The labelling of excipients relevant to food allergies or food intolerances in the product information for medicinal products for human use in the EU

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AMG	Arzneimittelgesetz (German Medicinal Products Act)
AMWarnV	Arzneimittel-Warnhinweisverordnung (German Medicinal Products Warning Ordinance)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices)
CHMP	Committee for Medicinal Products for Human Use
CMI	Consumer Medicine Information
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EU	European Union
ExcpDG	Excipients Drafting Group
IgE	Immunoglobulin E
INN	International non-proprietary name
INNM	International non-proprietary name modified
LMIDV	Lebensmittelinformations-Durchführungsverordnung (German Food Information Implementing Regulation)
MAH	Marketing authorisation holder
PI	(Australian) Product Information
QRD	Quality Review of Documents
SmPC	Summary of Product Characteristics
TGO	Therapeutic Goods Order

1 Summary

Some excipients in medicinal products for human use are substances derived from foods or food ingredients that are relevant to food allergies or food intolerances. Medicinal products containing these excipients may therefore be potentially harmful to users suffering from food allergies or intolerances. For this reason, it is necessary that users are adequately informed about excipients relevant to food allergies and intolerances in the product information for medicinal products. This is particularly important as the prevalence and awareness of food allergies and intolerances seem to have increased over the last decades.

This thesis analyses the EU requirements for the labelling of excipients relevant to food allergies or intolerances in the product information for medicinal products and compares them with EU requirements for food labelling. Thereby, the focus is on general aspects and principles of labelling. The aim of this work is to identify similarities and differences in the labelling of pharmaceutical excipients and food ingredients relevant to food allergies or intolerances. Based on this, the advantages and disadvantages of the labelling of excipients and food ingredients are discussed as well as possible proposals to align the labelling of excipients with the labelling of food ingredients in order to improve excipient labelling and to create more consistent information for users.

Differences in the national implementation of labelling rules, the way information is provided, the nomenclature, and the completeness and transparency of information on food ingredients and excipients are revealed. Furthermore, the substances defined as allergens or triggers of intolerance reactions differ between medicinal products and foods. Consequently, users of medicinal products cannot rely on the fact that labelling of excipients relevant to food allergies or intolerances corresponds to the labelling of food ingredients.

The Annex to the European Commission guideline on “Excipients in the labelling and package leaflet of medicinal products for human use” (excipients guideline) lists specific substances and chemical groups of substances as excipients with a known effect. In contrast, Annex II to Regulation (EU) No. 1169/2011 on food information contains broader categories of food ingredients relevant to allergies and intolerances that consist of a basic material and products thereof. As a result, the substances listed in the Annex to the excipients guideline and those included in Annex II are not identical. In order to provide more consistent information to users, it is proposed to align the Annex to the excipients guideline with Annex II to Regulation (EU) No. 1169/2011. To this end, relevant categories from Annex II could be integrated into the Annex to the excipients guideline, using the Australian approach for the labelling of excipients relevant to food allergies or intolerances as a model.

2 Introduction

2.1 Food allergies and food intolerances in today's society

Food allergies and food intolerances are adverse food reactions to a particular food that is normally tolerated. They are based on the individual's sensitivity to food components. While food allergies depend on immunological mechanisms, food intolerances are not immune-mediated [1,2]. Figure 1 provides an overview of the classification of non-toxic adverse food reactions, which are explained in detail below.

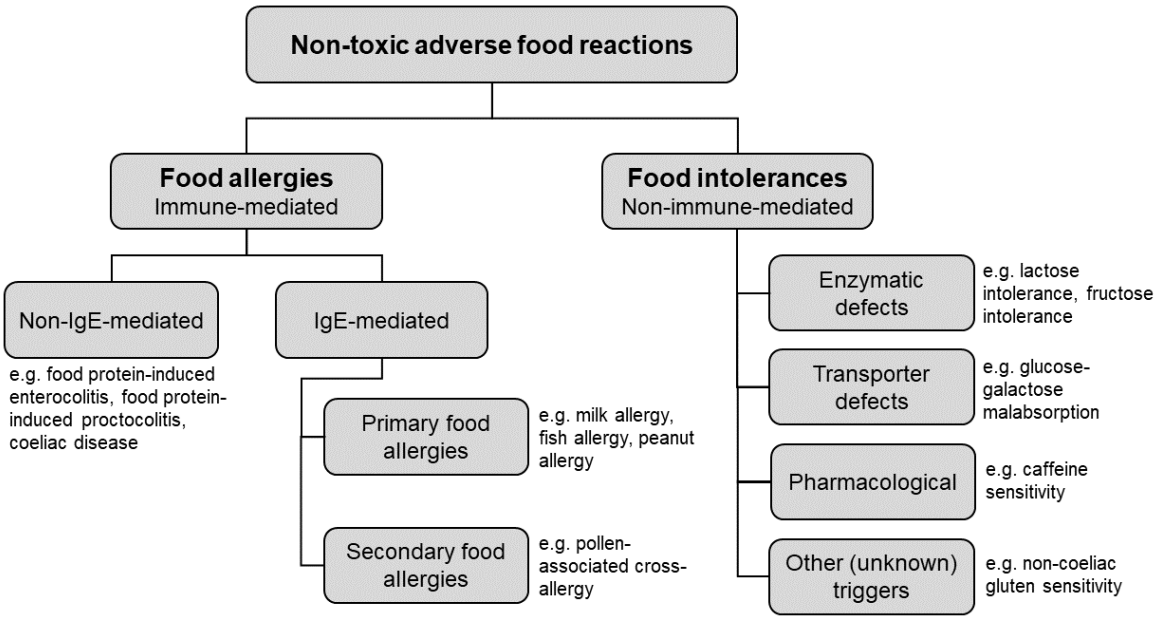

Figure 1: Classification of adverse food reactions (based on [1,3]).

Food allergies are defined as reproducible adverse reactions that are based on an abnormal immune response after exposure to a certain food. Most food allergens are proteins, although allergic reactions to certain types of meats are based on carbohydrate allergens. The immune reactions are usually mediated by immunoglobulin E (IgE) antibodies; however, they can also be non-IgE-mediated and exclusively based on other components of the immune system. Overall, there are many different types of food allergy, each with distinct clinical and pathophysiological characteristics [1,4,5].

IgE-mediated food allergies are characterised by allergic symptoms that typically develop within seconds to minutes, but usually at least within two hours after food intake. Even trace amounts of food can lead to unpredictable, serious allergic reactions. Typical signs and symptoms are pruritus; urticaria; flushing; swelling of the lips, face, or throat; nausea; vomiting; cramping; diarrhoea; dizziness; unconsciousness or hypotension. Furthermore, a

serious, life-threatening allergic reaction called anaphylaxis can occur in connection with IgE-mediated food allergies [5,6].

The oral allergy syndrome is a special kind of IgE-mediated food allergy occurring in patients sensitized to pollen. In these patients, proteins from raw fruits, vegetables or nuts cross-react with allergenic pollen proteins when they come into contact with the mouth or throat, which usually leads to mild symptoms in the mucosal area of the mouth and throat. Other special forms of IgE-mediated food allergy are food-dependent, exercise-induced anaphylaxis; occupational food allergy; food allergies related to latex allergy; and delayed allergy to red meat. Meanwhile, examples of non-IgE-mediated food allergy are food protein-induced enterocolitis syndrome that mainly occurs in infancy and is characterised by delayed vomiting and sometimes diarrhoea, and food protein-induced proctocolitis, which leads to blood and mucus in the stool of newborns [5,6].

The diagnosis of food allergy is performed by analysing the history of previous reactions to identify the triggering food. Subsequently, for IgE-mediated allergies, a skin prick test or an in vitro immunoassay for IgE antibodies specific to the suspected food can be conducted to determine sensitization. If these tests are not conclusive, graded food challenges can be performed. In contrast, non-IgE-mediated food allergies can be diagnosed via food elimination and rechallenge after some weeks [5,6]. Up to now, food allergy cannot be cured and the only available therapy is strict avoidance of the relevant food. Patients with IgE-mediated food allergy who have experienced serious allergic symptoms or anaphylaxis can be equipped with an epinephrine autoinjector that can be used by the patient in case of accidental food intake [5,7,8].

It is assumed that up to 5 % of adults and up to 8 % of children are affected by food allergy [5,7]. However, the prevalence of food allergy seems to vary globally and exact prevalence figures are uncertain. In the recent past, the European Academy of Allergy and Clinical Immunology has initiated a systematic review and meta-analysis on the epidemiology of food allergy in Europe. This analysis included primary studies published between 2000 and 2012 and revealed that sufficient study data on food allergy prevalence are not available for all regions of Europe. Furthermore, the methodology of available studies differed and estimates of prevalence of food allergies varied depending on whether they were based on subjective self-reported data or were combined with objective diagnostic methods. For example, the point prevalence for food allergy diagnosed by self-report in Europe was 5.9 %, whereas the point prevalence of food allergy diagnosed by oral food challenge was 0.9 %. Due to study heterogenicity, the data of the analysis have to be interpreted with caution [4,9,10].

Food allergies can develop at any age; however, most of them first appear during childhood with peak prevalence at approximately the age of one year. Common food allergies in childhood are cow's milk allergy, hen's egg allergy, peanut/tree nut allergy, wheat and soya allergy. The majority of childhood food allergies are lost until adulthood, whereby the mechanism behind this is not fully understood. In adults, allergies mostly arise during the early 30s, but the development of new allergies is also known in older people over 80. Adults are mostly affected by allergies to fish/shellfish and peanuts/tree nuts and by oral allergy syndrome. Also, cow's milk allergy seems to occur frequently in adults [5,7,11].

In contrast to food allergies, food intolerances are based on non-immunological reactions and usually result from difficulties in digesting or metabolizing a particular food in amounts that are normally tolerated. There are very different mechanisms of food intolerance, ranging from pharmacological effect mechanism to enzyme deficiency to non-specific gastrointestinal functions. Therefore, diagnosis is often not straightforward and is carried out by a trail-and-error approach with elimination and reintroduction of the suspected food. The symptoms of food intolerances vary; however, mostly gastrointestinal symptoms such as excessive intestinal gas, bloating, abdominal pain and diarrhoea occur [5,12]. Symptoms can appear several hours after food consumption and may last for hours to days [6]. The severity of symptoms of food intolerance is directly related to the amount of consumed food and symptoms remain similar whenever the particular food is eaten. Accordingly, food intolerances are classified as less dangerous than IgE-mediated food allergies, which can trigger unpredictable, life-threatening reactions after ingesting tiny amounts of food. About 15 % to 20 % of the population suffer from food intolerances. Thus, food intolerance is much more common than food allergy [5]. However, due to the huge spectrum of conditions, prevalence of food intolerances is less well established than prevalence of food allergies [4]. Typical examples of food intolerances are lactose intolerance, fructose malabsorption, intolerance of short-chain fermentable carbohydrates, non-coeliac gluten sensitivity, histamine intolerance, and caffeine sensitivity [5,12].

A small part of the population suffers from so-called pseudo-allergies. Pseudo-allergies belong to the category of food intolerances and lead to symptoms similar to allergic symptoms. However, pseudo-allergies are based on an activation of mast cells that is not immune-mediated. They can be triggered, for example, by food additives such as flavours, dyes or preservatives [13,14].

Although true prevalence rates of food allergy and food intolerances are uncertain, the prevalence seems to have increased over the past three decades, especially in countries with Western lifestyle. For example, in the US, prevalence of parentally reported food allergy in children has increased from 3.4 % between 1997 and 1999 to 6.2 % in 2016. In addition,

the prevalence of reported peanut allergy did increase from 0.4 % in 1997 to 1.4 % in 2008 [4,5,11,15]. Furthermore, increasing numbers of emergency hospital visits due to food-induced anaphylaxis have been reported [6]. In addition, there is a high level of public interest in food allergies and food intolerances and the topic is extensively discussed in public media. It is assumed that an increased prevalence of food allergy and food intolerance is attributable to Western lifestyle. The Western diet, which is characterised by a high intake of fat, protein, sugar, salt and processed foods, could promote the development of food allergies via affecting the gut microbiome. The gut microbiome plays an important role during the development of the immune system in early life. In addition, caesarean delivery, the absence of breastmilk feeding, growing up as an only child, and the use of antacids are suspected to increase the risk for developing food allergies [4,16].

2.2 Excipients relevant to food allergies or food intolerances in medicinal products for human use

Some excipients that are part of medicinal products for human use are foods, substances derived from foods or food ingredients that are related to food allergies or food intolerances. Therefore, medicinal products containing these excipients may potentially be harmful to users who are affected by food allergies or food intolerances. In addition, food-derived excipients that are not expected to be allergenic may contain contaminations of allergenic food proteins either by design or by accident [17,18].

Excipients are defined as constituents of a medicinal product other than the active substance and the packaging material. They are included in medicinal products for various reasons, for example as vehicle for the active substance, to support manufacturing steps, to improve stability, enhance bioavailability or to promote patient acceptance [19,20]. On average, excipients make up about two thirds of the total mass of a medicinal product administered [21]. Excipients can be, for example, colourants, flavouring and aromatic substances, preservatives, adjuvants, stabilisers, thickeners, emulsifiers or diluents. The constituents of the outer covering of a medicinal product that is administered to a patient, such as capsules or the coating of tablets, as well as transdermal patch constituents, and the ingredients of printing inks used to mark a dosage form are also defined as excipients. However, excipients do not include residues of substances arising from the manufacturing process of the finished drug product, impurities, residual solvents or degradation products. Excipients were originally defined as inert, but various excipients have a recognized effect under certain circumstances [19,20].

Examples of food-derived excipients in medicinal products are egg lecithin, casein and lactose from cow’s milk, gelatine, protamine from salmon testicles, fish oil, peanut oil,

sesame oil, soya lecithin, soya oil, and starch from plant sources. Also, carbohydrates and food sweeteners such as fructose, sorbitol or mannitol are used as excipients [17,18,21,22]. Although the amount of food-derived allergenic components in medicinal products is considered to be small, there are various case reports on allergic reactions ranging from skin reactions to anaphylaxis caused by food-derived substances in medicinal products. Also, symptoms of food intolerances have been reported after administration of medicinal products containing lactose [17,18,23]. In addition, it has to be taken into account that polypharmacy can lead to an increase in the amount of an excipient ingested [21].

Information on excipients that are relevant to food allergies or food intolerances can be provided to patients via the product information for a medicinal product. As the prevalence and awareness of food allergies and food intolerances appears to be increasing in the population [4,11], the product information becomes more and more important as a tool to prevent adverse reactions to food-derived excipients and to prevent confusion as well as insecurity among patients affected by food allergies or food intolerances.

2.3 The product information for medicinal products for human use in the EU

The product information for medicinal products for human use in the EU includes the Summary of Product Characteristics (SmPC), the package leaflet and the package labelling. It represents officially approved information about a medicinal product that is intended for healthcare professionals and users [24]. The elements of the product information are part of the application for marketing authorisation of a medicinal product. Within the structure of the Common Technical Document, they are presented in section 1.3 of module 1, which provides administrative and regional information [25]. The purpose, the content and legal basis of the individual product information elements are outlined in more detail below.

2.3.1 The Summary of Product Characteristics (SmPC)

The SmPC provides evidence-based scientific information on the benefits and risks of a medicinal product. It is mainly addressed to healthcare professionals such as doctors or pharmacists and provides them with the basic information on how to use a specific medicinal product safely and effectively. The SmPC contains, for example, information on the composition of the medicinal product, its therapeutic indications and method of administration, contraindications, special warnings and precautions for its use, as well as information on its pharmacological properties. The SmPC enables healthcare professionals to treat their patients according to their individual needs, for example, by providing information about interactions with other medicinal products, excipients with known effects,

and the usage of the medicinal product in the paediatric or elderly population, in patients with concomitant diseases or in other specific situations [26–28].

The SmPC represents a central reference document of a medicinal product, as the package labelling and the package leaflet addressed to the patients as well as the advertising of a medicinal product must comply with the content of the SmPC. Furthermore, the content of the SmPC is reviewed by the health technology assessment bodies that provide recommendations on funding or reimbursement of medicinal products by the healthcare system in a particular Member State or region [26,27,29,30].

According to Article 8(3)(j) of Directive 2001/83/EC and Article 6(1) of Regulation (EC) No. 726/2004, the SmPC must be included in the marketing authorisation application of a medicinal product. Article 11 of Directive 2001/83/EC defines the content of the SmPC and its order of presentation. The content of the SmPC is approved by the relevant competent authority during the marketing authorisation procedure, and, thus, the SmPC forms an integral part of the marketing authorisation of a medicinal product. After marketing authorisation has been granted, the SmPC must be updated regularly as new relevant information becomes available throughout the life cycle of the medicinal product. However, the content of the SmPC cannot be changed without approval of the originating competent authority. Granting of a marketing authorisation or acceptance of a change do not alter the general legal liability of a marketing authorisation holder (MAH) including his liability for the content in the various elements of the product information [26,27,30,31].

The European Commission's guideline on SmPC, also called "SmPC guideline" [26] must be considered by the applicant or MAH when drafting the SmPC. The SmPC guideline provides detailed guidance on how to present the information in the SmPC to ensure clear information on the benefits and risks of a medicinal product. Although guidelines are by definition not legally binding, deviation from the SmPC guideline has to be appropriately justified [26,27].

Furthermore, the European Medicines Agency's (EMA) Working Group on Quality Review of Documents (QRD) has developed templates for the creation of the SmPC, package leaflet and package labelling. These templates are intended to ensure high quality product information with consistent wording and structure. Two different QRD templates exist – one for medicinal products authorised via the centralised procedure and one for medicinal products authorised via the decentralised or mutual recognition procedure. The QRD templates are available as Word files in various EU languages and can be downloaded from the EMA website. Deviations from the QRD templates have to be justified and will be considered by the authorities on a case-by-case basis [26,32–34].

According to Article 15 of Directive 2001/83/EC, no SmPC has to be submitted for homeopathic medicinal products that comply with Article 14(1) and that are subject of a special, simplified registration procedure. Furthermore, Article 16c specifies that a SmPC without pharmacological properties must be included in the application for traditional-use registration of traditional herbal medicinal products [30,35].

2.3.2 The package labelling and the package leaflet

A medicinal product is accompanied by an outer packaging and/or immediate packaging as well as by a package leaflet. The immediate packaging is the packaging that is in direct contact with the medicinal product, whereas the outer packaging is the packaging into which the immediate packaging is placed [30,36]. The package labelling and the package leaflet are intended for the user of a medicinal product and should enable the user to apply the medicinal product safely and correctly. The key elements of the medicinal product such as name, strength and route of administration are indicated on the packaging to ensure clear identification and safe use of the medicinal product. In general, the package labelling must be easily legible, indelible, clear and easily accessible for the user [30,36,37]. Meanwhile, the package leaflet contains more detailed information on the medicinal product, for example, information on its therapeutic indications, safety information which must be considered before the medicinal product is taken, instructions for proper use, possible side effects, and information about its contents. The package leaflet must be clear and understandable to enable the user to act appropriately – if necessary with the help of a healthcare professional [30]. Nowadays, during discussion with healthcare professionals, patients are increasingly involved in the decision for a specific treatment. Therefore, it is especially important to provide them with comprehensible and transparent information on the risks and benefits of a medicinal product [38]. The package leaflet and package labelling are also of particular importance for non-prescription medicines, where no interaction with a pharmacist may take place [37].

According to Article 8(3)(j) of Directive 2001/83/EC and Article 6(1) of Regulation (EC) No. 726/2004, a mock-up of the outer packaging and of the immediate packaging together with the package leaflet have to be included in the application for marketing authorisation of a medicinal product [30,31]. A mock-up is a colour copy of the flat packaging design, from which, after cutting and folding, the three-dimensional presentation of the labelling can be reconstructed [36]. Title V “Labelling and Package Leaflet” of Directive 2001/83/EC lays down detailed provisions on package labelling and the package leaflet of a medicinal product. Article 54 specifies the information that must appear on the outer packaging or, if there is no outer packaging, on the immediate packaging. The information that must be printed on the immediate packaging is stated in Article 55, whereby reduced labelling

approaches apply to blister packs in a suitably labelled outer packaging and to small immediate packaging units. In addition, individual Member States may request further information on the packaging regarding the price, reimbursement conditions, legal status of supply, authenticity and identification of a medicinal product. The information specific to a Member State has to be presented in the so-called “blue box” [30,36].

The content of the package leaflet and its order of presentation are specified in Article 59 of Directive 2001/83/EC. According to Article 59(3) and Article 61(1), the package leaflet must reflect the results of consultations with target patient groups and these results must be provided to the competent authorities for marketing authorisation application. During consultation with potential users of a medicinal product, it is verified that the users can find and understand the key information in the package leaflet to ensure safe and effective use of the medicinal product. Pursuant to Article 58, the package leaflet may be omitted if the complete information of the package leaflet is displayed on the outer packaging or on the immediate packaging of a medicinal product. In addition, according to Article 15 and Article 69, the package leaflet is not mandatory for homeopathic medicinal products meeting the criteria of Article 14(1) for a simplified registration procedure, and there is a special labelling approach for this type of homeopathic medicinal products [30,39].

The package labelling as well as the package leaflet must be created in accordance with the content of the SmPC. Thus, if the SmPC is updated, the information on the packaging and the package leaflet must be adjusted accordingly. According to Article 61(3), changes to aspects of the package labelling and the package leaflet that fall under Title V of Directive 2001/83/EC but are not part of the SmPC must be submitted separately to the authorities and can be implemented after 90 days if the authorities have not rejected the change request [30].

The package labelling and the package leaflet must be provided to the user in the official language(s) of the Member State in which the medicinal product is marketed. According to Article 62, they may contain symbols or pictograms for clarification of certain information that is compatible with the SmPC, whereby these must not be of promotional nature. Furthermore, the name of a medicinal product must be given in Braille format on the packaging and the package leaflet must be provided on request in formats suitable for the blind and visually impaired [30].

The competent authorities may grant exemptions regarding the information required on the packaging and in the package leaflet and regarding the required language. These exemptions may be granted for the protection of human health if the medicinal product is not directly delivered to the patient or if the availability of a medicinal product is at risk [30].

The QRD templates developed by the EMA provide guidance on the content that has to be presented on the packaging and in the package leaflet according to Directive 2001/83/EC. However, after using the QRD templates, the applicant or MAH still needs to reformat the resulting texts into the intended layout for the preparation of full colour mock-ups and specimens of the packaging as well as for the preparation of specimens of the package leaflet. The “Guideline on the readability of the labelling and package leaflet of medicinal products for human use” offers guidance on the presentation of the content of the package labelling and the package leaflet including design and layout of the information. For example, requirements regarding font, font size, headings, print colour, syntax and style are specified to ensure that the package labelling and package leaflet information is accessible and understandable for the users of a medicinal product [36]. In addition, a draft recommendation of the EMA’s QRD working group specifies further details for the pack design and labelling of medicinal products which have to be considered [37].

2.4 Aim and scope of this thesis

This thesis analyses the EU requirements for the labelling of excipients relevant to food allergies or food intolerances in the product information for medicinal products for human use. The declaration of these excipients in the different elements of the product information is examined and compared with the EU regulations on food labelling. The aim of this thesis is to investigate whether the EU requirements for the labelling of pharmaceutical excipients relevant to food allergies or food intolerances could be improved through the implementation of aspects and principles of food labelling in the EU. It is also examined how the labelling of these excipients could be harmonised with the labelling of food ingredients to provide more consistent information to users. The focus is on general regulatory requirements and principles, while the scientific evaluation whether a specific excipient should be declared as allergen is not in the scope of this work. To comply with the length and scope of a master thesis, the analysis is restricted to medicinal products for human use that fall under Directive 2001/83/EC or Regulation (EC) No. 726/2004. Some excipients can also be used as active substances; however, the labelling of active substances is not part of this thesis. Therefore, the labelling of excipients that are part of herbal substances or herbal preparations that are the active substance of herbal medicinal products [30,40], is not discussed in this thesis. Also, the declaration of residues and contaminants is not the subject of this work.

At first, the EU requirements for the labelling of pharmaceutical excipients in the different elements of the product information are analysed. This analysis focuses on labelling aspects relevant to users affected by food allergies and intolerances. Therefore, information on excipients regarding interactions, the ability to drive and to use machines, fertility,

pregnancy and lactation is not examined in more detail. The national implementation of the European Commission guideline on “Excipients in the labelling and package leaflet of medicinal products for human use” is investigated by using Germany and Austria as examples. Subsequently, the EU requirements for the labelling of ingredients in food are examined and compared with the labelling of pharmaceutical excipients that are relevant to food allergies and intolerances. The Australian approach for the labelling of medicinal products is then described as a model, as it combines both elements of pharmaceutical excipient labelling in the EU and elements of food ingredient labelling in the EU. Ideas for harmonising the labelling of excipients and food ingredients in the EU can therefore be derived from the Australian approach. Finally, the outcome of the analysis is discussed with respect to whether EU labelling requirements for pharmaceutical excipients related to food allergies or intolerances could be improved by including aspects of EU food labelling. It is also discussed how more consistent labelling of allergens and substances that cause intolerance reactions could be achieved for medicinal products and food. The current version of legal texts and guidelines on which this thesis is based is indicated in the list of references.

It should be noted that in this thesis the term “labelling” is used in a broader sense to refer generally to the information contained in the product information for a medicinal product for human use. In contrast, the labelling of the package of a medicinal product is also referred to as such (“labelling of the outer/immediate packaging”, “package labelling”).

3 Analysis of the labelling of excipients relevant to food allergies or intolerances for medicinal products for human use in the EU

3.1 The information on excipients in the product information for medicinal products for human use in the EU

The EU requirements for the labelling of excipients in the product information for medicinal products for human use are laid down in Directive 2001/83/EC and are further specified in the European Commission guideline on “Excipients in the labelling and package leaflet of medicinal products for human use” (hereinafter referred to as “excipients guideline”). The excipients guideline applies to excipients as defined in Chapter 2.2 of this thesis. The excipients guideline is based on Article 65(e) of Directive 2001/83/EC and includes an Annex that lists excipients with a recognized action or effect. In addition, the SmPC guideline and QRD templates provide information on how excipients have to be stated in the product information for medicinal products [19,26,30,33,34].

Below, the content of the Annex to the excipients guideline is explained. Subsequently, the nomenclature of excipients and the information on excipients that is required in the different elements of the product information is outlined, focusing on the information relevant to food allergies and food intolerances. The national implementation of the excipients guideline is then described by using two examples.

3.1.1 The Annex to the excipients guideline

The Annex to the excipients guideline contains a list of excipients that have a known effect and that must be indicated on the packaging of medicinal products. In addition, for each excipient listed, the information that must be provided in the package leaflet is specified. This information also applies to excipients that are not explicitly stated in the Annex but that belong to a chemical group listed therein (e.g. other salts, related chemical structure). The Annex is available in 24 European languages on the EMA website. The information for the package leaflet is written in a style understandable for the patients and may only be altered if adequately justified (e.g. by user testing). However, the content and the meaning must remain unchanged. Information directed to a specific user group only needs to be stated if relevant. When using a statement from the Annex in the SmPC and package leaflet of a medicinal product, it must be clear that the statement relates to the presence of a particular excipient and not to the active substance [19,22,41].

In addition to the information for the package leaflet, the Annex contains for each listed excipient the date the information was last updated (if applicable), the route of administration to which the information applies, the threshold equal to or above which the information texts must be provided in the product information, and explanatory comments for the applicant and competent authorities. Threshold values are specified, because it is assumed that some excipients only have an effect above a certain amount. If the quantity of an excipient falls below the stated threshold, the excipient needs not to be handled as an excipient with a known effect throughout the product information. If the threshold is zero, the information must be provided in all cases were the excipient is present in a medicinal product. Unless otherwise stated, thresholds refer to the quantity of an excipient at the maximum daily dose of a medicinal product as indicated in the SmPC. If required by the Annex, the amount of an excipient per dosage unit should be stated for solid pharmaceutical forms, while for liquid pharmaceutical forms, the amount per unit volume should be given in the package leaflet. Explanatory comments may relate to the SmPC to ensure consistent information [19,22,42].

For new marketing authorisation applications, the latest version of the Annex must be implemented, whereas for existing marketing authorisations, the first upcoming regulatory procedure affecting the product information should be used to implement the new statements of the revised Annex, if necessary. For products with no regulatory activities, a type IB variation or an Article 61(3) notification should be submitted within three years after publication of the revised Annex [19].

The EMA's Excipients Drafting Group (ExcpDG) regularly reviews the Annex to the excipients guideline to update the information for excipients or to add new excipients. Since 2017, the ExcpDG has also been creating scientific background documents for each excipient reviewed, which are published on the EMA website. The ExcpDG was set up by the CHMP and is a multidisciplinary drafting group consisting of European experts who come from or are associated with national authorities. The ExcpDG currently consists of seven members, who have non-clinical, clinical and quality expertise [19,43,44].

The current version of the Annex was published in November 2019 and lists a total of 50 different excipients and excipient categories that must be indicated on the packaging of medicinal products. It includes several food-derived substances, characteristic ingredients of food as well as food additives that are used as excipients in medicinal products [22]. Food additives are not normally consumed as food per se or used as characteristic components of food, but are used for a technological purpose in the manufacture of food, where they or their by-products may become part of the food [45]. Some of the substances listed in the Annex to the excipients guideline are related to common food allergies and food

intolerances as outlined in Chapter 2.1. The information in the Annex on excipients related to common food allergies and intolerances is presented in more detail in Chapter 3.2.3, which compares the provisions for labelling of pharmaceutical excipients with the provisions for food labelling.

3.1.2 The nomenclature of excipients

The excipients guideline sets out the rules for the naming of excipients in the product information. Instead of proprietary names, the recommended international non-proprietary name (INN or INN modified (INNM)) should be stated together with the salt, if relevant. Alternatively, the European Pharmacopoeia name or, failing this, the usual common name should be indicated. If no usual common name exists, the chemical name can be used. In addition, chemically modified excipients must be declared as such to avoid confusion. The name of an excipient listed in the Annex to the excipients guideline should be accompanied by the E number, if available. E numbers are codes for food additives that are used in the EU. The E number alone can be stated on the packaging, provided that the full name of the excipient and the E number are given in the package leaflet. In general, no abbreviations for excipients should be used in the product information. However, abbreviations and/or Latin names of excipients may be used on the packaging if this is justified due to lack of space and the full name of the excipient is given in the SmPC and package leaflet [19,26].

In case of an integral marker for tracking, tracing and authentication of a medicinal product, the general term “authentication factor” can be added to the list of excipients instead of the name of the integral marker, unless it has a known effect [26]. Meanwhile, pH adjusters that may be added should be accompanied by the function “(for pH-adjustment)” in the SmPC. In the package leaflet, this function can also be mentioned; however, the function should not be stated on the packaging [19,26].

For excipient mixtures, all components must be listed under a general descriptive term in the product information (e.g. “printing ink containing x, y, z”). On the packaging, the general descriptive term of an excipient mixture alone can be mentioned; however, any component with a known effect must be stated. Proprietary flavours and fragrances can be declared in general terms throughout the entire product information (e.g. “orange flavour”), but any known major components and components with a known effect must be specified [19,26]. Remarkably, for established media with commonly known composition used as complex-multicomponent diluents in the formulation of vaccines, it is not necessary to list all ingredients, if justified. Instead, the composition of the media can be summarised in broad terms (e.g. “Medium X containing vitamins, mineral salts and amino acids”); however, components with a known effect still must be stated [46].

3.1.3 Relevant information on excipients in the SmPC

In accordance with Article 11 of Directive 2001/83/EC, excipients with a known effect have to be stated qualitatively and quantitatively in section “2. Qualitative and quantitative composition” of the SmPC. They should be listed under a separate subheading and the statement “For the full list of excipients, see section 6.1” should be placed below the list [26,30,33,34]. For vaccines, adjuvants and adsorbents must also be indicated qualitatively and quantitatively, and this information may be presented as a footnote on the name of the respective active substance in section 2. Adjuvants and adsorbents in vaccines are not defined as excipients; therefore, no further consideration of these ingredients is included in this thesis [26,46].

In SmPC section “4.3 Contraindications”, hypersensitivity to any of the excipients as well as any other contraindication arising from the presence of a certain excipient must be stated. Information on hypersensitivity in section 4.3 can only be omitted if the expected benefit of the drug is greater than the risk of hypersensitivity (e.g. treatment of a life-threatening disease without alternative therapy) [26,33,34,47]. Meanwhile, in SmPC section “4.4 Special warnings and precautions for use”, healthcare professionals are warned of any risks associated with excipients. To improve readability, a special subheading can be created. Except in specific cases of major clinical importance, warnings on topics for which separate SmPC sections exist should be moved to these sections (e.g. warnings regarding the ability to drive and to use machines, pregnancy or lactation). In contrast, section “4.8 Undesirable effects” includes all adverse reactions that have occurred due to the presence of a particular excipient. Reference to SmPC section 4.4 should be made for precautionary measures or actions to be taken if specific reactions occur [26,33,34].

Finally, all excipients contained in a medicinal product must be listed qualitatively in SmPC section “6.1 List of excipients”. Even excipients that are only present in trace amounts, such as printing inks, must be specified. Lubricants for prefilled syringes and ingredients of capsule shells for inhalation powders not intended to be taken are not included [26,30]. Each excipient should be listed on a separate line and, if useful, they can be listed according to the different parts of the product (e.g. tablet core and coat). In case of multiple containers or dual-chamber containers, excipients should be listed per container or per chamber [26].

3.1.4 Relevant information on excipients on the packaging

Article 54(d) of Directive 2001/83/EC specifies that excipients with a known effect and included in the Annex to the excipients guideline must be listed qualitatively on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging. The respective excipients must be indicated on the packaging together with a

statement such as “see leaflet for further information”. However, in case of parenteral medicinal products, topical or eye preparations, not only excipients with a known effect but all excipients must be stated on the packaging [19,30,33,34]. The excipients guideline defines topical medicinal products as medicinal products that are externally applied to the skin, respiratory products delivered to the lung by inhalation, and any medicinal product applied to the ear, oral, nasal, rectal or vaginal mucosa. The drug delivery can be local or transdermal [19]. According to the QRD template for centrally authorised medicinal products, the list of excipients on the packaging can be merged with the statement of the active substance to improve readability [33].

Pursuant to Article 55 of Directive 2001/83/EC, the same information as laid down in Article 54 must also appear on the immediate packaging of a medicinal product. However, Article 55 specifies two situations in which reduced labelling approaches apply to the immediate packaging of a medicinal product: blister packs that are placed in an outer packaging labelled in accordance with the provisions of Directive 2001/83/EC and small immediate packaging units (containers with a size up to 10 mL) on which not all necessary details can be displayed. In both cases, the labelling of the immediate packaging does not have to include any information on excipients. In exceptional cases, the responsible authority can also agree to a reduced labelling approach for other types of immediate packaging if it is not feasible to present all required information on the containers [30,33,34].

3.1.5 Relevant information on excipients in the package leaflet

According to Article 59(2)(c), the package leaflet must contain information on the excipients, knowledge of which is important for the safe and effective use of the medicinal product and which are included in the Annex to the excipients guideline [30]. This information has to be described in section “2. What you need to know before you <take> <use> X” of the package leaflet (whereby “X” stands for the name of the medicinal product and the <text> has to be selected or deleted as applicable). In subsection “Do not <take> <use> X”, contraindications resulting from the presence of an excipient must be listed, as mentioned in SmPC section 4.3. In addition, a statement that the medicinal product should not be taken if the user is allergic to any of the excipients listed in section 6 of the package leaflet should be included. Subsequently, warnings on excipients in accordance with SmPC section 4.4 must be presented in the excipient warnings subsection of the package leaflet. Information on excipients related to certain topics, such as the ability to drive, to use machines, pregnancy and lactation, should be given in the corresponding sections of the package leaflet. The specific warning or information statements specified in the Annex to the excipients guideline must be included in the package leaflet. In general, these statements should appear only once in the package leaflet and should not be repeated. To prevent the patient from missing

important information, reference to the excipient warnings section should be made from other sections that contain information on the effects of excipients and vice versa. Information on adverse reactions due to the presence of certain excipients, as described in SmPC section 4.8, must be provided in section “4. Possible side effects” of the package leaflet [19,30,33,34].

Finally, according to Article 59(1)(f)(iv), in section “6. Contents of the pack and other information” of the package leaflet, the names of all excipients must be listed in accordance with SmPC sections 2 and 6.1. Reference to the excipients warnings section should be made, if applicable [30,33,34].

3.1.6 Overview of the relevant information on excipients in the product information for medicinal products

Table 1 on the following page provides an overview of the information on excipients in the different elements of the product information that may be relevant to users with food allergies or food intolerances, as outlined in detail in the previous chapters. The information required on the packaging and the package leaflet is assigned to the appropriate SmPC sections with which it must comply.

It must be considered that the product information for homeopathic medicinal products referred to in Article 14(1) of Directive 2001/83/EC does not have to include a SmPC and package leaflet. Moreover, Article 69 specifies a reduced labelling approach for this type of homeopathic medicinal products. As part of this labelling approach, special warnings must be given on the packaging and, where appropriate, in the package insert, but no further information about the excipients contained must be provided. Nevertheless, some of the information specified in the Annex to the excipients guideline may be used in the context of this reduced labelling approach, if relevant [19,30]. For example, alcohol or wheat starch are often present in homeopathic medicinal products and information from the Annex could be applied.

Table 1: Overview of the information on excipients in the product information for medicinal products that may be relevant for users with food allergy or food intolerance [19,26,30,33,34].

SmPC	Packaging	Package leaflet
2. Qualitative and quantitative composition Qualitative and quantitative information on excipients with a known effect.	**Outer packaging and immediate packaging** Qualitative information on excipients with a known effect and included in the Annex to the excipients guideline. For parenteral, topical and ocular medicinal products, all excipients contained must be stated on the packaging. Reduced labelling approaches without information on excipients for blisters in an outer packaging and small immediate packaging units.	Please see the last line of the table for corresponding information in the package leaflet (section "6. Contents of the pack and other information").
4.3 Contraindications Statement on hypersensitivity to any of the excipients listed in section 6.1; any other contraindication arising from the presence of a certain excipient	Reference to the package leaflet for further information on an excipient that is stated on the packaging and included in the Annex to the excipients guideline.	**2. What you need to know before you <take> <use> X** **Do not <take> <use> X*** Statement on allergies to any of the excipients listed in section 6; any other contraindication arising from the presence of a certain excipient
4.4 Special warnings and precautions for use Information about risks associated with excipients. Warnings on certain topics should be moved to the appropriate SmPC section (e.g. fertility, pregnancy and lactation; effects on ability to drive and use machines).		**<X contains {name the excipient(s)}>*** Information about risks associated with excipients. Warnings on certain topics should be moved to the appropriate section of the package leaflet with a cross-reference (e.g. pregnancy, breast-feeding and fertility; driving and using machines; paediatric information).
4.8 Undesirable effects All adverse reactions specific to excipients.		**4. Possible side effects*** All adverse reactions specific to excipients.
6.1 List of excipients Qualitative declaration of all excipients contained in the medicinal product.	Please see the first line of the table for corresponding information on the packaging ("Outer packaging and immediate packaging")	**6. Contents of the pack and other information** **What X contains** Qualitative declaration of all excipients contained in the medicinal product.

* Information and warning statements from the Annex to the excipients guideline must be included.

3.1.7 National implementation of the excipients guideline

In contrast to Regulation (EC) No. 726/2004, Directive 2001/83/EC, which sets out the requirements for the labelling of medicinal products and forms the basis of the excipients guideline, is not directly applicable at national level of EU Member States. Therefore, Directive 2001/83/EC must be transposed into national law in each Member State, whereby the Member States can choose the form and method by which the Directive is implemented. Meanwhile, the excipients guideline itself is considered as non-legally binding soft law; however, deviations from the guideline must be duly justified by applicants or MAHs.

For example, in Germany, Directive 2001/83/EC is implemented via the Medicinal Products Act ("Arzneimittelgesetz", AMG), which describes the labelling requirements in Sections 10 to 11a. According to Section 28 subsection 2 number 3 of the AMG, the German Federal Institute for Drugs and Medical Devices ("Bundesinstitut für Arzneimittel und Medizinprodukte", BfArM) is authorised to define a standard wording for the labelling of excipients for reasons of drug safety, transparency or rational working. Furthermore, pursuant to Section 10 subsection 6 number 1 of the AMG, the BfArM may determine the name that must be used for an excipient in consultation with the Federal Institute for Vaccines and Biomedicines (Paul-Ehrlich-Institut) and the Federal Office of Consumer Protection and Food Safety (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit) [48,49]. The texts for the labelling of certain excipients are summarised in the list of special information required for specific excipients ("Besonderheitenliste") on the BfArM website. Applicants and MAHs must adhere to this list and any deviation must be reasonably justified. The list represents the national implementation of the Annex to the excipients guideline. However, in consultation with patient representatives, the BfArM has developed its own texts for the labelling of heparin, parabens and potassium. The list also contains information from the German Medicinal Products Warning Ordinance ("Arzneimittel-Warnhinweisverordnung", AMWarnV), which states additional provisions for the labelling of medicinal products containing ethanol or tartrazine [49,50].

Overall, the instructions on the BfArM website for using the specified texts in the product information for medicinal products are much more detailed than the instructions in the excipients guideline and its Annex. For example, the BfArM specifies that hypersensitivity to an excipient should be stated in the section on contraindications of the SmPC and package leaflet, and, in case of allergic reactions, this information should also be included in the section on side effects. However, the information should not be repeated in the warnings and precautions section. In addition, for ocular and nasal products, the term "skin" must be replaced by "conjunctiva" or "nasal mucosa" in the specified texts. Furthermore, in the package leaflet, the common name can be stated in parentheses after the official name

of an excipient to ensure patient understanding. A separate document is available on the BfArM website for each excipient listed, in which relevant sections of the SmPC, package leaflet and packaging as well as corresponding texts are described in detail. In contrast, in the Annex to the excipients guideline, the sections of the product information to which the given texts relate are usually not specified in detail. Although the texts in the German list of special information required for specific excipients are based on the Annex to the excipients guideline, the wording has sometimes been slightly modified and combined with additional information. Moreover, the list includes excipients that are not part of the excipients guideline. These excipients are flavourings and odorants with bergamot oil, β-asarone or safrole; camphor; eucalyptol; levomenthol; menthol; honey; soya lecithin; cinnamon and cinnamaldehyde [49].

In contrast, as another example, Austria's national provisions do not contain any instructions or information in addition to the excipients guideline. In Austria, Directive 2001/83/EC is implemented nationally by the Austrian Medicines Act ("Österreichisches Arzneimittelgesetz"), which specifies labelling requirements in Sections 15 to 17a [51]. The Austrian Medicines Act is supplemented by the Ordinance of the SmPC, the Ordinance on labelling of medicinal products and the Ordinance on package leaflet of medicinal products. These ordinances contain the rules for excipient labelling in the product information for medicinal products and refer exclusively to the excipients guideline for the declaration of excipients with known effects. No additional information is provided [52–54].

Thus, the national implementation of the excipients guideline varies in the different EU Member States. Whereas in Germany, for example, additional excipients are defined for the declaration and a modified wording is specified at national level, in Austria the excipients guideline is implemented without any changes or amendments. Therefore, the information on the websites of the national competent authorities must be considered when preparing the product information.

3.2 Comparison of excipient labelling for medicinal products with food ingredient labelling in the EU with regard to information relevant to food allergies and food intolerances

Article 2 of Regulation (EC) No. 178/2002 defines food as any substance or product that is processed, partially processed or unprocessed and that is intended to be, or reasonably expected to be ingested by humans. The term "food" also covers beverages, chewing gums and any substance, including water, intentionally incorporated into the food during its manufacture, preparation or treatment. By contrast, animal feed, live animals not prepared for marketing for human consumption, plants prior harvesting, medicinal products,

cosmetics, tobacco and tobacco products, narcotic and psychotropic substances, as well as residues and contaminants do not fall within the definition of food [55]. Meanwhile, pursuant to Article 1(2) of Directive 2001/83/EC, medicinal products for human use are defined as any substance or combination of substances presented as having properties for treating or preventing human disease, or any substance or combination of substances which is intended to be used in or administered to human beings in order to make a medical diagnosis or to restore, correct or modify physiological functions by pharmacological, immunological or metabolic action. Where a product falls within both the definition of foods and the definition of medicinal products, Article 2(2) of Directive 2001/83/EC provides that the rules governing medicinal product shall apply to the product [30].

The following chapters outline the labelling of food in the EU with regard to information relevant to consumers with food allergies or intolerances and then compare it with the labelling of relevant excipients in the product information for medicinal products. The aim is to identify differences between the two labelling approaches in order to develop proposals for improving and harmonising the labelling of excipients with the labelling of food ingredients in the final discussion in Chapter 4.

3.2.1 Food labelling requirements according to Regulation (EU) No. 1169/2011 on food information

Regulation (EU) No. 1169/2011 lays down the general requirements for the provision of food information to consumers, including the declaration of ingredients related to allergies or intolerances. The provisions of Regulation (EU) No. 1169/2011 are directly applicable in all EU Member States, although the Regulation may be supplemented and specified by national provisions. The Regulation aims to ensure a high level of protection of consumers' health and interests by providing comprehensive food information which enables the consumers to make informed choices when purchasing food and to use food safely [56].

According to Article 1(3), Regulation (EU) No. 1169/2011 applies to all foods intended for distribution to the final consumer, including foods delivered by mass caterers, as well as foods supplied to mass caterers. The term "mass caterer" means any establishment in which food is prepared for consumption by the final consumer as part of a business, such as restaurants and canteens. Furthermore, Regulation (EU) No. 1169/2011 applies to food business operators at all stages of the food chain, where their activities concern the provision of food information to consumers, whereby responsibilities are outlined in detail in Article 8 of the Regulation [56]. Allergen labelling according to Regulation (EU) No. 1169/2011 applies to all types of food, including food supplements [57].

Pursuant to Article 7 of Regulation (EU) No. 1169/2011, food information must be accurate, clear and easily understood by consumers and must not be misleading. Articles 9(1) and 10(1) specify mandatory information which must appear on the packaging or on a label attached thereto of prepacked food. “Prepacked food” means a food and its packaging in which it has been placed before being offered for sale to the final consumer or to mass caterers, provided that it is impossible to alter the contents without opening or changing the packaging. It is irrelevant whether the packaging encloses the food completely or only partially. Meanwhile, foods that are packaged at the place of purchase at the customer’s request or that are prepacked for direct sale are not considered as prepacked food. Article 9(2) specifies that the mandatory information listed in Article 9(1) must be given in words and numbers and may additionally be expressed by pictograms or symbols. Furthermore, Article 13 sets out that mandatory food information must be easily visible, legibly, and, where appropriate, indelible. It must not be hidden, obscured, disrupted or confused by other information or materials. In addition, a minimum font size is specified for mandatory particulars listed in Article 9(1) [56].

According to Article 9(1)(b), a list of ingredients must be indicated on prepacked food, whereby ingredients are defined as any substance or product, including flavourings, food additives, food enzymes and any constituent of a compound ingredient, used in the manufacture or preparation of a food and still present in the finished product, even if in an altered form. Residues are not considered to be ingredients. Article 18 provides that the list of ingredients must be preceded by an appropriate heading that contains the word “ingredients”. Subsequently, all the ingredients of a food must be listed by their specific name in descending order of weight as they were used during manufacturing of the food. Annex VII to the Regulation lays down additional rules on the indication of certain ingredients with regard to the order in which they are listed, the indication of the food category instead of the specific name (e.g. for fish species, spices and herbs), the designation of food additives, food enzymes and flavourings, and the indication of compound ingredients and their constituents. The provisions of Annex VII are without prejudice to Article 21, which lays down the rules for the labelling of ingredients causing allergic or intolerance reactions [56].

Article 19 specifies certain types of food for which the ingredient list may be omitted. These are, for example, foods composed of a single ingredient and having a food name identical to the ingredient name, or a food name that allows to clearly identify the ingredient. In addition, Article 16 provides that the list of ingredients is not required on glass bottles intended for reuse and indelibly marked without any removable labels, on packaging or containers with a maximum surface area of less than 10 cm^2 for which the list of ingredients is provided by other means or at the customer’s request, and on beverages containing more

than 1.2 % alcohol by volume. Furthermore, Article 20 states that certain constituents need not be included in the list of ingredients (e.g. food additives and food enzymes which are present in the ingredients of a food and which have no technological function in the finished product; food additives and food enzymes used as processing aids; carriers used only in strictly necessary quantities). However, the derogations of Article 20 apply without prejudice to Article 21, which lays down the labelling of ingredients and processing aids causing allergic or intolerance reactions [56].

The list of ingredients does usually not provide information on the exact quantities of food ingredients. Article 22 stipulates that the quantity of an ingredient must only be indicated where the ingredient or category of ingredients is part of the name of a food or is associated with that name by consumers, is highlighted by words, pictures or graphics on the labelling, or is of particular importance for characterising a food or distinguishing it from other products. Annex VIII of the Regulation specifies the way in which the quantity of an ingredient must be provided and lists specific cases exempted from the provisions of Article 22. In general, the quantity must be expressed as a percentage corresponding to the quantity of an ingredient or ingredient category at the time of its use. The quantity can be indicated in the name of the food, next to the name of the food or in the list of ingredients [56].

In addition to the list of ingredients, specific information on ingredients relevant to allergies or intolerances must be displayed on prepacked foods. Annex II to Regulation (EU) No. 1169/2011 contains a list of substances and products causing allergic or intolerance reactions. Article 9(1)(c) of the Regulation requires information on any ingredient or processing aid listed in Annex II or derived from a substance or product listed in Annex II and causing allergic or intolerance reactions, which is used in the manufacture or preparation of a food and still present in the finished product, even if in altered form. Article 21 provides that these ingredients or processing aids must be indicated in the list of ingredients with a reference to the name listed in Annex II. This name must be highlighted among the other information in the list of ingredients, for example, by a special font, font style or background colour. The Commission Notice on the provision of information on substances or products causing allergies or intolerances of 13 July 2017 further clarifies that in case of ingredient names consisting of several separate words or of a single word made up of different parts, only the word or part of the word referring to the name listed in Annex II needs to be highlighted. For compound ingredients consisting of substances related to allergies or intolerances and included in Annex II, these substances must also be emphasized in the list of ingredients of the final food product. In case a food does not require a list of ingredients, the word “contains” followed by the name of the substance or product in accordance with Annex II must be provided. Where several ingredients or processing

aids present in a food are derived from the same substance or product listed in Annex II, this must be indicated for each of them, for example, by a footnote at the end of the list of ingredients directly linked to the ingredients concerned. However, the information on an ingredient or processing aid causing allergic or intolerance reactions may be omitted if the name of the food clearly refers to the corresponding substance or product in Annex II and a list of ingredients is not required. Since consumers' understanding of the name of a food may vary from one Member State to another, a case-by-case analysis must be conducted. Annex II is regularly reviewed by the European Commission and may be updated through delegated acts to reflect scientific and technical progress and to ensure better information for consumers [56,58].

For non-prepacked food, the requirements for food information for final consumers and mass caterers are specified in Article 44 of Regulation (EU) No. 1169/2011. In general, the mandatory particulars laid down in Articles 9(1) and 10(1) do not apply to non-prepacked foods, with the exception of those relating to ingredients and processing aids causing allergic or intolerance reactions, as referred to in Article 9(1)(c). Thus, the information on ingredients and processing aids related to allergies or intolerances must be provided for both prepacked food and non-prepacked food. In contrast, the Regulation does not require a list of ingredients for non-prepacked foods. However, Member States may supplement the requirements of Regulation (EU) No. 1169/2011 with national provisions and require further mandatory information for non-prepacked food. Moreover, they may adopt national provisions to determine how mandatory information is to be provided for non-prepacked food and how the information is to be presented [56]. For example, the German Food Information Implementing Regulation ("Lebensmittelinformations-Durchführungsverordnung", LMIDV) stipulates that mandatory information for non-prepacked food can be provided by a label on or near the food, in the menu or price list, by a notice on the sales premises, or by other types of written or electronic information that is directly and easily accessible. Under certain conditions, the food information may also be provided by oral communication, with a clearly visible notice that the information is provided orally and that written information will be provided upon request [59]. If there are no national provisions in a Member State, the rules of Regulation (EU) No. 1169/2011 on prepacked food also apply to non-prepacked food in that Member State. In this case, information on ingredients and processing aids related to allergies or intolerances must be provided in written form and in accordance with Article 21. It is not possible to provide this information only at the customer's request [58].

3.2.2 Comparison of the labelling of foods and medicinal products with regard to information on ingredients and excipients relevant to food allergies and intolerances

Table 2 summarises ingredient labelling of foods in the EU in terms of information relevant to food allergies and intolerances and compares this with corresponding aspects of excipient labelling in the product information for medicinal products.

Table 2: Comparison of the labelling of ingredients in foods with the labelling of excipients in medicinal products for human use in the EU with regard to information relevant to food allergies and food intolerances [19,22,26,30,33,36,46,56,58,60,61].

Aspect	Foods	Medicinal products
Legal basis and guidances	Regulation (EU) No. 1169/2011 Commission Notice of 13 July 2017 (2017/C 428/01) Commission Implementing Regulation (EU) No. 828/2014 Commission Delegated Regulation (EU) 2016/127	Directive 2001/83/EC Excipients guideline SmPC guideline "Guideline on the readability of the labelling and package leaflet of medicinal products for human use" QRD templates and more
Definition of ingredient/excipient	Ingredient: Any substance or product, including flavourings, food additives and food enzymes, and any constituent of a compound ingredient, used in the manufacture or preparation of a food and still present in the finished product, even if in an altered form. Residues are not defined as ingredients.	Excipient: Any constituent of a medicinal product other than the active substance and packaging material. Residues of substances arising from the manufacturing process, impurities, residual solvents and degradation products are not defined as excipients.
Way of providing information	Prepacked food: Information directly on the packaging or on a label attached to it. Non-prepacked food: The way of providing information may be defined by Member States (e.g. label, accompanying material, modern technology tools, verbal communication).	SmPC (for healthcare professionals) Package labelling, package leaflet (for users) For homeopathic medicinal products according to Article 14(1), only package labelling is required under EU law.
Text design	For mandatory information on the packaging or label, such as the list of ingredients and information on ingredients related to allergies or intolerances, a minimum font size is specified in the Regulation.	The "Guideline on the readability of the labelling and package leaflet of medicinal products for human use" offers comprehensive guidance for text design (e.g. font, font size, print colour).

Aspect	Foods	Medicinal products
Nomenclature of ingredients/excipients	The specific name of an ingredient or name of a food when a food is used as ingredient. In special cases, the category of the food may be indicated instead of the specific name of an ingredient (unless the ingredient is related to allergies or intolerances). Food additives and food enzymes must be designated by the name of their functional class together with their specific name or E number. Flavourings can be given in general terms, the specific name or a description.	INN or INNM accompanied by salt if relevant, or the European Pharmacopeia name, the usual common name, or failing this, the chemical name. Chemical modifications should be specified. The E number should accompany the name of an excipient listed in the Annex to the excipients guideline, if available. Proprietary flavours or fragrances can be declared in general terms. Packaging: The E number alone, abbreviations and Latin names may be stated.
List of ingredients/excipients	The list of ingredients is mandatory for prepacked food, but not for non-prepacked food. For prepacked food there are several exemptions where the list of ingredients can be omitted (e.g. alcoholic beverages, certain types of packaging). In certain situations, food additives, food enzymes and similar substances do not need to be included in the list of ingredients (however, substances related to allergies or intolerances must still be stated). The ingredients are listed in descending order of weight at the time of use, with exceptions for certain ingredients (e.g. spices, herbs, ingredients < 2 % by weight of the food, components of compound ingredients).	SmPC: A comprehensive list of all excipients is provided. The excipients can be listed according to the different parts of the product or per container or chamber. Packaging: Only in the case of parenteral, topical or eye preparations are all excipients listed on the packaging. The list of excipients is not required for certain types of immediate packaging. For homeopathic medicinal products according to Article 14(1), no list of excipients is required on the packaging. Package leaflet: The names of all excipients are listed in accordance with the SmPC.
Declaration of compound ingredients/compound excipients	All components of a compound ingredient must be declared except in the following three cases: 1. The compound ingredient is a food for which no list of ingredients is required. 2. The composition is defined in an EU regulation and the compound ingredient constitutes less than 2 % of the finished product. 3. The compound ingredient is a mixture of spices and/or herbs and constitutes less than 2 % of the finished product.	All components of a compound excipient must be declared and listed under a general descriptive term for the compound excipient. The general descriptive term alone may be indicated on the packaging; however, any component with a known effect must be stated. For proprietary flavours or fragrances, only known main components and excipients with a known effect need to be declared. Vaccines: For established media with a generally known

Aspect	Foods	Medicinal products
	However, in all cases, components related to allergies or intolerances must still be stated. The components can be listed in the ingredient list under the designation of the compound ingredient or integrated directly into the list of ingredients.	composition, a short description is acceptable and only components with a known effect need to be specified.
Declaration of ingredients/excipients related to food allergies or intolerances	For prepacked food and non-prepacked food, ingredients and processing aids that are listed in Annex II to Regulation (EU) No. 1169/2011 or that are derived from substances or products listed in Annex II and cause allergic or intolerance reactions must always be indicated when present in the final product. The name of the ingredient must clearly refer to the name of the substance or product as given in Annex II. The relevant ingredients must be highlighted in the list of ingredients. Where no list of ingredients is required, the word “Contains” followed by the respective ingredients must be provided. The information may only be omitted if the food name clearly refers to the ingredient. Annex II is regularly updated.	SmPC: Qualitative and quantitative indication of excipients with a known effect and listed in the Annex to the excipients guideline. Further information is provided in sections “4.3 Contraindications”, “4.4 Special warnings and precautions for use” and “4.8 Undesirable effects”. Packaging: The excipient name given in the Annex is provided. Exemptions exist for certain types of immediate packaging. For homeopathic medicinal products according to Article 14(1), a warning may be placed on the packaging. Package leaflet: Information is provided in accordance with the SmPC, but excipients are not specified quantitatively. Only in individual cases do the statements for the package leaflet, which are specified in the Annex, contain quantitative information. The Annex is regularly updated.

For food, the rules for the labelling of ingredients related to allergies or intolerances are laid down in Regulation (EU) No. 1169/2011, which is directly applicable in all Member States and does not need to be transposed into national law. For non-prepacked food, however, the Regulation leaves the way of providing information to the Member States [56]. In contrast, Directive 2001/83/EC, which states the rules for the labelling of medicinal products for human use, must be implemented by national legislation in each Member State [30]. This allows the Member States a certain degree of flexibility and modification of the requirements when implementing the provisions of the Directive. This is also reflected in the different ways of implementing the excipients guideline, which complements Directive 2001/83/EC [19], as described in Chapter 3.1.7.

The definition of food ingredients and pharmaceutical excipients is quite similar. Both terms cover all components of the finished product, but do not include residues and unintentional contaminations. In addition, the definition of pharmaceutical excipients excludes the active substance of a medicinal product, whereas foods in general do not contain an active substance. Furthermore, the packaging of a medicinal product is not defined as an excipient. This is not explicitly stated in the definition of food ingredients; however, Regulation (EU) No. 1169/2011 does not consider the packaging to be part of the food [19,56].

While the product information for medicinal products consists of three elements – the SmPC directed to healthcare professionals, and the package labelling and package leaflet directed to the users –, food information for consumers is usually only provided via the packaging or a label attached thereto. In the case of non-prepacked foods, the way by which information is transmitted may vary, and the information may even be provided by oral communication. Remarkably, for homeopathic medicinal products complying with Article 14(1) and registered through a simplified registration procedure, Directive 2001/83/EC only requires the package labelling as information tool. No SmPC or package leaflet need to be provided, unless required by the national legislation of individual Member States [30,56].

Regulation (EU) No. 1169/2011 lays down a minimum font size for some mandatory particulars on the packaging or on the label attached to the packaging [56]. Meanwhile, the “Guideline on the readability of the labelling and package leaflet of medicinal products for human use” provides much more comprehensive guidance on the design of the packaging and package leaflet of medicinal products. For example, the guideline contains instructions for the font, font size, printing colour and more [36].

The nomenclature of pharmaceutical excipients is more specific than the nomenclature of food ingredients. Food ingredients should be indicated by their specific name, which is not further explained in the Regulation. If applicable, the provisions on the naming of foods in accordance with Article 17 should be applied to food ingredients, which means the legal name or, in the absence of such, the customary name, or a descriptive name. Some ingredients may even be indicated by the category of food to which they belong. In contrast, excipients in medicinal products must be stated by their INN or INNM, their European Pharmacopoeia name, the usual common name or the chemical name. In addition, chemical modifications must be indicated. Flavours and fragrances can be declared in general terms for both foods and pharmaceuticals. In the case of foods, food additives and food enzymes must be declared by the name of their functional class together with their specific name or E number (e.g. “colour: curcumin” or “colour: E 100”). In contrast, the product information for medicinal products must always contain the full name of an

excipient, which must be accompanied by the E number, if available and listed in the Annex to the excipients guideline. The E number alone can be used for an excipient on the packaging if the full name and the E number are given in the package leaflet. Where justified for space constraints, abbreviations or Latin names may be used for the labelling of excipients on the packaging of medicinal products, provided that the full name appears in the SmPC and package leaflet. By contrast, Regulation (EU) No. 1169/2011 does not provide for the use of abbreviations for food ingredients [19,56,62].

For food, the list of ingredients can be omitted in many cases (e.g. for non-prepacked foods and alcoholic beverages). In addition, certain substances such as food additives and food enzymes need not be included in the list of ingredients in certain situations. In contrast, the SmPC and the package leaflet of medicinal products always contain a complete list of excipients. The outer packaging of parenteral, topical and ocular medicinal products must also indicate all excipients contained, whereas for all other types of medicinal products no list of excipients is required on the packaging. For homeopathic medicinal products complying with Article 14(1) of Directive 2001/83/EC, a list of excipients on the packaging is also not required. It is therefore possible that this information may not be made available to users, as a SmPC and package leaflet are not mandatory under EU law for this type of homeopathic medicinal product. Thus, with the exception of homeopathic medicinal products registered under a simplified registration procedure, a complete list of excipients is always made available to healthcare professionals and users of a medicinal product, whereas in the case of food, consumers are often provided with no or an incomplete list of all ingredients contained. The ingredients of foods are listed in descending order of weight at the time of use, with exceptions for certain ingredients. In contrast, pharmaceutical excipients may be listed according to the different parts of the medicinal product or per container or chamber [19,30,56].

In general, all components of a compound ingredient or compound excipient must be declared for both foods and medicinal products. The components must be listed under the designation of the compound ingredient or compound excipient. In the case of foods, the components may also be integrated directly into the list of ingredients. However, there are certain exceptional cases for foods in which the components of a compound ingredient which are not allergens may be omitted, such as foods used as ingredients and for which an ingredient list is not required. In contrast, in the case of medicinal products, only the components of proprietary flavours or fragrances and established complex media for the formulation of vaccines can be omitted from the product information. The descriptive name of a compound excipient alone may appear on the packaging of medicinal products provided that the package leaflet contains further information. Thus, medicinal products for

which a list of excipients is required on the packaging do not have to indicate the full composition of compound excipients on the packaging [19,56].

For all foods, qualitative information must be provided on ingredients relevant to allergies or intolerances, unless the name of the food clearly refers to that ingredient (e.g. “Cheese” or “Cream”, which refer to milk). While for medicinal products only excipients with a known effect explicitly listed in the Annex to the excipients guideline are considered, food information follows a different approach and also includes information on ingredients derived from substances or products listed in Annex II to Regulation (EU) No. 1169/2011 and causing allergic or intolerance reactions. The names of these ingredients must refer to the names listed in Annex II, while for pharmaceutical excipients the specific names as given in the Annex to the excipients guideline must be used. Both Annex II to Regulation (EU) No. 1169/2011 and the Annex to the excipients guideline are regularly reviewed and updated to reflect the current state of knowledge. Remarkably, the labelling requirements of Regulation (EU) No. 1169/2011 also apply to processing aids causing allergic or intolerance reactions and present as residues in food, whereas the excipients guideline does not apply to residues. If a list of ingredients is required for a food, ingredients related to allergies or intolerances must be highlighted in that list of ingredients. In contrast, excipients with a known effect do not have to be visually highlighted in the list of excipients in the product information. They are only highlighted in the SmPC by including them in section 2 as well as by specific information texts in the SmPC and package leaflet. The SmPC provides qualitative and quantitative information on excipients with known effects, whereas the packaging and package leaflet only contain qualitative information. Thus, the information addressed to the users of medicinal products usually does not include quantitative information on excipients relevant to food allergies or intolerances. In individual cases, however, the statements specified in the Annex to the excipients guideline, which must be included in the package leaflet, may also contain information on the quantity of an excipient. Food information usually does not contain information about the exact amount of ingredients related to allergies or intolerances. The declaration of the quantity of an ingredient is only mandatory for prepacked foods in certain cases where the ingredient is of particular importance. In the case of homeopathic medicinal products as referred to in Article 14(1) of Directive 2001/83/EC, excipients with known effects do not need to be indicated on the packaging, but a warning may be included [19,26,30,56].

3.2.3 Comparison of Annex II to Regulation (EU) No. 1169/2011 with the Annex to the excipients guideline

Annex II to Regulation (EU) No. 1169/2011 is based on scientific opinions of the European Food Safety Authority (EFSA) and lists the 14 main categories of food components that cause allergic and intolerance reactions [56,58]. Table 3 lists the substances and products included in Annex II to Regulation (EU) No. 1169/2011 and compares them with corresponding excipients listed in the Annex to the excipients guideline.

Table 3: Comparison of Annex II to Regulation (EU) No. 1169/2011 with the Annex to the excipients guidelines [22,56,60,61].

Substances or products causing allergic or intolerance reactions and listed in Annex II to Regulation (EU) No. 1169/2011	Excipients with a known effect listed in the Annex to the excipients guideline
Cereals containing gluten, namely wheat (such as spelt and khorasan wheat), rye, barley, oats or their hybrid strains and products thereof, except for: - wheat-based glucose syrups including dextrose***** - wheat-based maltodextrins***** - glucose syrups based on barley - cereals used to produce alcoholic distillates, including ethyl alcohol of agricultural origin Voluntary statements in accordance with Commission Implementing Regulation (EU) No. 828/2014: “gluten-free” (if the food contains ≤ 20 mg/kg of gluten) “very low gluten” (if the food contains ≤ 100 mg/kg of gluten) The statements above can be accompanied by the following information: “suitable for people intolerant to gluten”/ “suitable for coeliacs” “specifically formulated for people intolerant to gluten”/ “specifically formulated for coeliacs”	Wheat starch (containing gluten) Route of administration: Oral Threshold: Zero Statement for the package leaflet: “This medicine contains only very low levels of gluten (from wheat starch). <It is regarded as ‘gluten-free’******> and is very unlikely to cause problems if you have coeliac disease. One <dosage unit> contains no more than x micrograms of gluten. If you have wheat allergy (different from coeliac disease) you should not take this medicine.” ****** The statement “gluten-free” applies only if the gluten content in the medicinal product is less than 20 ppm. All other medicinal products are considered to contain less than 100 ppm.
Crustaceans and products thereof	-
Eggs and products thereof	-
Fish and products thereof, except: - fish gelatine used as carrier for vitamin or carotenoid preparations - fish gelatine or Isinglass used as fining agent in beer and wine	-

Substances or products causing allergic or intolerance reactions and listed in Annex II to Regulation (EU) No. 1169/2011	**Excipients with a known effect listed in the Annex to the excipients guideline**
Peanuts and products thereof	Arachis oil (peanut oil) Route of administration: All Threshold: Zero Statement for the package leaflet: "<Medicinal product> contains arachis oil (peanut oil). If you are allergic to peanut or soya, do not use this medicinal product." SmPC: Contraindication
Soybeans and products thereof, except: - fully refined soybean oil and fat* - natural mixed tocopherols (E 306), natural D-alpha tocopherol, natural D-alpha tocopherol acetate, and natural D-alpha tocopherol succinate from soybean sources - phytosterols and phytosterol esters derived from vegetable oils from soybean sources - plant stanol ester produced from vegetable oil sterols from soybean sources	Soya oil, Hydrogenated soya oil Route of administration: All Threshold: Zero Statement for the package leaflet: "<Medicinal product> contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product." SmPC: Contraindication
Milk and products thereof (including lactose), except: - whey used for making alcoholic distillates including ethyl alcohol of agricultural origin - lactitol Voluntary statements related to lactose in infant formula and follow-on formula in accordance with Commission Delegated Regulation (EU) 2016/127: "lactose only" (if lactose is the only carbohydrate present in the product) "lactose free" (if the lactose content in the product is not greater than 2,5 mg/100 kJ or 10 mg/100 kcal). Where infant formulae and follow-on formulae are manufactured from protein sources other than soya protein isolates, the statement "lactose free" must be accompanied by the statement "not suitable for infants with galactosaemia".	Lactose Route of administration: Oral Threshold: Zero Statement for the package leaflet: "If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product." From a threshold of 5 g, the amount of lactose is stated, but with regard to diabetes mellitus: "Contains x g lactose (x/2 g glucose and x/2 g galactose) per dose. This should be taken into account in patients with diabetes mellitus." SmPC proposal: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
	Lactitol (E 966) Route of administration: Oral Threshold: Zero Statement for the package leaflet: "If you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicinal product." From a threshold of 10 g, the following statement must be given: "May have a mild laxative effect. Calorific value 2.1 kcal/g lactitol."

Substances or products causing allergic or intolerance reactions and listed in Annex II to Regulation (EU) No. 1169/2011	Excipients with a known effect listed in the Annex to the excipients guideline
	SmPC proposal: Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take this medicine.
Nuts, namely almonds, hazelnuts, walnuts, cashews, pecan nuts, Brazil nuts, pistachio nuts, macadamia or Queensland nuts, and products thereof, except for nuts used for making alcoholic distillates including ethyl alcohol of agricultural origin	-
Celery and products thereof	-
Mustard and products thereof	-
Sesame seeds and products thereof	Sesame oil Route of administration: All Threshold: Zero Statement for the package leaflet: "May rarely cause severe allergic reactions."
Sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/litre in terms of total SO_2 which are to be calculated for products as proposed ready for consumption or as reconstituted according to the manufacturer's instructions	Sulphites including metabisulphites, e.g.: Sulphur dioxide (E 220), Sodium sulphite (E 221) … Route of administration: Oral, Parenteral, Inhalation Threshold: Zero Statement for the package leaflet: "May rarely cause severe hypersensitivity reactions and bronchospasm."
Lupin and products thereof	-
Molluscs and products thereof	-

***** And the products thereof as long as the process they have undergone is not likely to increase the level of allergenicity determined by the EFSA for the relevant product from which they originate.

Table 3 shows that not all 14 categories of substances and products listed in Annex II to Regulation (EU) No. 1169/2011 are covered by the Annex to the excipients guideline. Moreover, Annex II is more general and, in most cases, refers to a food substance or product and all products manufactured thereof. In contrast, the Annex to the excipients guideline specifies individual excipients and therefore does not cover the entire scope of Annex II to the Regulation. For example, if a medicinal product would contain excipients with allergenic potential derived from eggs (e.g. phospholipids) [17], EU regulations do not require these excipients to be declared as allergens in the product information, whereas food ingredients derived from eggs must be declared as allergens for food. As a further example, according to the Annex to the excipients guideline, soya oil must be stated as an

allergen in the product information for a medicinal product, whereas soya lecithin is not included in the Annex and, thus, no specific statement is required in the product information for medicinal products containing soya lecithin. In contrast, in the case of food, both soya oil (not fully refined) and soya lecithin must be declared as allergens, as Annex II to Regulation (EU) No. 1169/2011 covers soybeans and all products made from them (with some exceptions). In addition, a threshold and route of administration are specified in the Annex to the excipients guideline. When the medicinal product has a different route of administration or the quantity of the excipient concerned is below the specified threshold, the requirements of the Annex can be disregarded. In contrast, it is not necessary to specify the route of administration for food. With the exception of sulphites, gluten and lactose (lactose in infant formula and follow-on formula), no thresholds are specified for food ingredients and the information on ingredients causing allergic or intolerance reactions must always be provided for foods regardless of the quantity of the ingredient [19,22,56,61].

The Commission Notice of 13 July 2017 provides further clarification on Annex II to Regulation (EU) No. 1169/2011. For example, the Notice specifies that the term “egg” refers to eggs from all farmed birds, while “milk” refers to milk from the mammary gland of farmed animals. It also states that, in the case of gluten-containing cereals and nuts, the ingredient indicated in the list of ingredients must refer to the specific type of cereal or nut listed in Annex II [58]. In contrast, the specific name of an excipient that must be provided in the product information is already given in the Annex to the excipients guideline [22].

According to Annex II, all cereals containing **gluten**, namely wheat, rye, barley, oats, or their hybrid strains, and products thereof, must be specifically declared when used as ingredient in food [56,60]. This information is relevant for people suffering from coeliac disease, which is an autoimmune disorder. In patients with coeliac disease, the ingestion of gluten triggers an abnormal immune response that leads to chronic inflammation of the small intestine and damage of the intestinal villi. Common symptoms of coeliac disease are, for example, pain and discomfort in the digestive tract, constipation, diarrhoea, weight loss, anaemia, nutrient or mineral deficiency, failure to thrive (in children), weakness and fatigue. The only effective treatment of coeliac disease is a lifelong gluten-free diet. There are also other forms of gluten intolerance, such as non-coeliac gluten sensitivity [63–65]. Since different people with gluten intolerance may tolerate different small amounts of gluten within a restricted range, Commission Implementing Regulation (EU) No. 828/2014 of 30 July 2014 establishes statements that can be provided to inform consumers about the gluten content of foods. In this way, people can choose their food according to their level of gluten sensitivity. The statement “gluten-free” can be used if the food does not contain more than 20 mg/kg of gluten. In contrast, the claim “very low gluten” can be stated if the food contains an ingredient made from cereals specially processed to reduce the gluten content and the

food does not contain more than 100 mg/kg of gluten. In addition, the information “suitable for people intolerant to gluten” or “suitable for coeliacs” can be added to these statements. Furthermore, the statement “specifically formulated for people intolerant to gluten” or “specifically formulated for coeliacs” can be included if the food has been specially processed to reduce the gluten content of an ingredient or if a gluten-containing ingredient has been replaced. In accordance with Article 7(c) of Regulation (EU) No. 1169/2011, the claims specified in Commission Implementing Regulation (EU) No. 828/2014 must not be misleading by suggesting that the food has special characteristics, whereas all similar foods also have these characteristics (e.g. the declaration of the absence of gluten when all similar foods are also gluten-free) [56,60].

In the Annex to the excipients guideline, only **wheat starch** and no other excipients containing gluten are listed. The statement for the package leaflet on wheat starch contained in a medicinal product has been prepared in accordance with Commission Implementing Regulation (EU) No. 828/2014 in order to provide uniform information and to facilitate user understanding. However, while the statements on gluten in foods can be provided on a voluntary basis, the statement for the package leaflet is mandatory [22,60,63]. For medicinal products containing wheat starch with a gluten content of less than 100 ppm (equivalent to 100 mg/kg), the package leaflet states that the medicine contains only very low levels of gluten. If the gluten content is below 20 ppm (equivalent to 20 mg/kg), the medicinal product is declared as gluten-free. In addition, the amount of gluten per dosage unit is provided, while food information does usually not contain information about the exact amount of gluten. Moreover, the wording in the package leaflet is more cautious than food information by stating that the medicinal product “is very unlikely to cause problems if you have coeliac disease” instead of “suitable for people intolerant to gluten” or “suitable for coeliacs”. Furthermore, a statement referring to wheat allergy, where sometimes even trace amounts of wheat must be avoided, must be given in the package leaflet [22,60,65]. The statements listed in the Annex to the excipients guideline may only be included in the package leaflet if the medicinal product contains wheat starch as an excipient. This prevents the misuse of the statement “gluten-free” for advertising purposes in cases where the medicinal product does not contain gluten-containing excipients [66].

While Annex II to Regulation (EU) No. 1169/2011 includes **peanuts, soybeans, sesame seeds** and all products made from them (with some exceptions), the Annex to the excipients guideline specifically refers to **peanut oil, soya oil, hydrogenated soya oil, and sesame oil**. These excipients must be declared as excipients with a known effect for all medicinal products in which they are contained regardless of the route of administration and the quantity (threshold of zero). The package leaflet must contain specific statements indicating that the medicinal product should not be taken in case of an allergy to peanut or soya, with

reference to the cross-reactivity between peanuts and soya. In the case of sesame oil, the package leaflet must indicate that severe allergic reactions may occur. According to Regulation (EU) No. 1169/2011, some products made from soybeans are considered non-allergenic, for example, fully refined soybean oil and fat. In contrast, the Annex to the excipients guideline generally refers to soya oil and does not exclude specifically processed oils [22,56]. Soya protein as well as peanut protein can cause potentially life-threatening allergic reactions. The protein content of soya or peanut products is process-related and the results for allergenic activity of refined oils can be considered contradictory [67,68].

Both Annex II to Regulation (EU) No. 1169/2011 and the Annex to the excipients guideline include **sulphur dioxide and sulphites** [22,56]. Sulphites can occur naturally in food after fermentation or they are used as food additives, which are added as preservatives, antioxidants or colourants. So far, the mechanism of sulphite sensitivity is unclear and IgE-mediated reactions, a sulphite-induced cholinergic response and a defect of the enzyme sulphite oxidase, which is responsible for the degradation of sulphites, have been discussed. Most reactions to sulphites are characterised by bronchospasms; however, other symptoms such as bradycardia, flushing, gastrointestinal symptoms, urticaria, angioedema and hypotension were also reported [67]. In the case of food, sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/litre total sulphur dioxide must be declared in accordance with the regulations on the labelling of ingredients causing allergic or intolerance reactions. In contrast, for all oral, parenteral and inhaled medicinal products, sulphur dioxide and sulphites must be indicated as excipients with a known effect irrespective of the quantity. The package leaflet must contain a statement indicating that the medicinal product may cause severe hypersensitivity reactions and bronchospasms [22].

Annex II to Regulation (EU) No. 1169/2011 lists **milk** and milk-based products including lactose, while lactitol is excluded and considered non-allergenic [56]. In contrast, the Annex to the excipients guideline lists **lactose and lactitol**, which must be declared as excipients with known effects for oral medicinal products, regardless of the quantity contained. The Annex to the excipients guideline does not refer to milk allergy and instead contains statements for the package leaflet that ask users to contact their doctor if they have been informed of an intolerance to some sugars. The amount of lactose per dose must be stated in the package leaflet from a threshold of 5 g, whereby this statement does not refer to sugar intolerance but to diabetes mellitus. In the case of lactose, the SmPC should indicate that the medicinal product should not be taken by patients with hereditary galactose intolerance, total lactase deficiency (lactose intolerance) or glucose-galactose malabsorption. Meanwhile, in the case of lactitol, the SmPC should state that patients with hereditary fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take the medicinal product [22]. A draft scientific document to

update the information on lactose in the Annex to the excipients guideline is available on the EMA website. Since lactose of bovine origin may contain traces of cow's milk proteins, which can lead to severe allergic reactions in patients with cow's milk allergy, a statement to this effect is proposed for the package leaflet of oral, inhaled and parenteral medicinal products. In addition, the amount of lactose per dosage unit should be stated in the package leaflet of all lactose-containing medicinal products, regardless of the route of administration and the quantity of lactose ingested. Furthermore, the statement on sugar intolerance is refined by reference to the specific types of carbohydrate intolerance, taking into account oral and inhaled medicinal products. In addition, separate statements for patients with lactose intolerance are proposed, which vary depending on the amount of lactose contained in a medicinal product. Overall, this would provide patients with more comprehensive information so that they could decide whether to take a medicinal product according to their degree of hypersensitivity and further daily lactose intake. However, up to now it is unclear when the draft document will be finalised [69]. Meanwhile, specific claims on the absence or presence of lactose in foods are only laid down for infant formulae and follow-on formulae by delegated Regulation (EU) 2016/127 [61].

Intolerance to **carbohydrates** is the most common type of non-immunological adverse food reactions. Carbohydrate intolerance is primarily based on enzymatic defects, transporter defects or an overload of transport systems. For example, lactose intolerance is based on reduced or no activity of the lactase enzyme in the intestine, which is responsible for the hydrolysis of lactose into its components glucose and galactose, which are absorbed. Meanwhile, lactose malabsorption can be the consequence of other diseases which damage the intestinal epithelium (e.g. coeliac disease). Fructose malabsorption is caused by dose-dependent transporter overloading, while hereditary fructose intolerance is due to a lack of the enzyme aldolase B, which leads to incomplete fructose degradation in the liver, kidneys and intestine. As another example, glucose-galactose malabsorption results from a defect in a gene encoding a transporter that transfers glucose and galactose out of the intestinal lumen. Meanwhile, galactosaemia is characterised by enzymatic defects in galactose metabolism. Overall, non-absorbed carbohydrates cause an osmotic gradient that leads to an influx of fluids into the intestine, which results in diarrhoea. Further symptoms of carbohydrate intolerance are, for example, bloating, flatulence, nausea, abdominal pain, vertigo and headache. Patients suffering from carbohydrate intolerances must follow a restricted diet that takes into account all types of carbohydrates relevant to the affected metabolic pathway [3,69].

The Annex to the excipients guideline includes several excipients that are relevant to carbohydrate intolerances, namely:

- Fructose
- Galactose
- Glucose
- Invert sugar
- Lactitol (E 966) (see also Table 3)
- Lactose (see also Table 3)
- Maltitol (E 965)
- Isomalt (E 953)
- Maltitol liquid
- Mannitol (E 421)
- Sorbitol (E 420)
- Sucrose
- Xylitol (E 967)

As with all other excipients included in the Annex to the excipients guideline, the substances listed above must be indicated on the outer packaging of a medicinal product in which they are contained and the quantity must be stated in the SmPC. For most of them, the package leaflet of oral and sometimes parenteral medicinal products must include a warning about specific carbohydrate intolerances or a general warning about an intolerance to sugars. In most cases, the amount per dosage unit must also be stated in the package leaflet. However, sometimes the specific information is only required above a certain threshold of the excipient and is therefore not mandatory for all medicinal products containing any of the above-mentioned excipients. For fructose and sorbitol, the quantity per dosage unit must be stated for all oral and parenteral medicinal products (threshold of zero), whereas the warning about fructose intolerance is only required from a threshold of 5 mg/kg/day (with the exception of the intravenous route of application, for which a threshold of zero applies). In contrast, all the other excipients listed above, with the exception of mannitol and xylitol, require a warning of sugar intolerance from a threshold of zero. The specific quantity, if required at all, is only indicated in the package leaflet if a certain threshold is exceeded and this information refers to diabetes mellitus. For mannitol and xylitol, neither information on the amount nor a warning regarding intolerances is required and a threshold of 10 g must be exceeded for the two substances to be listed in the product information as excipient with a known effect [19,22].

Unlike the Annex to the excipients guideline, Annex II to Regulation (EU) No. 1169/2011 does not contain most of the substances relevant to carbohydrate intolerances [22,56]. Annex II is supported by a scientific opinion of the EFSA from 2014, which focused on IgE- and non-IgE-mediated food allergies, coeliac disease and on adverse reactions to sulphites in food, but did not address non-immune-mediated adverse reactions to food [67]. The carbohydrate fructose was the subject of a scientific opinion from the EFSA in 2005, but it was not included in the Annex [70]. Therefore, carbohydrates associated with intolerances and added to a food are not declared in the same way as allergens, except for lactose, which is listed in Annex II. On prepacked food, a notice stating that the food contains sweeteners and added sugars must accompany the name of the food. Furthermore, a nutrition declaration indicating the amount of carbohydrates and sugars must be provided. However, the amount is not given for the different types of carbohydrates. Therefore, the amount stated in the nutrition declaration is only a rough guide for patients suffering from carbohydrate intolerance. The specific types of carbohydrates added to a food can only be found in the list of ingredients, if available [56].

Regulation (EC) No. 1924/2006 allows the voluntary claims “low sugar”, “sugars-free” and “with no added sugars” to be made for foods that meet certain criteria [71]. Meanwhile, a draft recommendation of the EMA's QRD working group for centrally authorised non-prescription medicines also proposes to allow the information "sugar-free" on the packaging of medicinal products. However, other statements about the absence of excipients should be prohibited. In addition, a warning on the packaging on relevant formulation changes is proposed, such as the warning that a new excipient with known effects has been added [37]. So far, the declaration of the absence of excipients is not explicitly prohibited at EU level, but declarations must generally comply with the current rules on the advertising of medicinal products in the Member States [30].

The Annex to the excipients guideline also lists several food additives which are used as pharmaceutical excipients and which may cause an allergic reaction or other symptoms of intolerance after ingestion. These food additives are, for example, aspartame (E 951), azo colouring agents, benzyl alcohol (E 1519) and parahydroxybenzoates and their esters, for which specific statements on allergic reactions or intolerances must be given in the package leaflet from a threshold of zero [22]. Meanwhile, the EFSA decided in 2010 that there is no need to include azo colours in the Annex of substances and products relevant to allergies and intolerances. This decision took into account the maximum permitted levels for the use of these food additives, which are now laid down in Regulation (EC) No. 1333/2008 [45,72]. Thus, although the Annex to the excipients guideline does not cover the entire scope of Annex II to Regulation (EU) No 1169/2011, it does include a number of other substances

which are not listed in Annex II but which are important for people suffering from food intolerances or allergies.

3.3 The Australian approach for the labelling of excipients relevant to food allergies and intolerances

The Australian approach for the labelling of excipients related to food allergies and intolerances is outlined below, as this approach combines both elements of food ingredient labelling in the EU and elements of excipient labelling in the EU. Ideas for harmonising the labelling of food ingredients and pharmaceutical excipients in the EU can therefore be derived from the Australian approach.

Similar to Europe, most medicinal products in Australia are not required to list all their excipients on the outer packaging. In 2016, Australia introduced new labelling rules with a four-year transitional period, which ended on 31 August 2020. Under the new labelling rules, more allergens must be indicated on the packaging of medicinal products to inform users. The new labelling rules are laid down in Therapeutic Goods Order (TGO) No. 91 “Standard for labels of prescription and related medicines” and TGO No. 92 “Standard for labels of non-prescription medicines”. Two different orders have been prepared to better consider the different risk levels of prescription and non-prescription medicines [73,74]. Paragraph 8(1)(j) of TGO 91 and TGO 92 stipulates that excipients listed in Schedule 1 of the TGOs must be indicated on the packaging of medicinal products in which they are contained. In addition, Schedule 1 defines the circumstances (e.g. concentration or amount of the excipient) and the route(s) of administration for which the listed excipients must be declared on the packaging. Furthermore, Schedule 1 specifies the name which must be used to refer to the excipient on the packaging and, where appropriate, additional statements. Usually, an excipient must be presented on the packaging in the form “Contains ‘name as specified in Schedule 1’”. Where several excipients have to be stated, simple sentences can be used for the declaration [75,76]. For prescription medicines, the indication of relevant excipients on the packaging may be omitted if a notice on the packaging asks patients to read the Consumer Medicine Information (CMI) leaflet for information on excipients [74,75]. Meanwhile, for most over-the-counter medicines, information on allergens must be provided in the critical health information, which is presented in a tabular form on the outer packaging. Information on allergens can be found there under the heading "Warnings" [74,76].

The Australian Product Information (PI) corresponds to the EU’s SmPC, while the Australian CMI corresponds to the package leaflet. The PI is prepared for prescription medicines, some non-prescription medicines and some biologicals. It has been aligned with the format of the EU’s SmPC. However, in section “2 Qualitative and quantitative composition”,

excipients with known effects only have to be indicated qualitatively and, unlike in the EU, the quantity of these excipients does not have to be stated. Within the PI, the excipients listed in Schedule 1 of TGO 91 and TGO 92 are considered as excipients with known effects [77–79]. The CMI must be consistent with the PI of a medicinal product. There are separate templates for the CMI for prescription medicines and non-prescription medicines. The first page of the CMI provides users with the most critical information about their medicinal product and includes a warning against taking the medicinal product in case of an allergy to any of the excipients. However, for non-prescription medicines, the first page is optional. Although the structure is different, the content of the CMI is similar to the EU package leaflet. The warning section of the CMI warns users to take the medicinal product if they are allergic to any of the excipients listed at the end of the CMI and asks them to check the excipients before using the medicinal product. At the end of the CMI, all excipients are listed with a separate section for potential allergens [80].

Remarkably, the name used for an excipient must be approved by the Australian Therapeutic Goods Administration. This is to ensure that the same name is always used for a particular excipient and that excipient names are clear and unambiguous and comply with international conventions [81] .

Overall, Schedule 1 of TGO 91 and TGO 92 lists 29 substances and groups of substances. Sometimes residues are also included [75,76]. An extract from Schedule 1 is shown in Table 4 below. The extract is non-exhaustive with a compressed structure and is only intended to illustrate the Australian principle of labelling allergens.

Table 4: Extract from Schedule 1 of TGO 91 and TGO 92 on substances or groups of substances present in medicines that are required to be declared on the label of medicines [74–76].

Substance name or group of substances name	Circumstances and requirements, route of administration, and name for the packaging
Crustacea and crustacean products* (e.g. crab, lobster, white shrimp)	Circumstances and additional requirements: - Route of administration: All Name to be indicated on the packaging: crustacea, or crustacean products
Egg, egg products*, and products manufactured in eggs (e.g. dried egg yolk, egg lecithin, influenza vaccine)	Circumstances and additional requirements: - Route of administration: All Name to be indicated on the packaging: egg, or egg products, or manufactured in eggs
Fish and fish products* (e.g. cod, cod liver oil, halibut, tuna)	Circumstances and additional requirements: - Route of administration: All Name to be indicated on the packaging: fish, or fish products

Substance name or group of substances name	Circumstances and requirements, route of administration, and name for the packaging
Galactose	Circumstances and additional requirements: - Route of administration: Oral Name to be indicated on the packaging: galactose
Gluten or ingredient derived from gluten-containing grain* (e.g. wheat starch)	Circumstance: Where gluten is present in a concentration of 20 ppm or more. Route of administration: All, except skin and mucous membrane applications Name to be indicated on the packaging: gluten
Lactose Note: Lactose, where obtained from milk, does not require the "contains milk product" statement.	Circumstances and additional requirements: - Route of administration: Oral Name to be indicated on the packaging: lactose
Milk and milk products* (e.g. casein, hydrolysed milk protein, non-fat dry milk, whey powder, whole dry milk)	Circumstances and additional requirements: - Route of administration: All Name to be indicated on the packaging: milk, or milk products
Peanuts and peanut products* (e.g. *Arachis hypogaea*, arachis (peanut) oil)	Circumstances and additional requirements: - Route of administration: All Name to be indicated on the packaging: peanuts, peanut products
Saccharin (e.g. saccharin calcium, saccharin sodium)	Circumstances and additional requirements: - Route of administration: Oral Name to be indicated on the packaging: saccharin
Sesame seeds and sesame seed products* (e.g. sesame seed, sesame oil, *Sesamum indicum*)	Circumstances and additional requirements: - Route of administration: All Name to be indicated on the packaging: sesame seeds, or sesame seed products
Soybeans and soybean products* (e.g. *Glycine max,* soybean, soya oil) excluding: - soya oil that is fully refined - d-alpha tocopherol, d-alpha tocopheryl acetate, d-alpha tocopheryl acid succinate, mixed (high-alpha type) tocopherols concentrate, or mixed (low-alpha type) tocopherols concentrate when derived from soybean sources - vegetable oils derived phytosterols and phytosterol esters from soybean sources - plant stanol ester produced from vegetable oil sterols from soybean sources	Circumstances and additional requirements: - Route of administration: All Name to be indicated on the packaging: soybeans, or soybean products

Substance name or group of substances name	Circumstances and requirements, route of administration, and name for the packaging
Sucralose	Circumstances and additional requirements: - Route of administration: Oral Name to be included on the label: sucralose
Sugar alcohols (e.g. erythritol, isomalt, lactitol, maltitol, mannitol, polydextrose, sorbitol, xylitol)	Circumstance: Where the total sugar alcohol content of the formulation exceeds 2 g per maximum recommended daily dose. Requirement: To declare on the label the quantity of sugar alcohols present per recommended maximum daily dose; and a statement 'Products containing (name of sugar alcohol) may have a laxative effect or cause diarrhoea'. Route of administration: Oral Name to be included on the label: sugar alcohols, or name of sugar alcohol
Sugars – monosaccharides and disaccharides (e.g. fructose, glucose, honey (as a mixture of sugars), invert sugar, lactose, maltose, sucrose)	Circumstance: Where the presence of sugars may have a significant glycaemic effect and the total sugar content (including lactose which requires a separate declaration) exceeds 100 mg per recommended daily dose. Route of administration: Oral Name to be included on the label: sugars
Sulphites* (e.g. potassium metabisulphite, sodium bisulphite, sodium metabisulphite, sodium sulphite, sulphur dioxide) Note: If a medicine may contain sulphur dioxide as a residue, for example, gelatine, it must be identified on the label.	Circumstances and additional requirements: - Route of administration: All Name to be included on the label: sulphites
Tree nuts and tree nut products* (e.g. almond oil, *Juglans nigra*, macadamia nut oil, *Macadamia ternifolia*, *Prunus dulcis*, walnut)	Circumstances and additional requirements: - Route of administration: All Name to be included on the label: tree nuts, or tree nut products

* This type of category is also included in Annex II to Regulation (EU) No. 1169/2011 on food information.

Like the Annex to the excipients guideline of the European Commission, Schedule 1 of TGO 91 and TGO 92 restricts the declaration of listed excipients to certain routes of administration and thresholds of the excipient. If an excipient must always be declared, irrespective of a certain threshold, Schedule 1 does not specify any circumstances for the declaration and leaves the field empty. Meanwhile, the Annex to the excipients guideline specifies a threshold of zero to state that the information on an excipient must be provided in all cases where the excipient is present in a medicinal product. Schedule 1 lists the substance or group of substances to be declared and, in addition, defines the name that

must appear on the packaging. In contrast, the Annex to the excipients guideline covers both items via the specific name of an excipient that must be used in the product information. The statements specified in Schedule 1, if any, refer to the label on the packaging, while the statements in the Annex to the excipients guideline are explicitly intended for the package leaflet [19,22,75,76].

Both the Annex to the excipients guideline and Schedule 1 of TGO 91 and TGO 92 list specific individual excipients and groups of excipients that must be declared. However, Schedule 1 not only lists chemical groups of substances, but also lists much broader groups of substances that resemble the categories given in Annex II to Regulation (EU) No. 1169/2011 on food information. The groups of substances in Schedule 1 that correspond to certain categories in Annex II are marked in Table 4. In total, Schedule 1 includes ten of the 14 categories listed in Annex II. Here, Schedule 1 and Annex II follow the same principle by listing a basic material and all of its products. According to Article 21(1) of Regulation (EU) No. 1169/2011, relevant food ingredients must be indicated on the packaging with a clear reference to the name of the substance or product as given in Annex II. Meanwhile, in Schedule 1, the names to be used on the packaging are often very general and may be just a category instead of a specific substance name (e.g. “egg products”). In contrast, the excipients guideline of the European Commission requires that the specific name of an excipient with a known effect must be indicated on the packaging. For example, according to Schedule 1, the information "Contains gluten" must be stated on the packaging of medicinal products that contain gluten or other ingredients made from gluten-containing grains, while in the EU only wheat starch containing gluten must be specially declared with its name on the packaging. In addition, Schedule 1 does not define a “gluten-free” statement, as only gluten present in a concentration of 20 ppm or more must be declared [22,56,75,76]. As the broader categories in Schedule 1 cover various substances whose specific names may not be associated by users with the relevant allergen group, the general reference to the substance group ensures users' understanding.

Schedule 1 also includes groups of substances that are relevant to users affected by carbohydrate intolerances. In this case, the generic name “sugars” on the packaging will not help users to identify the carbohydrates relevant to their specific type of intolerance. In addition, sugars and sugar alcohols only have to be indicated on the packaging above a certain threshold of total sugar content or total sugar alcohol content [75,76].

For some groups of substances, Schedule 1 lists individual selected substances separately. For example, lactose is specifically listed in addition to milk and milk products. Lactose must therefore be indicated on the packaging with its specific name, which is similar to the principle of the European Commission’s excipients guideline. However, in this way

information about the source of lactose on the packaging is lost, which is relevant for people who suffer from milk allergy [75,76].

Thus, Schedule 1 of TGO 91 and TGO 92 contains a combination of broader categories covering the scope of Annex II to Regulation (EU) No. 1169/2011, together with specifically listed excipients as in the European Commission's excipients guideline. Therefore, the Australian labelling approach can be used as a basis to develop ideas for harmonising the labelling of excipients and the labelling of food ingredients in the EU, which will be discussed in the next section.

4 Discussion

As the prevalence of food allergies and intolerances appears to be increasing in the population and there is a high level of public interest in this subject [4,11], it is of particular importance that users of a medicinal product are adequately informed about excipients relevant to food allergies and intolerances. Proper labelling of excipients is the only way for a patient affected by food allergies or intolerances and for the responsible healthcare professional to choose the most suitable drug therapy for the individual patient [28]. The declaration of relevant excipients in the product information for medicinal products can help to avoid intolerance reactions in users suffering from food allergies or intolerances. In addition, the provision of transparent information on excipients relevant to food allergies or intolerances prevents affected users from becoming insecure and discontinuing or not starting a drug therapy at all because they are afraid of possible intolerance reactions.

Most people suffering from food allergies or intolerances are probably more familiar with the labelling of food in their daily lives than with the labelling of medicinal products. It could therefore be helpful to align allergen information for medicinal products to a certain extent with food information in order to provide consistent information for both types of products and to reduce confusion for users of medicinal products. However, it must be taken into account that the presentation of a medicinal product must be clearly distinguishable from non-medicinal products such as food [37]. This thesis aimed to compare the labelling of pharmaceutical excipients relevant to food allergies or intolerances with the labelling of corresponding food ingredients in the EU. Below, the outcome of this comparison is discussed with regard to the advantages and disadvantages of the two labelling approaches as well as possible ideas for their harmonisation and improvement of excipient labelling.

4.1 The legal basis of the labelling of food ingredients and excipients relevant to food allergies or intolerances

The labelling of food ingredients related to allergies or intolerances is defined in Regulation (EU) No. 1169/2011 [56], which is directly applicable at national level in the EU Member States. In contrast, Directive 2001/83/EC, which lays down the rules for the labelling of medicinal products and forms the basis of the excipients guideline [30], must be transposed into the national legislation of the Member States. Thereby, minor modifications and supplemental provisions may be introduced at national level. This also applies to the implementation of the excipients guideline and its Annex as demonstrated by the example of Germany and Austria. While the Austrian ordinances refer exclusively to the excipients guideline without national amendments [52–54], Germany has drawn up the list of special

information required for specific excipients which constitutes the national implementation of the Annex to the excipients guideline. Although this national list is based on the Annex to the excipients guideline, the wording sometimes differs slightly and additional information has been added. Moreover, additional excipients not listed in the Annex are included [49]. These differences can be explained by the history of both compilations. The German list of special information required for specific excipients already existed before the adoption of the original version of the excipients guideline in 2003. The German list was based on national provisions such as the AMWarnV, German graduate plan decisions and court decisions. These provisions remained applicable after the publication of the excipients guideline, so that the excipients guideline has been implemented in Germany with national supplements. Not all the excipients included in the German list have been included in the excipients guideline, and the German list therefore contains additional excipients [82,83].

Thus, the labelling of excipients related to food allergies or intolerances varies slightly in the different Member States and national provisions must be considered. This leads to an increased regulatory effort during preparation of the product information. On the one hand, a uniform application of the Annex to the excipients guideline similar to the application of Annex II to Regulation (EU) No. 1169/2011 would be preferable, as citizens could rely on identical information on excipients in all EU Member States. The declaration of an additional excipient not included in the excipients guideline could lead to confusion and adverse events if citizens who are used to the declaration of this excipient buy medicinal products in another Member State where this excipient is not explicitly mentioned on the packaging. This is especially important for non-prescription medicines where there may be no interaction with a pharmacist [37]. On the other hand, a certain degree of flexibility at the national level of Member States can help to ensure that excipients are declared as clearly as possible for the respective citizens. The wording of the texts for the package leaflet may be adapted by the Member States and supplemented with additional explanations. In addition to the official name of an excipient, the name most commonly used in a country for that excipient may also be requested. Furthermore, Member States may define additional excipients with a known effect, as the prevalence and awareness of certain allergies and intolerances may vary from one Member State to another [10]. Meanwhile, in Annex II to Regulation (EU) No. 1169/2011 neither texts nor the specific name to be used for the declaration of a food ingredient are specified. Instead, only broad categories of substances and products causing allergic or intolerance reactions are defined [56]. Therefore, national flexibility seems to be less important for the implementation of Annex II.

4.2 Differences in the nomenclature of excipients and food ingredients

Overall, the rules on the designation of pharmaceutical excipients are much more specific than the rules on the nomenclature of food ingredients. The excipients guideline defines different types of names that can be used for an excipient in the product information, whereby these types of names should be used with different priority. The preferred order for selecting an excipient name is as follows: INN or INNM accompanied by the salt if relevant, or the European Pharmacopoeia name, the usual common name, and the chemical name. In addition, chemical modifications of an excipient must be indicated. Thus, the usual common name should be used only where no INN or INNM or European Pharmacopoeia name exist for an excipient [19,26]. However, in the information on the packaging and the package leaflet, it would be preferable to use the name of an excipient which is best understood by the users of a medicinal product. The BfArM website already states that the official name of an excipient may be followed by its trivial name to ensure patient understanding [49]. This will provide both appropriate information for healthcare professionals, who can interpret the more specific names of an excipient, and comprehensible information for the average user of a medicinal product. In contrast, food ingredients should be stated by their specific name, which is not further specified in Regulation (EU) No. 1169/2011. Where applicable, the rules on the designation of food laid down in Article 17 should be applied to food ingredients, which means the legal name or, failing that, the customary name, or a descriptive name. Article 7(2) of the Regulation stipulates that food information must be easily understood by the consumer and it can be assumed that this also applies to the name of food ingredients. In a few cases, the specific name of an ingredient can be replaced by the category of the food, unless the ingredient is related to allergies or intolerances [56]. In this way, information on the ingredients contained in a food is disguised and consumers do not receive transparent information on all ingredients. Furthermore, for both foods and medicinal products, flavours and fragrances can be declared in general terms [19,56], which also leads to non-transparent information.

The name of pharmaceutical excipients listed in the Annex to the excipients guideline must be accompanied by the E number, if available. The E number alone can be indicated on the packaging provided that the full name together with the E number appears in the package leaflet [19]. Meanwhile, food additives and food enzymes present in food must be indicated by their functional class together with their specific name or E number, which are defined for food additives in Regulation (EC) No. 1333/2008 [45,56]. Thus, different information is provided for medicinal products and foods. While the product information for medicinal products must always include the full name and the E number of a food additive, foods may

only show the E number together with the functional class. For some food additives (e.g. common sweeteners such as aspartame or sorbitol), the full name is probably clearer to users than the E number, especially if a user has to consider a combination of food additives in his diet and would need to remember several numbers. It is therefore reasonable to always state the full name of a food additive in the product information for medicinal products. Additionally, it should be reconsidered whether the E number alone on the packaging of a medicinal product is sufficient as information for users.

In the case of medicinal products, abbreviations or Latin names of an excipient may be given on the packaging for reasons of space, provided that the full name appears in the SmPC and package leaflet [19]. By comparison, Regulation (EU) No. 1169/2011 does not allow the use of abbreviations or Latin names [56]. Abbreviations and Latin names may not be understood by users. For this reason, consideration should be given to whether the use of abbreviations and Latin names should be prohibited - particularly for non-prescription medicines, where users may purchase the product solely on the basis of the information on the packaging [37].

4.3 Differences in the labelling of components relevant to food allergies or intolerances and possible approaches for harmonisation

The declaration of ingredients or excipients that are relevant to food allergies and intolerances is mandatory for both foods and medicinal products [19,22,30,56]. The special case of homeopathic medicinal products referred to in Article 14(1) of Directive 2001/83/EC, for which this information is not required under EU law [30], is not the focus of this chapter and is discussed in Chapter 4.5.

For medicinal products, information on excipients with a known effect is provided in the SmPC, the package leaflet and on the packaging. In SmPC section 2, excipients with a known effect must be specified qualitatively and quantitatively. Furthermore, these excipients are repeated qualitatively in SmPC section 6 together with all other excipients contained in the medicinal product. In addition, specific information on contraindications, risks and undesirable effects associated with excipients with a known effect is given in the SmPC. The information in the package leaflet is analogous to the information in the SmPC. However, the package leaflet does not include standard information on the quantity of an excipient with a known effect. The package leaflet provides information on the quantity of excipients only in individual cases, as specified in the Annex to the excipients guideline [22,26,30,33,34]. In all other cases, users must therefore ask their healthcare professionals (e.g. their doctor or pharmacist), who have access to the SmPC, for information on the

quantity of an excipient with a known effect. This information can be useful for users to plan their daily intake of substances that they cannot tolerate above a certain amount, considering the additional intake from their daily diet and other medication. However, in the case of allergies, where unpredictable, severe allergic reactions can be triggered even by trace amounts of the respective substance [5], the information on the quantity of an excipient is of no additional value. As some users will not be able to interpret the given amounts of an excipient correctly, it makes sense to discuss them with a healthcare professional.

On the outer packaging of a medicinal product, excipients with a known effect are listed qualitatively together with a note that directs users to the package leaflet for further information [19,30]. Similarly, the packaging of prepacked foods or a label attached thereto must also contain qualitative information on ingredients that cause allergic or intolerance reactions. This is the only information about ingredients related to allergies or intolerances that is provided for food and usually there is no additional information for food as provided in the SmPC and package leaflet. In the case of non-prepacked food, the way in which information on ingredients associated with allergies or intolerances is provided may be determined at national level in each Member State, whereby even verbal communication is allowed [56,58]. Thus, in some cases, consumers have to actively ask for information on allergens when they buy non-prepacked food. However, some consumers may feel uncomfortable asking for information about allergens in public. In addition, verbal miscommunication can occur if the staff is not sufficiently trained in allergen information. It should therefore be reconsidered whether verbal provision of allergen information is sufficient. In contrast, for medicinal products, qualitative information on excipients with a known effect is always provided in a written form, and users of a medicinal product may request additional information from healthcare professionals.

Where a list of ingredients is displayed on prepacked food, ingredients related to allergies or intolerances must be highlighted in that list [56]. In this way, consumers can easily identify ingredients which cause allergic or intolerance reactions among the other ingredients. So far, there is no similar provision for the product information for medicinal products, and excipients that have a known effect do not need to be visually highlighted in the list of excipients. However, excipients with a known effect are emphasised by including them in SmPC section 2, and specific information texts in the SmPC and package leaflet [19,22,26,33,34] also draw the attention of healthcare professionals and users to excipients with a known effect. Nevertheless, as users of a medicinal product may not read the entire package leaflet, it may be helpful to visually highlight excipients with a known effect in the list of excipients in section 6 of the package leaflet, for example, by using bold print. This could also be applied to the list of excipients on the packaging of parenteral, topical and ocular medicinal products. Visual highlighting would help users suffering from food allergies

or intolerances to identify relevant excipients and they would already be familiar with this type of highlighting through the process of selecting appropriate foods in their daily lives.

The Annex to the excipients guideline lists both individual substances and chemical groups of substances [19,22]. In contrast, Annex II to Regulation (EU) No. 1169/2011 defines broad categories of substances and products triggering allergic or intolerance reactions, which cover a basic material and all products derived from it. Exceptions are specified for some of these categories, as some products of the basic material lose their allergenicity during processing. Overall, Annex II includes the 14 main categories of food components causing allergic and intolerance reactions [56]. As the Annex to the excipients guideline is more specific, it only contains single substances from these 14 main categories and some of the categories are completely omitted, such as the category of crustaceans, eggs, fish, nuts, celery, mustard, lupin and molluscs. Instead, the Annex to the excipients guideline contains other substances, such as carbohydrates or food additives, which are related to frequent food intolerances but are not included in Annex II to Regulation (EU) No. 1169/2011 [22,56]. Thus, certain components in medicinal products are declared as substances related to allergies or intolerances, whereas they do not have to be declared as such for food and vice versa.

In order to provide more consistent information, the Annex to the excipients guideline could be aligned with Annex II to Regulation (EU) No. 1169/2011. The statements for the package leaflet of medicinal products containing wheat starch have already been brought into line with food legislation to enhance user understanding [63], and it would therefore be consequential to further align the Annex to the excipients guideline with food legislation. To this end, the relevance of the 14 categories listed in Annex II should be checked for medicinal products, since some of these categories may not be used as excipients in medicinal products. Relevant categories from Annex II could be added to the list of excipients in the Annex to the excipients guideline, while maintaining all excipients currently listed in the Annex. In this way, people who are affected by food allergies or intolerances could rely on the fact that all components that are considered to cause allergic or intolerance reactions for food are also taken into account as such for medicinal products. As a result, the Annex to the excipients guideline would list single excipients and chemical groups of substances with specific information for the package leaflet, as well as the broader categories of Annex II, for which more general information could be specified. This approach is similar to the Australian approach for the labelling of excipients relevant to food allergies and intolerances. In Australia, Schedule 1 of TGO 91 and TGO 92 also lists individual excipients and broad categories of excipients derived from a particular material, resembling the categories in Annex II to Regulation (EU) No. 1169/2011 [75,76].

Table 5 uses the example of eggs and egg products to illustrate how the broader categories of Annex II could be integrated into the Annex to the excipients guideline. For example, egg lecithin is used as an excipient in drug emulsions [17]. In contrast to the single excipients listed in the Annex, no excipient name and package leaflet information can be specified for the broader categories from Annex II, as these must be adapted to the specific excipient falling within this category. Table 5 has been prepared in accordance with the requirements applicable in Australia for the category "eggs and egg products" in Schedule 1 of TGO 91 and TGO 92 [75,76].

Table 5: Exemplary integration of the category "Eggs and products thereof" from Annex II to Regulation (EU) No. 1169/2011 into the Annex to the excipients guideline.

Name	Updated on	Route of Administration	Threshold	Information for the package leaflet	Comments
Eggs and products thereof (The specific name of the excipient must be provided with a clear reference to eggs.)		All	Zero		Appropriate information on the allergenicity of the excipient must be included in the package leaflet.

Regulation (EU) No. 1169/2011 stipulates that food ingredients related to allergies or intolerances must be indicated with a clear reference to the name of the substance or product listed in Annex II [56]. As part of the harmonisation proposed above, a similar rule could be established for excipients falling into one of the broad categories from Annex II. In Australia, only a general description of the substance must be given on the packaging, such as “Contains egg products” [75,76]. However, the European excipients guideline requires that the specific name of an excipient is stated throughout the product information for a medicinal product [19]. The specific name of an excipient could therefore be given together with a reference to the name of the category to ensure that users associate the specific name with the corresponding basic material causing allergic or intolerance reactions (e.g. “Casein derived from milk”). If a specific excipient is listed individually in the Annex to the excipients guideline and also falls under a broad category from Annex II, the broad category may be disregarded and only the specific name as given in the Annex to the excipients guideline and the specific information for the package leaflet should be included in the product information. In this case, the specific name set out in the Annex can be considered to be sufficient to ensure user understanding. This again resembles the Australian approach, where lactose is listed separately in addition to the category "milk and milk

products" and the indication "contains milk products" is not required for lactose, just the specific name [75,76].

It should be noted that synthetic lactose or lactose of bovine origin can be used as an excipient. Lactose of bovine origin may contain traces of cow's milk protein, which must be avoided by users who are allergic to cow's milk [69]. For this reason, it would be useful to indicate the origin of lactose in the product information for medicinal products. The EMA's draft scientific document to update the information on lactose in the Annex to the excipients guideline already considers the origin of lactose by defining a statement on the presence of cow's milk protein. This statement, however, only has to be made if lactose of bovine origin is used as an excipient, whereas in the case of synthetic lactose the origin is not explicitly stated [69]. In order to provide consumers with more transparent information, the origin of lactose could be indicated for both synthetic lactose and cow's milk lactose.

4.4 Differences in the declaration of all ingredients or excipients contained in a food or medicinal product

Annex II to Regulation (EU) No. 1169/2011 includes only the main food ingredients which cause allergic and intolerance reactions. This is in line with Article 4(2) of the Regulation, which states that mandatory food information is justified where there is a need for it among the majority of consumers [56]. Likewise, the Annex to the excipients guideline is not an exhaustive list of excipients with known effects [46] and is only intended to cover the majority of people affected [66]. Rare allergies and intolerances may therefore not be covered by Annex II to Regulation (EU) No. 1169/2011 and the Annex to the excipients guideline. Neither Regulation (EU) No. 1169/2011 nor the excipients guideline require that ingredients or excipients related to allergies or intolerances and which are not listed in the annexes are declared as allergens. Only the EMA's "Guideline on quality aspects included in the product information for vaccines for human use" explicitly states that all excipients used must be assessed to determine whether they have a known effect [46]. Thus, rare allergens may not be covered by the rules on allergen labelling and it is the MAH's own responsibility whether additional excipients are labelled as having a known effect. It is therefore of particular importance for users and consumers suffering from rare allergies or intolerances to receive a complete list of ingredients or a complete list of excipients so that they can identify the substance they cannot tolerate.

In the case of human medicinal products, a list of all excipients contained is provided in section 6.1 of the SmPC and in section 6 of the package leaflet. In addition, the section on contraindications in the SmPC and package leaflet contains a standard reference to hypersensitivity to any of the excipients listed in section 6.1 of the SmPC or section 6 of the

package leaflet. On the outer packaging, a list of excipients is only given for parenteral, topical and ocular medicinal products [26,30,33,34]. For all other medicinal products, the user must therefore read the package leaflet in order to be informed about the complete composition. Remarkably, also the list of excipients on the outer packaging of parenteral, topical and ocular medicinal products may not be exhaustive, since only constituents with a known effect have to be specified for compound excipients on the packaging [19]. No or an incomplete list of excipients on the outer packaging can be particularly problematic for non-prescription medicines, as in some countries there may not be a pharmacist available to answer specific questions at the time of sale [37], and the user would therefore have to open the packaging to read the full composition of the medicinal product. With regard to this scenario, it would be useful to have a complete list of excipients on the packaging.

There are reduced labelling approaches for the immediate packaging of medicinal products without any information on excipients [30]. When the immediate packaging is placed in an appropriately labelled outer packaging containing information on excipients, the immediate packaging is generally less important for informing users about excipients. However, in contrast to the reduced labelling approach for blister packs, Article 55(3) does not explicitly state whether small immediate packaging units with reduced labelling must be placed in an appropriately labelled outer packaging [30]. The author of this thesis is not aware of any case in which a small immediate packaging unit with no information on excipients with a known effect is sold without an outer packaging. This scenario seems implausible as important information to ensure the safe use of the medicinal product would be missing. Nevertheless, this aspect should be clarified in the legal texts.

Although the SmPC and package leaflet of a medicinal product contain a complete list of excipients, there are certain cases where this list does not specify all the constituents of a medicinal product. These cases include authentication factors, which need only be indicated by their specific name if they are excipients with known effects; proprietary flavours and fragrances declared in general terms for which only known major components and excipients with known effects need to be specified; and established media used in the formulation of vaccines whose composition can be roughly summarised and for which only components with known effects must be stated [19,46].

While a list of excipients is included at least in the SmPC and package leaflet of a medicinal product, various types of food are exempted from the obligation of a list of ingredients. For example, EU law does not require a list of ingredients for non-prepacked foods, which constitute a broad category of food. There are also several exemptions for prepacked food where a list of ingredients is not required, such as certain alcoholic beverages and certain types of packaging. Furthermore, in specific cases, certain types of ingredients, such as

food additives, food enzymes, or carriers, need not be included in the list of ingredients. Also with regard to the declaration of compound ingredients, foods need to be labelled less precisely than medicinal products since, in addition to specific cases, ingredients of a food for which no list of ingredients is required do not have to be declared if this food is used as an ingredient for another food [56]. In summary, it can be stated that in many cases no or an incomplete list of ingredients is required for food, while the user of a medicinal product can rely on the fact that a list of excipients is always provided in the product information, and there are only a few well-defined exceptions where not all excipients are specified in this list.

For both medicinal products and foods, it is not necessary to indicate the quantity of each component contained. In this way, the interests of the MAH and the food manufacturer are protected as they do not have to reveal the exact composition of their product to competitors. In the case of food, ingredients are listed in descending order of weight at the time of their use in the manufacture of the food product. This order gives only a rough indication of the quantity of an ingredient. Furthermore, as this order can be ignored for certain ingredients [56], the benefit is limited. The author of this thesis therefore sees no need to introduce such an order for the list of excipients in the product information for medicinal products.

4.5 Homeopathic medicinal products referred to in Article 14(1) of Directive 2001/83/EC – a special case of product information

The product information for homeopathic medicinal products, which comply with Article 14(1) of Directive 2001/83/EC and which are subject to a simplified registration procedure, differs from the product information for other medicinal products. Homeopathic medicinal products referred to in Article 14(1) are administered orally or externally, do not include a specific therapeutic indication in their labelling, and are sufficiently diluted to ensure safety. According to Directive 2001/83/EC, only package labelling is mandatory for this type of homeopathic medicinal product. No SmPC and package leaflet is required unless specified by national legislation in an EU Member State. In addition, a reduced labelling approach applies to the packaging, which contains specific warnings but no further information on excipients [30]. The excipients guideline is not addressed to homeopathic medicinal products authorised under a simplified registration procedure, but the information listed in the Annex may be used if relevant [19]. Thus, there are no provisions at EU level on the labelling of excipients with known effects in homeopathic medicinal products referred to in Article 14(1). This means that the labelling of excipients that cause allergic or intolerance reactions is even less regulated here than in the case of foods for which labelling of

allergens is always mandatory [56]. Remarkably, this type of homeopathic medicinal product often contains excipients with known effects, such as alcohol in homeopathic dilutions, wheat starch and lactose in homeopathic tablets, or sucrose in homeopathic globules. The author of this thesis is not aware of any justification why homeopathic medicinal products should be labelled less precisely than food and the other types of medicinal products. It is therefore proposed to extend the scope of the excipients guideline to homeopathic medicinal products referred to in Article 14(1) in order to provide sufficient information on excipients with known effects and to prevent intolerance reactions. As no SmPC and package leaflet have to be included in the product information, it may even be worth considering the need to include a full list of excipients on the packaging in order to provide transparent information to users.

5 Conclusion and outlook

In this thesis, the EU requirements for the labelling of excipients relevant to food allergies or intolerances were analysed for medicinal products and compared with the EU provisions on food labelling. Thereby, the focus was on general aspects and principles of labelling and not on the scientific assessment of whether a particular substance should be declared as an allergen.

The aim of the work was to identify similarities and differences in the labelling of pharmaceutical excipients and food ingredients relevant to food allergies or intolerances. Based on this, the advantages and disadvantages of the labelling of excipients and food ingredients were discussed as well as possible proposals for aligning the labelling of excipients with the labelling of food ingredients in order to improve excipient labelling and to create more consistent information for users.

The comparison of the labelling of pharmaceutical excipients and food ingredients revealed differences mainly in the national implementation of labelling rules, the way information is provided, the nomenclature, and the completeness and transparency of information on ingredients and excipients. Furthermore, the substances defined as allergens or triggers of intolerance reactions vary between medicinal products and food. Consequently, users of medicinal products cannot rely on the fact that the labelling of excipients is identical to the labelling of food ingredients.

By using Austria and Germany as example, it was shown that the national implementation of the excipients guideline and its Annex varies between the EU Member States. National flexibility allows the Member States to adapt the texts for excipient labelling to the needs of their citizens and to specify further excipients with a known effect. For this reason, Regulatory Affairs Managers must consider national provisions when preparing the information on excipients for a medicinal product. Meanwhile, Annex II to Regulation (EU) No. 1169/2011 is directly applicable at national level and national flexibility seems to be less important as Annex II does not contain any information texts.

Although the nomenclature of excipients is more specific than the nomenclature of food ingredients, care must be taken to ensure that the name of an excipient is understood by users, as the common name of an excipient is not the first priority for the official name of an excipient [19]. In particular, for non-prescription medicines which can be dispensed without the presence of a pharmacist [37], the labelling requirements for the packaging should be reconsidered, as most medicinal products do not require a complete list of excipients on the packaging and the current nomenclature, including abbreviations on the packaging [19], may not be understood by users. Overall, however, information on excipients is much more

reliable than information on food ingredients, as a complete list of excipients is always provided in the SmPC and package leaflet. There are only a few well-defined exceptions where not all excipients are specified in this list [19,30]. In contrast, several types of food have no or an incomplete list of ingredients [56].

While the Annex to the excipients guideline lists specific substances and chemical groups of substances [22], Annex II to Regulation (EU) No. 1169/2011 contains broader categories of food ingredients causing allergic and intolerance reactions that consist of a basic material and products thereof [56]. As a result, the substances listed in the Annex to the excipients guideline and those included in Annex II are not identical. Medicinal products and foods therefore differ in the components which are labelled as allergens or triggers of intolerance reactions. In order to provide more consistent information to users, it is proposed to align the Annex to the excipients guideline with Annex II to Regulation (EU) No. 1169/2011. Relevant categories from Annex II could be integrated into the Annex to the excipients guideline, which would be similar to the Australian approach for labelling of excipients related to allergies or intolerances. Care must be taken to ensure that the origin of excipients, which can be both food-derived and synthetic, is explicitly stated in order to provide transparent information. In addition, it is recommended to extent the scope of the excipients guideline to homeopathic medicinal products referred to in Article 14(1) of Directive 2001/83/EC, for which, so far, no EU provisions on excipient labelling exist. In order to further harmonise allergen labelling of medicinal products and foods, excipients with a known effect could be visually highlighted in the list of excipients, similar to food, in order to make it easier for users to identify relevant allergens.

The next step could be to review the relevance of the categories in Annex II to Regulation (EU) No. 1169/2011 for pharmaceutical excipients. For each category, it is necessary to check whether corresponding excipients are available and whether these excipients are likely to cause allergic or intolerance reactions. Subsequently, relevant categories or single excipients could be integrated into the Annex to the excipients guideline. In addition, the declaration of residues and contaminants relevant to food allergies and intolerances could be investigated for medicinal products and foods. Moreover, the national implementation of the excipients guideline and its Annex in other EU countries could be examined to obtain an overview of national modifications. It could then be checked whether it makes sense to include certain national modifications in the excipients guideline.

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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