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What we learned from TAO – 10 years of German therapy allergen ordinance

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Abstract

Purpose The Therapy Allergen Ordinance (TAO) came into force in Germany in 2008 in order to ensure proven and tested quality, efficacy and safety of therapy allergens for the treatment of allergies to frequent allergen sources (birch, alder, hazel, sweet grasses (without maize), bee-, yellow jacket-venom). It excludes exemptions from marketing authorizations (MA) for AIT-products containing these allergens. Due to the particular nature of the therapeutic allergens, rather long transitional periods are legally defined to resolve deficient clinical data. The aim was to analyze the status quo of AIT products developed according to TAO.

Methods Quality data and clinical trials of AIT products subjected to TAO (obtained until 2019) were analyzed and findings were clustered.

Results The first two AIT products (for tree-pollen allergy) received a national MA in 2018. Of the 123 initial MA applications submitted, 65 are still active (26 for grass-, 17 for tree-, 5 for grass-/tree-pollen-mix and 17 for house dust mite allergy). Quality issues frequently identified were: Lack of comparability of the drug due to extensive changes in the manufacturing process, insufficient/missing stability data or process validation, insufficiently validated analytical

methods, unsuitable in-house reference preparations, inadequate specifications and/or in-process controls. Dose-finding and phase III studies are required for MA. Doses of best benefit/risk balance were recommended for phase III studies. PEI takes measures to ensure that products of presumptive lacking efficacy based on study results do not gain access to the market.

Conclusions In Germany, TAO ensures that all previously untested named patient products for the treatment of frequent allergies are subjected to an assessment of their risk/benefit ratio according to the current state of science.

Keywords Allergen immunotherapy · Quality · Safety · Efficacy · Marketing authorization · Named patient product

Abbreviations

AIT	Allergen immunotherapy
AMG	Arzneimittelgesetz, German Medicinal Products Act
BGBL	Bundesgesetzblatt, Federal Law Gazette
DCP	Decentralized procedure (glossary: The procedure for authorizing medicines in more than one European Union Member State in parallel.)
EC	European Commission
EEC	European Economic Community
EMA	European Medicines Agency
GCP	Good Clinical Practice (glossary: GCP is an international ethical and scientific quality standard for the performance of a clinical trial on medicinal products involving humans.)

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GMP	Good Manufacturing Practice (glossary: GMP is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.)	TAO	Therapy Allergen Ordinance (glossary: With the therapy allergens ordinance which has been in effect in Germany since 14 November 2008, the exemption from marketing authorization was restricted to therapy allergens indicated for the treatment of rare allergies.)
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (glossary: Initiative that brings together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product development and registration. The mission of the ICH is to promote public health by achieving greater harmonization through the development of technical Guidelines and requirements for pharmaceutical product registration.)	TAV	Therapieallergene-Verordnung, Therapy Allergen Ordinance
MA	Marketing authorization (glossary: The approval to market a medicine is based on a Process of reviewing and assessing the dossier to support a medicinal product in view of its suitability for being marketed based on quality, efficacy and safety.)		
MAA	Marketing authorization application		
MRP	Mutual recognition procedure (glossary: A procedure through which an authorization of a medicine in one European Union Member State is recognized by another Member State.)		
NPP	Named patient product (glossary: individually prepared specific allergen product on the market without the requirement of a marketing authorization.)		
PDCO	Pediatric Committee (glossary: European Medicines Agency's scientific committee responsible for activities on medicines for children and to support the development of such medicines in the European Union by providing scientific expertise and defining pediatric needs.)		
PEI	Paul-Ehrlich-Institut (glossary: German Federal Institute for Vaccines and Biomedicines.)		
PIP	Pediatric investigation plan (glossary: A PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorization of a medicine for children. All applications for marketing authorization for new medicines have to include the results of studies as described in an agreed PIP, unless the medicine is exempt because of a deferral or waiver.)		

Introduction

The Therapy Allergen Ordinance (TAO; German: Therapieallergene-Verordnung (TAV); 7. November 2008, BGBl. I S. 2177) came into force in Germany in 2008 and set in motion a process of gaining increasing evidence on the quality, efficacy and safety of therapeutic allergen products previously put on the market as named patient products. Legal background, current status of implementation of the TAO and interim findings are summarized.

Legal and regulatory background

European legal grounds

Allergens have been subject to European law since 1989 (Directive 89/342/EEC). According to the definition in Directive 2001/83/EC, today's Community code relating to medicinal products for human use into which the Directive 89/342/EEC has been incorporated, both test and therapeutic allergens are medicinal products. According to Article 6 of this European Directive, a medicinal product may not be placed on the market in a Member State unless a marketing authorization (MA) has been granted by the competent authority of that Member State (Fig. 1).

German Medicinal Products Act (AMG)

In Germany, the scope of Directive 2001/83/EC is fully transposed into the German Medicinal Products Act (Arzneimittelgesetz—AMG) (Fig. 1). According to Section 21 (1) AMG, finished medicinal products may only be placed on the market in Germany if they have been approved under a MA procedure by the competent authority which for test and therapy allergens is the Paul-Ehrlich-Institut (PEI) located in Langen near Frankfurt (Main). For approval of a MA, it must be proven according to the current state of knowledge that the respective drugs are of appropriate quality and are effective and safe.

Approval of marketing authorization and exemptions

The assessment of the necessary positive benefit/risk balance of therapy allergens for human application is based on applicable national and European legal principles and guidelines of the European Medicines Agency (EMA) as well as further regula-

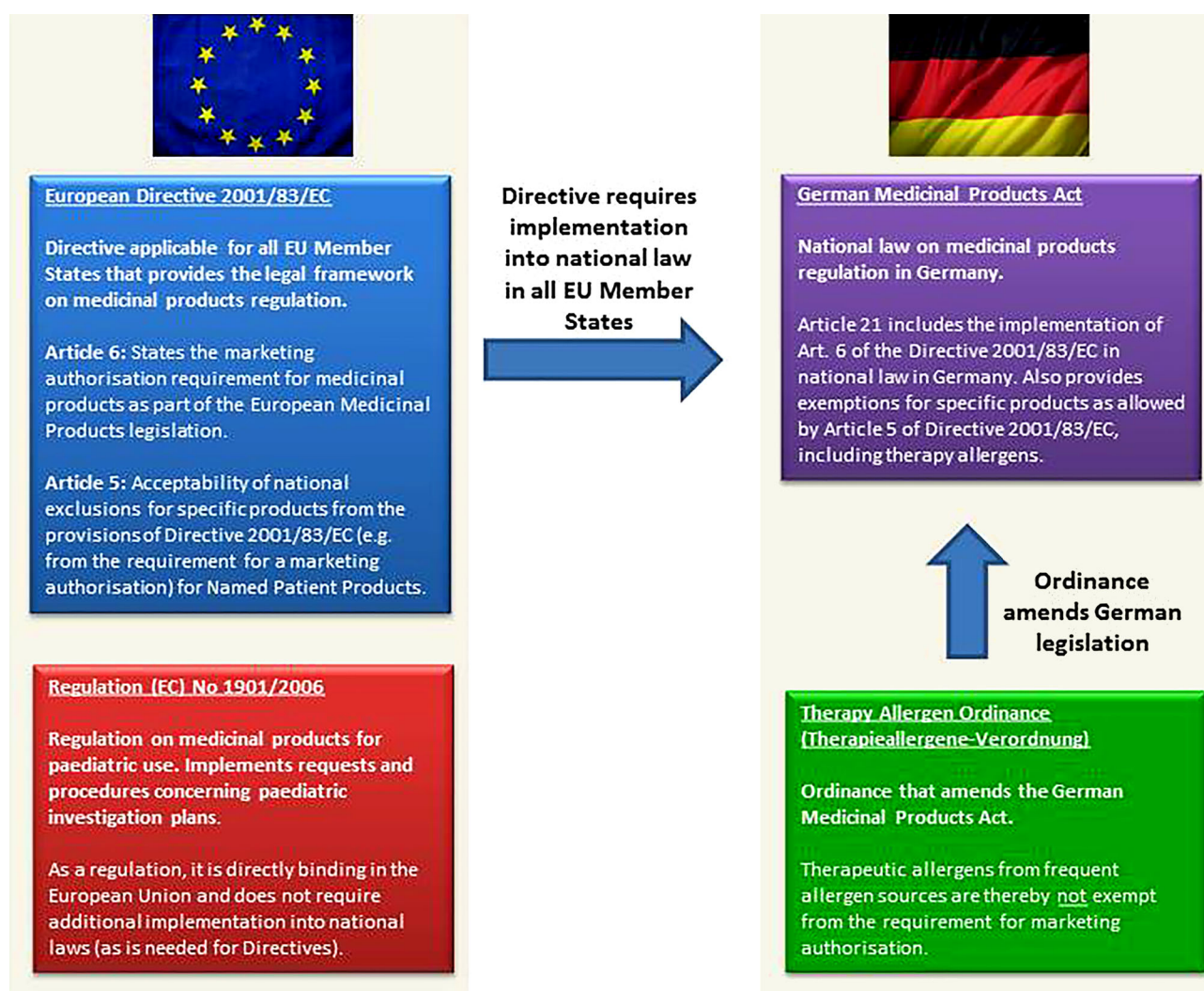


Fig. 1 Fundamental European and national legal principles relevant for the German Therapy Allergen Ordinance (TAO)

tory guidelines (e.g. by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use [ICH]) [1–6]. Authorized medicinal products (www.pei.de/DE/arzneimittel/allergene/allergene-node.html) can be distinguished from “therapeutic allergens manufactured to order for individual patients” by the marketing authorization number (Zul.-Nr.) on the outer packaging and in the package information leaflet/Summary of Product Characteristics (SmPC). The vast majority of therapeutic allergen products with a MA have been approved in Germany based on national approval procedures. A few allergen products have successfully undergone a European Mutual Recognition Procedure (MRP) or Decentralized Procedure (DCP) and received on this basis an identical marketing authorization in each requested Member State.

However, there are exceptions to the above-mentioned authorization requirement according to Article 5 of Directive 2001/83/EC: a Member State may exempt medicinal products from the provisions of this Directive in special cases of need, e.g. for individual

formulations, in accordance with the applicable legal provisions. Also in the German AMG there is an exemption according to Section 21 (2): A marketing authorization shall not be required for medicinal products which [...] 1g; are therapeutic allergens manufactured to order for individual patients.

This exemption is important for the availability of allergen-specific immunotherapies for allergies to rare allergen sources as named patient products (NPPs). However, before the TAO came into force, using this exemption or as the result of the reference to an earlier definition of the term of “finished medicinal product” also therapeutic allergens derived from frequent allergen sources could be placed on the German market as individual formulations (NPPs) without marketing authorization and accordingly without official assessment of the quality, the therapeutic efficacy and benefit/risk balance.

The German Therapy allergen Ordinance (“Therapieallergene-Verordnung”) and area of its application

In order to ensure that the quality, efficacy and safety of therapy allergens for the treatment of allergies to frequent allergen sources is proven and tested, the TAO came into force in Germany on 14 November 2008. The TAO restricts the above mentioned exemption in section 21 (2) AMG concerning patient-specific prepared therapeutic allergens, which are manufactured from prefabricated containers and contain allergens listed in the appendix of the TAO.

It requires, after having previously run through a notification and application procedure, for specific allergen sources a MA procedure in which the evidence for flawless quality, as well as efficacy and safety is reviewed. It applies to all individual formulations for the treatment of allergies to sweet grasses without maize; birch, alder, hazel; house dust mites; bee venom, wasp venom [2]. All therapy products that were on the market in November 2008 and that contained one or more of these allergen sources had to be notified to the PEI by 14 May 2009 and, if an application for MA was planned, the corresponding application had to be submitted to the PEI by 30 November 2010 at the latest [7]. The TAO states that the applicant has the opportunity to correct addressed deficiencies within one year. This period may be extended by up to seven years if necessary to clear out defective clinical data. In practice, therefore, a two-step evaluation of submitted data procedure was decided: on quality preceding evaluation of pre-clinical and clinical data-resulting in two consecutive deficiency letters (one on quality, one on clinical data). After this one-year-response time for the applicant following the deficiency letter the deadline may be extended by the competent authority as described above to resolve deficient clinical data due to the particular nature of the therapeutic allergens. If the deficiencies are not resolved within the specified periods, approval must be declined. Until the decision on the application for MA is made, these products in the transitional period under the TAO are treated in the same way as approved therapy allergen preparations with regard to their prescription and marketability, as well as the official batch release testing, including experimental testing, by PEI. Since October 2009 batch release testing of these individual formulations under the transitional provision of the TAO is mandatory. Batch control is done on the level of the manufactured bulk, while in authorized preparations it is carried out on the end product wherever possible [8].

In contrast, NPPs concerned by TAO for which no MA application had been submitted were only allowed on the market for a transitional period, which expired on 14 November 2011 for these products. Since then, they are no longer marketable in Germany.

By contrast, all therapy allergens produced as individual formulations which do not contain any of the common allergens listed in the Appendix to the TAO are further on exempt from the obligation to obtain a MA. According to the AMG, a manufacturing authorization is required for their production to ensure compliance with the Good Manufacturing Practice (GMP) criteria. They are neither subject to official quality, efficacy and safety assessment nor to official batch release testing.

Reduction of mixtures of uncertain effectiveness

Of 6654 NPPs which were notified to PEI in 2009 to be on the German market containing one or more of the frequent allergens sources subject to the TAO, a MA application was submitted to PEI for 123 products by the due date of 30 November 2010. Products for which no MA application was filed consisted mainly of mixtures of (i) perennial and seasonal allergen sources, (ii) three and more different allergen sources not belonging to homologous groups, (iii) different concentrations of allergen sources with shares of as low as 5%, (iv) allergens belonging to homologous groups in very slightly stratified concentrations (e.g. birch/alder/hazel pollen in 18 different ratios were notified from one company). Most of the mixtures (i–iii) were not in concordance with the state of the art for allergen immunotherapy (AIT) at that time [9], since due to the rather low concentration of the respective single allergen source in such mixtures its effectiveness is doubtful and some of the allergen sources (e.g. house dust mites) contain proteases which might contribute to degradation of other allergen components in these mixtures.

Current list of marketing authorization applications

Licensed products and active marketing authorization applications under the TAO

The first two preparations under the TAV development program received a national MA in August 2018 (both sublingual drops containing natural extracts from birch pollen or, respectively, the mixture of the homologous groups birch/alder/hazel as active substances). Of the 123 initial marketing applications submitted for “TAO products”, 65 are still active (as of 10 April 2019: Table 1). These include 26 applications for AIT products based on extracts from grasses/mixtures of grasses, 17 applications based on extracts of early flowering trees, 17 applications based on extracts of house dust mites and 5 applications based on extracts of mixtures of grasses/tree pollen as active substances. These MA applications under the transitional provision of the TAO are subject to constant progress in development and the corresponding list will be regularly updated on the

Table 1 Marketing authorization applications under the TAO (status: April 2019)

Pharmaceutical company, address
ALK-Abelló Arzneimittel GmbH; Griestr. 75, Haus 25, 22763 Hamburg, Germany
SLITone ULTRA 108 Birke (50 SRU/150 SRU)
SLITone ULTRA 1242 Frühblühermischung (50 SRU/150 SRU)
SLITone ULTRA 1010 Gräsermischung und Roggen (50 SRU/150 SRU)
SLITone ULTRA 510 Milbenmischung (50 SRU/150 SRU)
Allergopharma GmbH & Co. KG; Hermann-Körner-Straße 52, 21465 Reinbek, Germany
Acaroid 708 Dermatophagoides farinae 100% Stärken A und B/Stärke B (1 × 3 ml Stärke B)/Stärke B (2 × 3 ml Stärke B)
Acaroid 725 Dermatophagoides pteronyssinus 100% Stärken A und B/Stärke B (1 × 3 ml Stärke B)/Stärke B (2 × 3 ml Stärke B)
Acaroid 708 Dermatophagoides farinae 50%/725 Dermatophagoides pteronyssinus 50% Stärken A und B/Stärke B (1 × 3 ml Stärke B)/Stärke B (2 × 3 ml Stärke B)
ATL (UK)/BENCARD Allergie GmbH; Leopoldstraße 175, 80992 München, Germany
TyroMILBE (521 TU/ml/4167 TU/ml/33332 TU/ml)
POLLINEX Quattro Gräser/Roggen 50% + Beifuß 50% (300 SU/ml/800 SU/ml/2000 SU/ml)
POLLINEX Quattro Birke 100% (300 SU/ml/800 SU/ml/2000 SU/ml)
POLLINEX Quattro Gräser/Roggen 50% + Birke/Erle/Hasel 50% (300 SU/ml/800 SU/ml/2000 SU/ml)
POLLINEX Quattro Plus/Starter/Booster 1.0 ml Birke/Erle/Hasel 100%
POLLINEX Quattro Gräser/Roggen 100% (300 SU/ml/800 SU/ml/2000 SU/ml)
POLLINEX Quattro Gräser/Roggen 50% + Birke 50% (300 SU/ml/800 SU/ml/2000 SU/ml)
ORALVAC Bäume (7680 TU/ml/76800 TU/ml/768000 TU/ml)
ORALVAC Gräser/Roggen (7680 TU/ml/76800 TU/ml/768000 TU/ml)
ORALVAC Milben (3200 TU/ml/32000 TU/ml/320000 TU/ml)
HAL Allergie GmbH; Poststr. 5–6, 40213 Düsseldorf, Germany
PURETHAL Milbenmischung (20.000 AU eq/ml)
SUBLIVAC FIX Milbenmischung (10.000 AU/ml)
SUBLIVAC FIX Wiesenlieschgras (10.000 AUN/ml)
SUBLIVAC FIX Mischung von Gräserpollen (10.000 AUN/ml)
SUBLIVAC FIX Mischung von Gräserpollen/Roggen (10.000 AUN/ml)
LETI Pharma GmbH; Gutenbergstr. 10, 85237 Ismaning, Germany
Depigoid Birke (100 DPP/ml/1000 DPP/ml)
Depigoid Bäume-Mix (100 DPP/ml/1000 DPP/ml)
Depigoid Lieschgras (100 DPP/ml/1000 DPP/ml)
Depigoid Gräser-Mix (100 DPP/ml/1000 DPP/ml)
Depigoid Gräser-Mix/Roggen 50/50 (100 DPP/ml/1000 DPP/ml)
Depigoid Gräser-Mix/Roggen 75/25 (100 DPP/ml/1000 DPP/ml)
Depigoid Lieschgras/Roggen 50/50 (100 DPP/ml/1000 DPP/ml)
Depigoid Gräser-Mix/Birke 50/50 (100 DPP/ml/1000 DPP/ml)
Depigoid Gräser-Mix/Bäume-Mix 50/50 (100 DPP/ml/1000 DPP/ml)
Depigoid XT Birke (1000 DPP/ml)
Depigoid XT Bäume-Mix (1000 DPP/ml)
Depigoid XT Lieschgras (1000 DPP/ml)
Depigoid XT Gräser-Mix (1000 DPP/ml)
Depigoid XT Gräser-Mix/Roggen 50/50 (1000 DPP/ml)

Table 1 (Continued)

Pharmaceutical company, address
Lofarma SpA; Viale Cassala 40, 20143 Milano, Italy
Lais Frühblüher 300 UA/1000 UA Sublingualtabletten—Einleitungsbehandlung und Fortsetzungsbehandlung
Lais Gräser 300 UA/1000 UA Sublingualtabletten—Einleitungsbehandlung/Fortsetzungsbehandlung
Lais Milben 300 UA/1000 UA Sublingualtabletten—Einleitungsbehandlung/Fortsetzungsbehandlung
Lais Frühblüher 3.000 UA/ml Tropfen zur Anwendung in der Mundhöhle
Lais Gräser 3.000 UA/ml Tropfen zur Anwendung in der Mundhöhle
ROXALL Medizin GmbH; Meessen 20, 22113 Oststeinbek, Germany
ROXOID Birke 10.000 TU/mL
ROXOID Birke/Erle/Hasel 10.000 TU/mL
ROXOID Wiesenlieschgras 10.000 TU/mL
ROXOID Gräser 10.000 TU/mL
ROXOID Gräser/Roggen 10.000 TU/mL
ROXOID Dermatophagoides farinae 10.000 TU/mL
ROXOID Dermatophagoides pteronyssinus 10.000 TU/mL
ROXOID Dermatophagoides pteronyssinus/Dermatophagoides farinae 10.000 TU/mL
CLUSTOID Birke 10.000 TU/mL
CLUSTOID Birke/Erle/Hasel 10.000 TU/mL
CLUSTOID Wiesenlieschgras 10.000 TU/mL
CLUSTOID Gräser 10.000 TU/mL
CLUSTOID Gräser/Roggen 10.000 TU/mL
CLUSTOID Gräser/Birke 10.000 TU/mL
CLUSTOID D. pteronyssinus 10.000 TU/mL
CLUSTOID D. farinae 10.000 TU/mL
CLUSTOID D. pteronyssinus/D. farinae 10.000 TU/mL
SULGEN SPRAY Birke 30.000 TU/mL
SULGEN SPRAY Birke/Erle/Hasel 30.000 TU/mL
SULGEN SPRAY Wiesenlieschgras 30.000 TU/mL
SULGEN SPRAY Gräser 30.000 TU/mL
SULGEN SPRAY Gräser/Roggen 30.000 TU/mL
SULGEN SPRAY D. pteronyssinus 30.000 TU/mL
SULGEN SPRAY D. pteronyssinus/D. farinae 30.000 TU/mL

PEI homepage (<https://www.pei.de/EN/medicinal-products/allergens/allergens-content.html>).

Declined or withdrawn MA applications under the TAO

Of the 56 initial MA applications which have not been further pursued, MA applications were either declined by the competent authority (PEI) or withdrawn by the pharmaceutical company. According to Section 34 (1b) AMG, the withdrawal of an application for authorization as well as the refusal of the marketing authorization and the grounds are to be made publicly accessible. Also, a notification to the EMA is made, including the grounds for rejection of the MA. It is noteworthy to mention that prior to an intended rejection of a MA application the competent authority

(PEI) informs the applicant of the immanent rejection allowing a withdrawal by the applicant instead.

In few cases, the MA was declined: after the deadline to reply to the quality letter of deficiency had expired without response of the applicant ($n=1$) or due to persistent quality issues ($n=1$).

In most cases MA applications were actively withdrawn by the applicants in the context with the following occasions:

- i. Prior to the delivery of the letters of deficiency concerning quality and clinical data (as reasons were put forward, e.g., no placing on the market at present or planned at the time TAO entered into force or economic reasons) ($n=19$).
- ii. The letter of deficiency concerning quality had been delivered to and was not answered by the applicant. The letter of deficiency concerning the clinical data had not yet been delivered at time of withdrawal by the applicant ($n=16$).
- iii. The letter of deficiency concerning quality had been delivered to and had been (partially) answered by the applicant leaving several quality issues unresolved. The letter of deficiency concerning the clinical data had not yet been delivered at time of withdrawal by the applicant ($n=6$).
- iv. Merger of originally separately submitted MA applications ($n=3$).
- v. After delivery of the letter of deficiency concerning clinical data ($n=4$).
- vi. Existing MA in other EU countries, therefore MRP required ($n=6$).

Quality issues

Quality deficiencies must be resolved and are not included in the benefit/risk assessment.

Insufficient quality leads to rejection of the MA application. Frequent quality issues identified in AIT products subject to TAO were the following:

- Lack of comparability of the drug due to extensive changes in the manufacturing process during the clinical development program.
- Insufficient or missing stability data.
- Insufficient or missing process validation.
- Analytical methods not validated or insufficiently validated.
- In-house reference preparations (IHRP) not suitable for ensuring consistent quality and strength of the medicinal product.
- Specifications and/or in-process controls inadequate or not in concordance with applicable requirements.

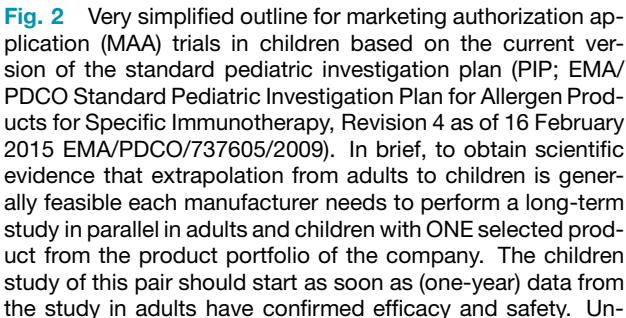
Dose finding and efficacy

Of 45 clinical trial applications with TAO allergens submitted to PEI, 10 were rejected (mostly due to quality deficiencies) and 35 were approved (thereof 7 with requirements, of which 1 was withdrawn).

Until now, 28 studies of the 35 approved trials have been completed (thereof 16 dose-finding studies and 7 phase III studies [as of 1 March 2019]); the remaining studies were performed with products subjected to TAO, but not within the clinical development plan for the marketing authorization application (MAA), e.g. open safety studies, comparisons of up-dosing schemes and proof-of-concept studies. Study reports have to be submitted to PEI within a year after study completion (According to § 13 (9) of the national GCP Ordinance of 9 August 2004 “the sponsor shall within one year from termination of the clinical trial provide the competent federal authority and the competent ethics committee with a summary of the report on the clinical trial which covers all the essential results of the clinical trial.”) The competent authorities in Germany are not authorized to make these reports available to the public. To date, 25 study reports have been submitted to PEI. Results from dose-finding studies as available showed for several of the NPPs subject to TAO that the marketed dose had a positive benefit/risk balance, but was not always the “optimal” dose: For seven products a higher dose showed a better benefit/risk balance, for 9 products the result concerning a superior benefit/risk balance was not unequivocally clear. In cases where a different (i.e. higher dose) than the market dose showed a better benefit/risk balance, this dose was recommended for phase III studies. If no efficacy over placebo is demonstrated in the clinical studies, PEI declines further batch release until the MA can be rejected. This ensures that products of presumptive lacking efficacy based on study results no longer gain access to the market.

Since the transitional periods are granted only gradually for the different phases of clinical development, this means that the marketability of a product already ceases if, for example, the results of the phase II or phase III studies do not provide any indication of possible efficacy. In these cases, the PEI immediately initiates appropriate measures. The same applies in case of a lack of product safety (which to this end has not yet occurred).

AIT products are subjected to regulation (EC) No. 1901/2006 on medicinal products for pediatric use (Fig. 1). This regulation on medicinal products for pediatric use implements and requests procedures to ensure that medicinal products are researched, developed, and authorized to meet the therapeutic needs of children. In concordance with this regulation, all applications for MA for all products subjected to the TAO had to be accompanied by a pediatric investigation plan (PIP) approved by the Pediatric Committee (PDCO) of the EMA. Due to the special vulnerability of the pediatric population, clinical trials in children may not be initiated until one year data on the efficacy and safety of the respective product has been collected in clinical trials with adult patients (Fig. 2). To this point, clinical studies in children have not started with



any of the products under the TAO. There are concerns concerning a lack of availability of authorized therapeutic allergens for the use in children and adolescents, especially for those therapy allergens which will have obtained their MA in adults for a higher dose than previously marketed as NPP. Furthermore, also legal problems are anticipated: as a prerequisite for approval of MA for the treatment of adults (after successful phase III studies in adults) applicants must comply with the approved pediatric investigation plan (PIP). The standard PIP for these products requires long-term studies in adults and children to the same therapy allergen chosen by the applicant. Each applicant has to perform these long-term studies only to one allergen from the company's portfolio. Thereafter, all other study designs as outlined by the Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases [5] are possible. However, none of the required clinical trials in children has yet started. In order to identify obstacles and to remove possible hurdles, a multi-stakeholder meeting was held on

- The clinical development in adults is hugely delayed. As according to current legislation and the standard PIP, pediatric studies should only start after confirmation of short-term efficacy in adults, the start of pediatric trials is also seriously delayed.
- For 6 selected products (i.e. one per manufacturer) long-term studies in adults and children are still needed. Until now no studies in children were/are performed with products being subject to TAO.
- Although the main reason for the delay in initiating pediatric studies is the delay of studies in adults,

manufacturers repeatedly pointed out that the requirements for long-term studies (both in adults and particularly in children) are too high and the requested studies are not feasible for several reasons, including unwillingness or ethical concerns of patients/parents/investigators to enroll children into a 3-year placebo-controlled study with a 2-year blinded follow-up, as well as the high administrative and financial burden of conducting large long-term studies.

- Moreover, the risk of long-term study failure is regarded as too high as there are currently no validated standardized endpoints for children and there is insufficient knowledge regarding patient eligibility criteria.
- Following this comment disappointment was expressed that after so many years of use of AIT in the currently marketed but not authorized way these well-known gaps in knowledge have been not yet been adequately addressed.
- Among clinicians and investigators there was consensus that long-term studies are considered feasible in children with sublingual immunotherapy products (SLIT) but not with subcutaneous immunotherapy (SCIT) products; the requirement for placebo injection for three years within SCIT trials is seen as a too high burden.
- Extrapolation of efficacy data from adults and perform only safety studies in pediatrics is only possible after scientific proof of concept that extrapolation from adults to pediatrics is feasible. This proof may be performed in SLIT products.
- Pediatric study designs and endpoint alternatives to symptom medication scores were discussed (for complete information: see meeting minutes (in preparation)).
- Manufacturers are encouraged
 - to explore the use of exposure chambers and compare results to field results, at least in adults.
 - to seek regulatory qualification advice for new outcome measures and use of exposure chambers.
 - to collaborate among pharmaceutical companies to explore new biomarkers (as endpoint or for prediction/therapy decision), study designs, study networks and others.

It is now primarily the task of the pharmaceutical companies to further develop appropriate proposals in order to meet the requirements of the pediatric investigation plans.

Summary and outlook

Allergen mixtures in NPPs under the TAO with lacking proof of efficacy were reduced. Compilation of clinical

data in concordance with the current state of science allows assessment of the risk/benefit balance during the statutory transitional provision for individual formulations under the TAO. Findings from dose-finding studies show that current individual formulations in many cases show a certain efficacy but not the optimal benefit/risk balance. In these cases, the doses with a better risk/benefit balance were recommended for phase III studies. First marketing authorizations for products with optimized allergen content developed under the TAO were granted in 2018 for two AIT products.

Without regulatory requirements as outlined by the TAO a status *ex ante* concerning treatment of patients with NPPs for frequent allergen sources of lacking benefit/risk assessment has to be assumed.

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Conflict of interest V. Mahler, A. Bonertz, C. Ruoff, D. Hartenstein, D. Mentzer, S. Kaul and S. Vieths declare that they have no competing interests.

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