producing allergen products from biological material in order to be able to offer the highest possible quality and standardized drug product. The quality of the product can be affected by improper storage or transport. It is therefore a legal requirement to organize, control and validate storage and transport accordingly and to contractually define responsibilities in order to ensure product quality in the logistics chain as well.

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Conflict of interest J. Rost, S. Langhein, D. Bartel, A. Bonertz and V. Mahler declare that they have no competing interests.

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References

1. Bonertz A, Mahler V, Vieths S. Manufacturing and quality assessment of allergenic extracts for immunotherapy: state of the art. Curr Opin Allergy Clin Immunol. 2019;19:640–5.
2. Anderson M, Baerh H. Antigenic and allergenic changes during storage of a pollen extract. J Allergy Clin Immunol. 1982;69:3–10.
3. Lorenz A-R, Scheurer S, Vieths S. Food allergens: molecular and immunological aspects, allergen databases and cross-reactivity. Chem Immunol Allergy. 2015;101:18–29.
4. Verhoeckx KCM, Vissers YM, Baumert JL, Faludi R, Feys M, Flanagan S, et al. Food processing and allergenicity. Food Chem Toxicol. 2015;80:223–40.
5. Nelson HS, Iklé D, Buchmeier A. Studies of allergen extract stability: the effects of dilution and mixing. J Allergy Clin Immunol. 1996;98:382–8.
6. Jeong KY, Yuk JE, Lee J, Jang SW, Park KH, Lee J-H, et al. Stability of extracts from pollens of allergenic importance in Korea. Korean J Intern Med. 2020;35:222–30.
7. Nelson HS. Effect of preservatives and conditions of storage on the potency of allergy extracts. J Allergy Clin Immunol. 1981;67:64–9. https://doi.org/10.1016/0091-6749(81)90047-6.
8. Deutsche Institut für Normung. DIN 58345 Kühlgeräte für Arzneimittel – Begriffe, Anforderungen, Prüfung 09.2007. 2007.
9. Plunkett GA, Schell M. Allergen extract stability following short term temperature variations. J Allergy Clin Immunol. 2010;125:AB37.
10. Soldatova LN, Paupore EJ, Burk SH, Pastor RW, Slater JE. The stability of house dust mite allergens in glycerinated extracts. J Allergy Clin Immunol. 2000;105:482–8.
11. van Metre TE, Rosenberg GL, Vaswani SK, Ziegler SR, Adkinson N. Pain and dermal reaction caused by injected glycerin in immunotherapy solutions. J Allergy Clin Immunol. 1996;97:1033–9.
12. Puccinelli P, Natoli V, Dell'Albani I, Scurati S, Incorvaia C, Barbieri S, et al. Evaluation of stability of allergen extracts for sublingual immunotherapy during transport under unfavourable temperature conditions with an innovative thermal insulating packaging. Eur Ann Allergy Clin Immunol. 2013;45(Suppl 2):39–48.
13. Niemeijer NR, Kauffman HF, van Hove W, Dubois AEJ, de Monchy JGR. Effect of dilution, temperature, and preservatives on the long-term stability of standardized inhalant allergen extracts. Ann Allergy Asthma Immunol. 1996;76:535–40.
14. Plunkett G. Update: stability of allergen extracts to establish expiration dating. Curr Opin Otolaryngol Head Neck Surg. 2016;24:261–9.
15. European Medicines Agency, Committee for Human Medicinal Products. Guideline on declaration of storage conditions: annex to note for guidance on stability testing of new drug substances and products & annex to note for guidance on stability testing of existing active substances and related finished products. CPMP/QWP/609/96/Rev 2. 2007.
16. Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten. Frage- und Antwortpapier zum Betreiben eines Großhandels mit Arzneimitteln: EFG 09 „Großhandel/Arzneimittelvertrieb". 2015.
17. Europäische Kommission. Leitlinien vom 5. November 2013 für die gute Vertriebspraxis von Humanarzneimitteln: 2013/C 343/01. 2013f.

18. World Health Organization. WHO good distribution practices for pharmaceutical products: annex 5. 2010.
19. Bundesgesetz. Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz – AMG); zuletzt geändert durch Art. 5 G v. 9.12.2020 I 2870. 2020.
20. Bundesrechtsverordnung. Verordnung über den Großhandel und die Arzneimittelvermittlung (Arzneimittelhandelsverordnung – AM-HandelsV). 2020. Arzneimittelhandelsverordnung vom 10. November 1987 (BGBl. I S. 2370), die zuletzt durch Artikel 2c des Gesetzes vom 18. November 2020 (BGBl. I S. 2397) geändert worden ist.
21. Deutsches Institut für Normung. DIN SPEC 91323 Klimatisierte Nutzfahrzeuge für die Distribution von Arzneimitteln (human und veterinär) – Leitlinien für die Qualifizierung 03.2016. 2016.
22. Funkhouser TA, Nelson M, Song T, Martin B, DeGuzman R, Engler R. Decreased allergen extract stability with dilution and ambient temperature change: effect of shipping temperature on prescription extract stability and potency. J Allergy Clin Immunol. 2005;115:S264.
23. Moore M, Tucker M, Grier T, Quinn J. Effects of summer mailing on in vivo and in vitro relative potencies of standardized timothy grass extract. Ann Allergy Asthma Immunol. 2010;104:147–51.
24. Bundesrechtsverordnung. Verordnung über den Betrieb von Apotheken (Apothekenbetriebsordnung – ApBetrO); zuletzt geändert durch Art. 2 V v. 21.10.2020 I 2260. 2020.
25. Das europäische Parlament und der Rat der europäischen Union. Richtlinie 2001/83/EG – Schaffung eines Gemeinschaftskodexes für Humanarzneimittel vom 6. November 2001 zur Schaffung eines Gemeinschaftskodexes für Humanarzneimittel. 2001.
26. European Medicines Agency, Committee for Human Medicinal Products. Q 1 A (R2) stability testing of new drug substances and products: note for guidance on stability testing: stability testing of new drug substances and products. CPMP/ICH/2736/99. 2003.
27. European Medicines Agency, Committee for Human Medicinal Products. ICH topic Q 5 C quality of biotechnological products: stability testing of biotechnological/biological products: note for guidance on quality of biotechnological products: stability testing of biotechnological/biological products. CPMP/ICH/138/95. 1996.
28. Lorenz AR, Lüttkopf D, May S, Scheurer S, Vieths S. The principle of homologous groups in regulatory affairs of allergen products—a proposal. Int Arch Allergy Immunol. 2009;148:1–17.
29. European Medicines Agency, Committee for Human Medicinal Products. Guideline on allergen products: products for quality issue. EMEA/CHMP/BWP/304831/2007. 2008.
30. Zimmer J, Bonertz A, Vieths S. Quality requirements for allergen extracts and allergoids for allergen immunotherapy. Allergol Immunopathol. 2017;45(Suppl 1):4–11.