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Regulatory burden, adequate to Allergen Specific Immunotherapy?

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ABSTRACT

Regulatory burden, adequate to Allergen Specific Immunotherapy?

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Allergies belong to the wide spread disease with an incidence of about 20 %. Worldwide more than 500 million people suffer from those overshooting reactions of the immune system. The only way for a causal treatment against Type I allergies caused by aero allergens is an allergen specific immunotherapy (AIT) which re-educates the immune system and which inures it to the allergens of the environment.

Over the last few years, especially the German regulatory framework for AIT has undergone multiple changes. The therapy allergen ordinance (TAV), the institutional batch release criteria and the implementation of the updated European Pharmacopeia are challenging the AIT manufacturers. In addition, other health care specific developments show a big impact on the German AIT as well. The increase of the mandatory rebate, the consequences of the *pharma package* of 2012, and the implementation of the updated GDP guideline requirements lead to an overwhelming catalog of new challenges in AIT.

Considering all these duties and responsibilities and comparing the regulatory situation against the financial side of the business, this leads to the question whether the regulatory burden on AIT is still adequate. Of course, in conclusion most regulatory requirements are useful and eligible to raise the levels of CMC development, product safety and clinical. But the missing attempt to harmonize AIT within the EU on a regulatory level and the shrinking diagnostic width in Germany are a cause of concern. In addition, it needs to be questioned whether the general regulatory burden is too much in conflict with the financial situation of the German AIT companies. Until today, it is not totally clear if the national AIT industry can afford to fulfill their regulatory related development duties within a decreasing market.

CONTENT

ABBREVIATIONS

Advanced Therapy Medicinal Product	ATMP
Allergen Specific Immunotherapy	AIT
Allergic Rhinitis and its Impact on Asthma	ARIA
Biological Activity Unit	BAU
Chemistry, Manufacturing, Control	CMC
Common Technical Document	CTD
Double Blind Placebo Controlled (Trial)	DBPC
Enzyme-Linked Immunosorbent Assay	ELISA
European Medicines Agency	EMA
European Pharmacopeia	Ph. Eur.
Early Value Assessment	EVA
First expired, first out	FEFO
First in, first out	FIFO
German Drug Law (Arzneimittelgesetz)	AMG
Gesetzliche-Krankenkassen-Änderungsgesetz	GKV-ÄndG
Good Distribution Practice	GDP
Good Manufacturing Practice	GMP
Good Pharmacovigilance Practice	GVP
Health Technology Assessment	HTA
Immunglobulin E	IgE
In House Reference Preparation	IHRP
Marketing Authorization Application	MAA
Named Patient Product	NPP
Paul-Ehrlich-Institute	PEI
Periodic Safety Update Reports	PSUR
Pediatric Investigation Plan	PIP
Pharmacovigilance System Master File	PSMF

Post Authorization Safety Study	PASS
Protein Nitrogen Unit	PNU
Quality Review Document	QRD
Randomized Controlled Trial	RCT
Reactivity Index	IR
Research and Development	R&D
Subcutaneous Immunotherapy	SCIT
Sublingual Immunotherapy	SLIT
Summary of Product Characteristics	SmPC
Therapy Allergen Ordinance (Therapieallergeneverordnung)	TAV
World Allergy Organization	WAO
World Health Organization	WHO

FIGURES & TABLES

1 INTRODUCTION

THE FOLLOWING SHORT INTRODUCTION WILL LEAD INTO THE CONTEXT, IDEA, AND INTO THE GENERAL STRUCTURE OF THIS THESIS. IN ADDITION IT WILL DESCRIBE THE FACTUAL CONTEXT WITH REGARD TO OTHER SCIENTIFIC LECTURES IN THIS FIELD.

1.1 GENERAL CONTEXT

Allergies belong to the wide spread diseases (1) and all over the world up to 500 million people (2) (3) suffer from that. For years, the incidence of allergies is increasing, making these diseases more and more noticeable and important (1), (4). Despite their high incidence, most allergies are only treated symptomatically. But this may be insufficient to treat them effectively (2). The only causal treatment which exists against (Type I) allergic reactions is the allergen specific immunotherapy (AIT). AIT modifies the patient's immune system and attunes it to the allergenic substances it is sensitive towards (5). This kind of therapy has a long history; 2013 was the year of the 100th anniversary of the AIT principle. Within one century, this kind of therapy has widely developed. This is the case for the product development and the evolution of the concomitant regulatory framework. Since the 1990s and in Germany especially since 2008, this process of regulatory evolution is speeding up as a reason of new legislations and other regulatory requirements.

1.2 SUBJECT OF THE DISCUSSION

It is the aim of this thesis to illustrate the general development and regulatory background of German AIT. It will list and explain the different impact factors that affect AIT and will try to demonstrate their effect on real time examples. As German AIT is currently undergoing rapid changes it may be worthwhile to analyze the potential future impact of some of these impact factors, too.

Finally, this will lead to the discussion whether the regulatory burden that AIT is facing, is still adequate for this kind of therapy, or if AIT is over regulated and misunderstood. It will lead to an assumption how German AIT will develop over time and how the AIT industry might be able to handle the current regulatory challenges without disregarding the patients and especially children.

1.3 FACTUAL CONTEXT AND SIMILAR EXPERTISE

The following thesis will provide a very general overview from a meta perspective on the whole regulatory AIT framework and will clearly separate it from the two already existing theses, that focus either on AIT Chemistry-Manufacturing-Control (CMC) and quality aspects of the common technical document (CTD) [module 3] (6) or on the therapy allergen ordinance (TAV) (7).

2 FUNDAMENTALS ABOUT ALLERGIES

THE FOLLOWING CHAPTER WILL INTRODUCE THE MEDICAL, TECHNICAL, AND REGULATORY BASICS OF ALLERGIC DISEASES AND ALLERGEN SPECIFIC IMMUNOTHERAPY.

2.1 ALLERGIES AS DISORDER OF THE IMMUNE SYSTEM

Per definition, allergies are hypersensitivity disorders of the immune system (5). These hypersensitivity reactions occur towards substances that are part of our daily normal environment and that are normally harmless for a healthy human. The substances that may cause an allergic reaction are called allergens. The variety of allergens is very wide and nearly anything could be an allergen for a specific sensitized person (5).

Allergic reactions are mainly characterized by two factors which may vary from allergy type to allergy type: The first factor is the mode of action and the second factor is represented by the time span between the contact to the allergen and the incidence of the allergic reaction [= onset time]. Therefore, allergens are classified according to their reaction type and onset time into four categories. This classification is based on the ranking of Coombs and Gell and was founded in 1963. The following table lists the four basic categories of allergic reaction types including their mode of action, onset time and a typical example (8).

Class	Reaction Type	Mediator	Onset Time
Type I	Immediate Reaction Type	IgE Antibody	A few minutes
Type II	Cytotoxic Reaction Type	IgG Antibody (vs. stationary target)	A few hours
Type III	Immunocomplex Reaction Type	IgG Antibody (vs. floating target)	Up to several hours
Type IV	Delayed Hypersensitivity Type	T-Lymphocytes	Hours up to days

1 - Allergic Reactions by Type and Class ***[Modified and concluded according to (7)]***

These different types of allergy reactions lead to various kinds of diseases with individual symptoms. Because of the nearly unlimited number of potential allergens in our environment, the allergic diseases differ widely as well. *Table 2* connects the existing allergic reaction type to their corresponding diseases.

Class	Reaction Type	Example
Type I	Immediate Reaction Type	Allergic Rhinitis and / or Conjunctivitis, Anaphylaxis
Type II	Cytotoxic Reaction Type	Reaction against inapplicable blood transfusion or against Antibiotics
Type III	Immunocomplex Reaction Type	Vasculitis, Alveolitis
Type IV	Delayed Hypersensitivity Type	Contact dermatitis, Organ rejection

2 - Allergic Diseases by Type and Class ***[Modified and concluded according to (7)]***

2.2 Allergenic Diseases, Allergens and their Vector

Allergic reactions of eyes and nose, as well as of the bronchial tubes, and up to systemic reactions are possible consequences of the immediate allergic reactions [Type I]. Reactions of the nose and the eyes are the most common ones, manifesting as allergic rhinitis, conjunctivitis or as the joint allergic rhinoconjunctivitis. The common parlance has named this type of diseases the hay fever. This common name resulted from the fact that the Type I allergic reactions, including allergic rhinoconjunctivitis, are most commonly triggered by grass pollen. Other types of pollen as of trees or weeds are very usual as well. In general, Type I allergic reactions, and therefore allergic rhino-conjunctivitis, may be initiated by any kind of aero allergen [any allergen that is transported by the vector of air] that finds its way into the patients respiratory system or onto the patients mucosa.

On the mucosa, aero allergens come into contact with the immune system and the overshooting reaction starts by emitting inflammatory substances like histamine (4), (6). The following table shows the main classes of allergens that are currently under perception as a potential source of allergic rhinoconjunctivitis and/or allergic asthma:

Pollen	Animal	Moulds	Insects	Other
Grasses incl. Cereals	Bird feathers	Candida strains	House Dust Mites	Food stuff
Trees	Animal Hair	Aspergillum strains	Storage Mites	Contact allergens
Weeds			Bee Venom Wasp Venom	

3 - Allergens by Class ***[Modified and concluded according to (7), (17)]***

Other allergens that are linked to other vectors like food [= ingestion] or insect venoms [=injection] may cause type I reactions or type IV reactions as well, and are treated in the same way even if they are not linked to the mass syndrome of allergic rhinoconjunctivitis. (4), (7)

Today, allergic rhinoconjunctivitis has been discovered as a pre-stage of allergy induced asthma (8). Due to the continuous stress which affects the upper airways, untreated allergies will follow the allergic march down the respiratory system from the upper respiratory organs [= rhinitis] down to the deeper lungs system [= asthma] (9). This is why allergic rhinitis has come into the focus of the "Allergic Rhinitis and its Impact on Asthma" working group (ARIA) which set up a guideline about allergic rhinitis and its link to asthma. This guideline sets AIT as one of the key treatments for allergic rhinitis for asthma prevention (10).

2.3 Prevalence and Financial Burden of Disease

The number of people suffering from allergic diseases varies, depending on the source of information and on the individual and definition of the disease itself. It is estimated that about 500 million people worldwide are affected over all (3) (2).

About 113 million of these are Europeans. In Germany, the life time prevalence to suffer from allergic diseases is about 20% (3). This proves allergies to be a real wide spread disease (9). According to latest study research the most common allergies are those against the following allergens: Pollen [43%], Mites [23%], Foodstuff [20%], Animal Hair, Dander, Feathers or Epithelia [18%], followed by contact allergens [15%], medicinal products [14%], and finally insect venoms [9%] (11).

The treatment costs for allergic rhinitis are calculated with 1089 € [children] / 1543 € [adults] per patient and year. The follow up costs of asthma make this disease even more expensive [7928 € per child and year / 9287 € per adult and year]. Assuming that more than 15 million Germans are afflicted, this leads to enormous costs for the public health system (12). The only chance to break this circle is to increase the number of causal treatments especially of allergic rhinitis and rhinoconjunctivitis which will reduce the number of asthma cases including the follow up costs of asthma. This way, the economic impact of allergic diseases could be reduced significantly (13).

2.4 DIAGNOSE AND DIAGNOSTICS

There are different options to diagnose an allergy. Basically each diagnosis starts with an individual patient anamnesis. To support this anamnesis scientifically, each patient will have to undergo a specific allergy testing. For Type I allergies, the most ordinary way of testing, which is even mentioned in the summary of product characteristics (SmPC) of most AIT products (14), is the skin prick test. When performing a skin prick test, the doctor or nurse sets little spots of allergenic preparation [liquid prick test solutions] on the patient´s skin. Main area to place a prick test is the downside of a patient´s forearm. In a second step a needle, lancet, or special prick test instrument is used to prick through the liquid dot into the skin (15).

By this procedure the allergenic prick test preparation is transferred into the epidermis. If the tested patient is allergic towards the used preparation [allergen] this procedure will cause an allergic reaction. A so called wheal will become visible. This wheal will be compared to a positive control [triggered by a histamine solution] and a negative control [saline solution].

Reactions towards the prick substances that are more close to the positive control than to the negative control are deemed to be positive and indicate a sensitization against the tested allergen. Other diagnostic tools also used are the Immunoglobulin E (IgE) blood test, the nasal provocation test, the intracutaneous test and the atopy patch tests. These tests are mainly used to answer specific diagnostic questions (5; 8).

2.5 IMMUNOTHERAPY AS THE ONLY CAUSAL TREATMENT

To avoid the causing allergen is the best way to prevent allergic diseases. This is practically feasible for food allergies or for allergic reactions against a specific pet hair for example. For more common and more present allergies like hay fever this is nearly impossible. This is why allergies need a treatment. Basically there are two different ways of treatment that counter allergic diseases, focusing on Type I allergies:

A) Symptomatic pharmacotherapy:

Pharmacotherapy focuses on fighting the symptoms of an allergic reaction by using antihistamines [H1 receptor antagonists of the 2nd and 3rd generation] or steroids [mainly nasal corticosteroids]. While antihistamines block the H1 receptor they inhibit the inflammatory reaction of the overshooting immune system. Steroids and corticosteroids are natural cortical hormones that act by genomic receptor effects and in higher doses by non genomic mechanisms [interaction with cell membranes] which both reduce the effects of the allergic reaction by suppression (4), (16), (17).

B) Causal AIT

The second way to act against Type I allergic reactions is to provide patients with a causal AIT treatment that offers real protection. It does not only block the effects of an allergic reaction. AIT is able to reeducate the wrongly sensitized immune system of a patient and to reduce the number and intensity of IgE mediated allergic reactions in this way. The full and detailed mechanism of AIT has not yet been totally assessed but today it is proven that AIT corrects the wrong TH_2–Cell response of the immune system towards an allergen. This process could be compared to a progressive inurement (8).

During an AIT, patients are continuously exposed [usually through 3 consecutive seasons / years] to special preparations that contain the allergen(s) they are sensitized towards. Based on the chosen route of administration these allergen preparations are either administered daily [for the sublingual/oral preparations] or in complex intervals every few weeks/months [subcutaneous route]. By these routes the allergen preparation gets into the body where it starts to modify the immune system. The active substances of these allergen preparations are either natural allergens or chemically modified allergens [allergoids]. This leads to the following product matrix:

	Oral Application	Invasive Application
Native Allergens	Sublingual Tablet Lyophilisate Tablet Sublingual Solution Solution for Ingestion Sublingual Spray	Suspension for Subcutaneous Injection
Modified Allergens (Allergoids)	Sublingual Tablet Sublingual Solution	Suspension for Subcutaneous Injection

4 - AIT Products by Type and Vector ***[Modified and derived from (4), (8)]***

This matrix is based on all products that are officially marketed in Germany by April 2014 and that are either listed in the Red List (Rote Liste) 2014 (18) or published on the PEI website. (19) Each entry does at least represent one single product. The range of different available products and of available allergens per field may differ widely, especially for the native sublingual solutions route and for the modified subcutaneous injections. Other routes like intradermal injection or intralymphknot injection are not listed here as they are not among the standard treatment options in AIT. These special and seldom application forms are related to special diagnostic and therapeutic questions or to clinical therapeutic research (20; 18).

2.6 FINISHED PRODUCTS AND NAMED PATIENT PRODUCTS

According to the results of diagnostic allergy testing, different patients may show a big variety of allergic reactions against an endless range of potential allergens. This variety may range from the very common hay fever [triggered by grass pollen] to allergies against exotic substances that are uncommon in the country where the patient lives. As AIT can only train and rebuild the immune system of a patient if the used preparation contains the corresponding allergenic ingredient for the patient's disease, this leads to an endless variety of AIT products. Therefore, there are two basic approaches to manufacture AIT products:

A) Finished products in prefabricated batches

Finished products are defined by the German Drug Law (AMG) §4 *(1)* (21). According to this definition finished AIT products have a fixed formula of ingredients like any other regular medicinal product. They are manufactured in large batches in advance and kept on stock. Every single pack of this batch is totally identical to all other packs of the same batch. Pharmacies and wholesalers may hold stocks of these prefabricated finished products. Physicians prescribe these products to patients with applicable allergies and the products are available at the stock keeping pharmacy immediately. These kind of finished products are available to treat the common grass and tree pollen allergies (14), (22).

B) Named Patient Products

AIT Named Patient Products (NPPs) products are defined by the AMG §21 *(2)* 1g. (21). Opposed to the prefabricated batches of finished products these NPPs are individually manufactured for every single patient. The formulation of NPPs is based on the results of the physician's anamnesis and diagnostic testing. The final diagnosis for each individual patient leads to a product prescription and this prescription is transferred into a patient specific formulation.

In conclusion, each NPP is individually manufactured based on the patient´s specific diagnosis. The final NPP formulation contains exactly the allergens that are required by the sensitized patients (23). *[See also page 36; NPP Distribution Cycle]*

This means that every NPP is manufactured exclusively for a single patient based on the results of the diagnostic testing that has been performed before. The prescription is transferred into an order which is provided to special AIT companies. These companies are specialized in the manufacturing of allergy products on named patient basis. Depending on the formulation and the requested allergens, the manufacturing process of the NPP may take several weeks. As a result the patient receives his individual NPP AIT product, which is customized to his allergy. Because of this procedure NPP products can never be manufactured in advance and no stocks can be built as for finished products.

3 THE HISTORY OF AIT

THE FOLLOWING SHORT CHAPTER WILL LIST THE HISTORY OF AIT DEVELOPMENT. IN ADDITION IT WILL EXPLAIN THE HISTORICAL ROW OF THE DIFFERENT REGULATORY FRAMEWORKS AND LEGISLATIONS UNTIL TODAY.

3.1 THE HISTORY OF AIT PRODUCT DEVELOPMENT

Allergic reactions had been reported for the first time during the early 19th century and were described as a summer cold or as the *catarrhus aestivus* (24). C. H. Blackley [England] was the first person who initiated systematic research on this disease (25). In a self-experiment in 1873 he identified pollen as the root cause for his summer cold. His observation, that farmers show a comparatively lower ratio to suffer from the summer cold led him to the conclusion *it may be that in this disease there is a possibility of a patient being rendered insusceptible to the action of pollen by continued exposure to its influence*. (25) The real evidence, that pollen are responsible for the summer cold or hay fever as it is called today was given by W. Dunbar in 1903 (26). He was able to extract the allergy relevant proteins from the pollen and named them *toxins*. In the beginning of the 19th century L. Noon and J. Freeman (27) deepened the research of C. H. Blackley and W. Dunbar. Together they published results of a clinical exercise, where they administered the *toxin* in different dosages to several people and over different periods of time by subcutaneous route. Today, this clinical experiment is known as the first immunotherapy study (28; 27). During the 1930s this early form of AIT became more common because the results of Noon and Freeman were continuously distributed in the scientific community. This was also the time, when the first sublingual therapies occurred and were reported to be efficacious (29).

During and especially after World War 2nd immunotherapy became less important. One reason was the appearance of other, chemical drugs that were able to suppress allergy symptoms. These drugs were the first adrenaline near compounds, adrenaline itself, and antihistamines of the first generation. Another reason for the continuous fall of AIT was the lack of safety of the immunotherapy products.

More and more systemic reactions and adverse events were observed – due to missing standardization as we know today (30). The Protein Nitrogen Unit (PNU) that was and still is able to express the amount of protein within a formulation became less important (31). To push the standardization of AIT products for more safety and to express the reactivity or potency of the products, the allergy manufacturing companies established their own extract concentration units (14; 32). This kind of biological standardization became more and more common and was established also in the Scandinavian countries and in the USA [Biolequivalent Activity Unit – BAU] during the 1970s. The units and the kind of reactivity testing based on sensitization tests exists until today, however nowadays IgE binding tests and ELISA tests are more state-of-the-art.

With development of aluminum absorbed depot products, conduction of the first randomized placebo controlled trials in 1965 (33), and with discovery and establishment of the chemically modified allergen preparations called allergoids in 1972 (34), the immunotherapy and its products reached the basic level for modern AIT knowledge.

All this basic research and knowledge that has been acquired over more than one century was later written down and summarized by the WHO in the immunotherapy memorandum of 1989 (35) as the first organizational memorandum in this field.

3.2 Regulatory History of AIT

The regulatory history of AIT products is much shorter than their clinical development time. For a long time AIT products were simply not recognized as medicinal products that should be subject of any standard legislation. From the German national regulatory perspective, therapy allergens were first noticed in 1992 in a publication authored by the competent authority, the Paul-Ehrlich-Institute (PEI), regarding dossier updates of already marketed allergy products (6). Probably this publication was resulting from the first AIT marketing authorization applications (MAA) in the early 1990s and aimed to improve the marketing authorization dossier quality in general.

The requirements for AIT marketing authorizations were specified more precisely in the *Guidance on Allergy Products* (36) in 1996 and in the publication of the revised *Monograph on Allergy Products* in 1997 (37). But even this revised framework was still not applicable to most of the German AIT products that were historically based on NPP prescription and manufacturing. With the implementation of the 14th AMG amendment to the German Drug Law in 2005 [*Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften*] (38), all allergen products, that were manufactured in an industrialized process, were subject to the obligation to apply for a marketing authorization. Even if NPPs were still excluded according to the AMG §21 (2) 1g, those products that were manufactured in large batch quantities in advance were no longer defendable as NPPs.

Finally the European Medicines Agency (EMA) Guideline on the *Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases* (39) was implemented in June 2009 and filled the gap of missing clinical requirements in AIT. By this last step the regulatory framework on AIT was basically completed. Quality and clinical guidelines were available, monographs and therefore specifications were established and a clear guidance for marketing authorizations was set up to regularize allergy products for AIT.

4 THE REGULATORY FRAMEWORK OF AIT

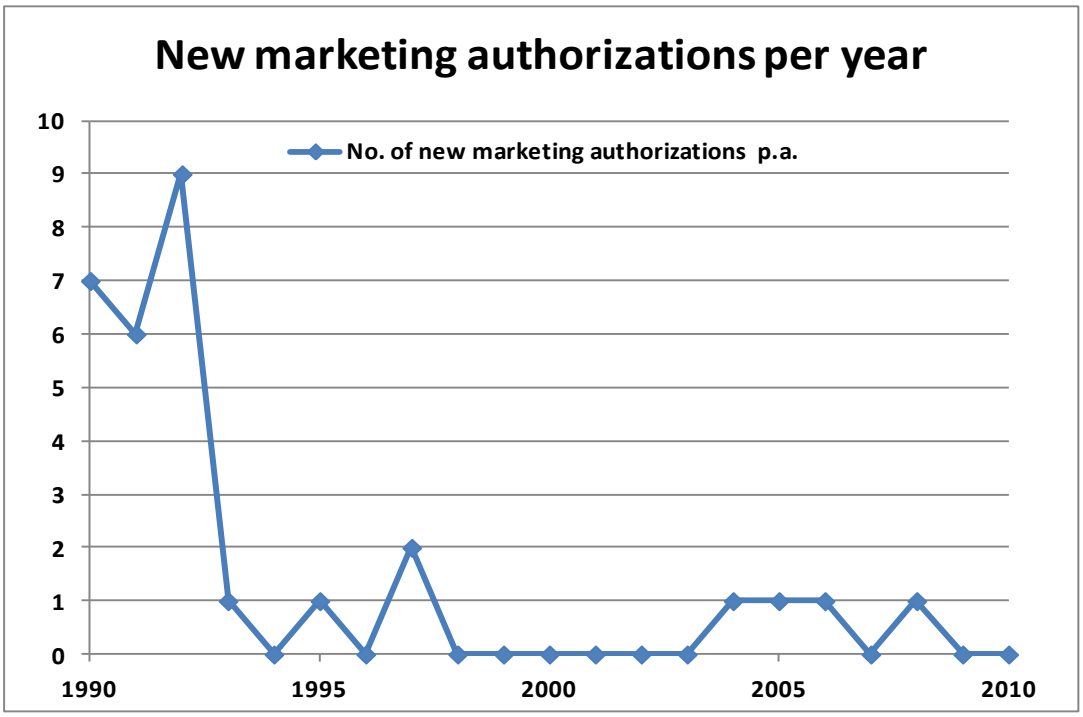
THE FOLLOWING CHAPTER WILL LIST AND EXPLAIN THE FOUR PILLARS OF THE GERMAN AIT LEGISLATION. THIS WILL INCLUDE AIT MARKETING AUTHORIZATIONS, QUALITY ASPECTS AND CLINICAL ASPECTS FOR DIAGNOSTIC AND THERAPEUTIC PRODUCTS.

4.1 MARKETING AUTHORIZATION OBLIGATIONS IN GERMANY

The process of the therapy allergen ordinance (TAV)

As already described in chapter 3.2, there was no need to apply for a marketing authorization for AIT products in Germany before the implementation of the 14th AMG amendment. (38) AIT products were manufactured, prescribed, and marketed as NPPs without any marketing authorization or registration. The rationale behind was defended by the fact that it was very difficult to provide safety and efficacy data for products that were only manufactured upon request in accordance with the diagnostic result for a single patient [as it is the NPP principle]. It was impossible to conduct robust clinical trials with a sufficient number of patients as long as products were individual and not standardized as a finished medicinal product. Since the implementation of Directive 2001/83/EC (40) it is defined that *all medicinal products […] either prepared industrially or manufactured by a method involving an industrial process* (40) require a marketing authorization. Transferred into national German law by the 14th AMG amendment this definition is applied with a national exception: The §21 *(2)* 1g of the German Drug Law (21) states that therapy allergens that are manufactured for a single patient on the basis of an individual prescription do still not require a marketing authorization. This exception has been introduced to accommodate the special nature of allergen products that are intended to treat exceptional rare allergies. Again, that fact that NPPs would never allow to roll out robust clinical trials [for a sufficient number of patients] is comprehensible. Even more, a company would never try to achieve a marketing authorization for a product that would only treat very rare allergies [and a very limited number on patients] as the return on investment would be very questionable. So this exception is kept to prevent those special patients from being untreated. This is why NPPs are still needed today.

But even if now under perception of the competent authority [because of the update of the 14th AMG amendment in 2005] the number of new marketing authorizations was very limited and did not increase much. It was still difficult for the allergen manufactures to switch from the NPP products to prefabricated product batches by a standardized and industrialized process that would require a marketing authorization. The first [and until today even latest)] marketing authorizations that were granted after the AMG amendment were those of Grazax [2006] and Oralair [2008] (19).

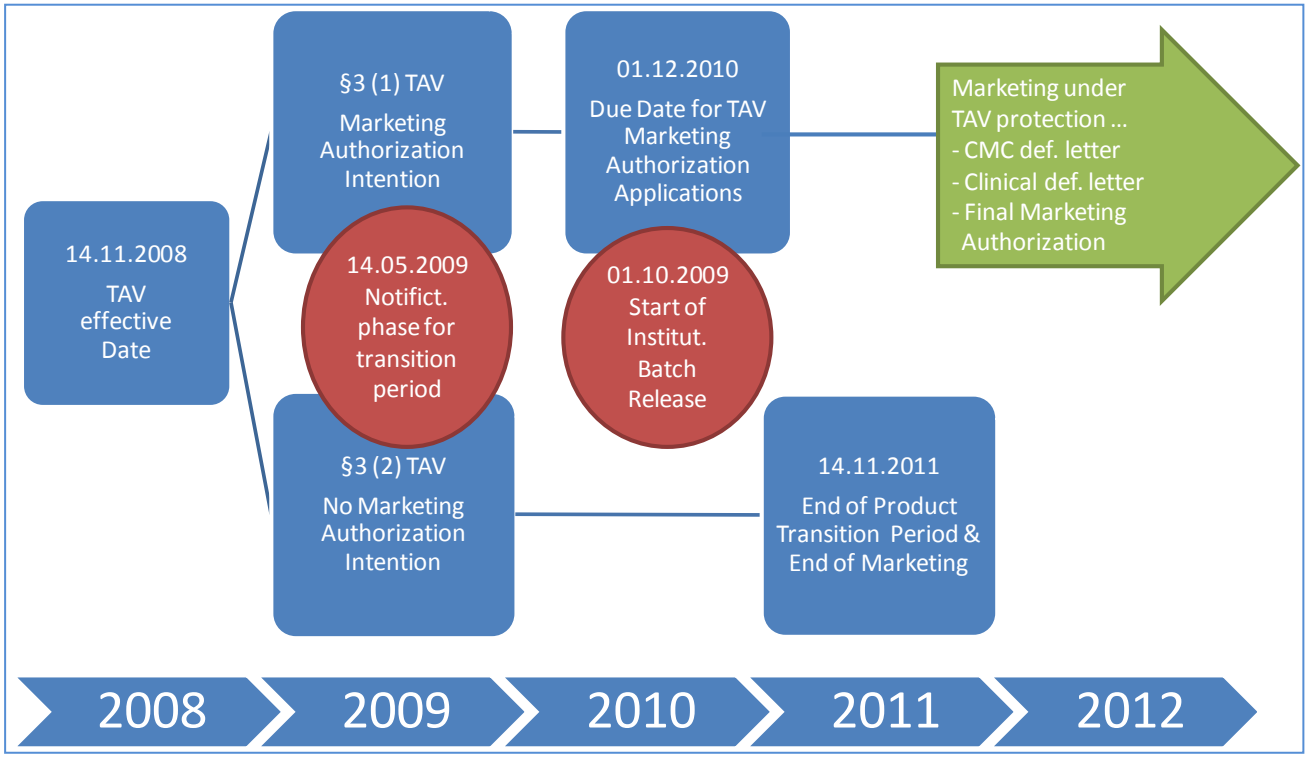


5 - Number of new Marketing Authorizations in AIT per Year (41)

[Numbers are given in product-families or product-ranges. Each product-family or product range may cover several different individual allergens and contain multiple marketing authorizations.]

In order to specify the requirements of the German Drug Law and to regulate the German AIT market, the TAV [*„Verordnung über die Ausdehnung der Vorschriften über die Zulassung der Arzneimittel auf Therapieallergene, die für einzelne Personen auf Grund einer Rezeptur hergestellt werden, sowie über Verfahrensregelungen der staatlichen Chargenprüfung“]* (42) was issued in 2008. According to the official bulletin of the German ministry of health the TAV aimed to avoid any risk at a patient level due to uncontrolled medicinal products, reflecting the frequent use of NPPs for all kinds of allergens (43).

The TAV regulates the most common allergens of the following species: Poaceae (Sweet Grasses) except Poa Mays (Corn), Betula (Birch), Alnus (Alder), Corylus (Hazel), and Dermatophagoides (house dust mites). Because of their high risk potential [frequency and intensity of systemic adverse reactions] the venoms of the bee and wasp species are covered by this legislation, too. (42) (43) The process of the German TAV has already been deeply discussed in thesis "*Implications of the German Regulation on Therapy Allergens [Therapieallergene-Verordnung] on the allergen manufacturing industry* (7). So the following graph will just briefly show how the TAV process was originally planned by the national legislators and the Paul-Ehrlich-Institute.



6 - The German TAV Process ***[Translated and slightly modified according to* (44)*]***

As visualized by the figure above, the German AIT companies had to decide whether they either wanted their products to undergo the TAV process or to drop out of the market after a transition period of three years [which ended in November 2011]. This transition period would allow even the patients who started their treatment last to complete their therapy for a full set of three years of treatment, which is the most recommended therapy duration according to product SmPCs (45). All other products have to undergo the TAV as a long but guided MAA process.

During the TAV marketing authorization procedure, the TAV products were and are allowed to stay on the market (42) and it was and is allowed to include new patients in unlimited numbers. In return, the concerned AIT product manufacturers have to update or build the quality part, the preclinical and clinical part of their MAA dossiers by performing extensive research activities. In principle all the TAV products are undergoing a redevelopment and improvement under guidance of the TAV. Considering public health and product availability, the TAV products remain on the market.

The TAV status early 2014

The TAV originally included 123 products from different manufacturers. By January 2014, 96 products are still included within the procedure [38 for grass pollen, 26 for tree pollen, 21 for mites, 11 for others or mixtures] while applications for 27 products [~20%] were either rejected or withdrawn (46). To fulfill their development obligations, the AIT manufacturers submitted 30 clinical trial applications until September 2013. These 30 applications include 8 dose finding studies (47). Compared to the number of 96 TAV products under review, the clinical development response is questionable low. On the quality side each manufacturer involved in the TAV process has at least received one quality deficiency report according to PEI information (47). Compared to the first industry's assumptions, that the TAV deficiency reports for the quality parts of the MAAs would be available by July 2011 [justified by the seven months period for the assessment of national MAAs in the German Drug Law] it can be stated that the review process is under delay (46).

Discussion of the regulatory up- and downsides of the TAV

The German TAV is a national procedure. Even if it is in line with Directive 2001/83/EC it sets up very detailed national requirements for Germany around the exception and allowance of NPPs. But as the interpretation, handling, and regulation of allergens differ widely among the competent authorities within the EU, this might lead to confusion between the different requirements in the individual countries, especially on the industry side in future.

Other countries have and will set up their own legislation that will represent their understanding of Directive 2001/83/EC. The outcome may partially match the German approach but may even not. Other countries might totally skip this approach and wait for a harmonized European initiative. The EMA would appreciate any harmonized and joint activities but those are far away (48). So the regulatory picture in Europe will not be harmonized very soon and allergy manufacturers will have to deal with different requirements all over Europe.

Once an AIT company receives a TAV marketing authorization approval in Germany, such an approval would comply with the EU Directive 2001/83/EC. In this case marketing authorization holders would be able to extend this marketing authorization to any other EU country by a MR procedure. Regardless of any national rules on allergens [and probably NPPs] existing in these other countries, the national authorities in the concerned member states could not prevent any marketing authorization attempt. This would even be the case even if the regulatory instruments of the other countries are not ready for such an approach in AIT. Form the opposite perspective a running TAV MAA does not automatically block parallel MAAs for the same product in another EU country. But as soon as one application [of this specific product] would be approved in only one member state, the other running MAAs would be opposed to the harmonization principle of the EU Commission (49). It is not clearly described what would happen under such circumstances as the European regulatory framework does not cover national re-registration procedures like the TAV. From the European perspective therefore it is not guaranteed that health authorities would continue to work on such parallel submitted national MAAs. Finally any further country acceding to the EU [like Croatia in 2013] may cause a new regulatory problem. As soon as there is a national marketing authorization in the acceding state for a product, which is already running the TAV, the running TAV procedure would stay in conflict with the already existing marketing authorization in the accession state (39).

Of course the TAV procedure is welcomed by physicians, allergy associations, and the industry because it will bring a wide basis for improved evidence into AIT that has not been inured to the AIT market yet. So the TAV instrument is very beneficial to raise the level of knowledge, evidence, and patient benefit in the AIT sector.

Financial burden of the TAV

The bureaucratic costs on the industry's side for all TAV MAAs together have been estimated at approximately 7.9 Million € based on about 500 MAAs with a lead allergen ratio of 20% (43). Reflecting the fact that only ¼ of this number of applications has been filed in 2010 this number may be reduced to ~ 2 million €. This number of 2 million € bureaucratic [mainly regulatory] costs represents approximately 1% of total turnover of the annual AIT market which is about 200 million € in Germany. (50) Compared to millions of € that need to be calculated to conduct pivotal clinical trials [to demonstrate clinical safety and efficacy] these regulatory costs are negligible. When calculating costs, it is highly questionable if the nine German AIT companies participating in the German 200 million € market will be able to drive nearly a hundred marketing authorization procedures for the next years. Calculating a research and development (R&D) rate of 20% [which is the maximum rate among the big players in the pharmaceutical industry (50)], all AIT companies together would have to be able to invest 40 million € per year. Based on about a hundred pending marketing authorizations this would lead to an average research budget of about 400 K€ per pending MAA and year. Even under the assumption that the AIT companies would invest their entire R&D budget into the clinical TAV development they would never be able to conduct such an amazing clinical program. And as other challenges are also influencing the AIT companies [see further chapters] this clinical budget is still overestimated as it cannot be invested into the TAV exclusively. For that financial reason the overall number of clinical trials required by the TAV is not plausible comparing the available resources against the numbers of products that need a clinical development. In conclusion not all TAV products will complete their MAA procedures and will drop out of the procedure at some stage.

4.2 THE HURDLES OF BATCH RELEASE AND PHARMACOPOEIA

The institutional batch release requirement

Beside the TAV process there are other regulatory factors that highly impact the quality development of AIT products. The German national legislation [§ 32 AMG] (21) requests institutional batch releases from the competent authority for all AIT products that are finished medicinal products and manufactured in advance.

The batch release requirement for allergen products has also been included into § 2 TAV (42) and becomes an obligation for all products that are currently marketed in Germany under TAV provisions. The acceptance criteria for these institutional batch releases are represented by the specifications that are part of the marketing authorization dossier and normally listed in CTD section 3.2.P.5.1 (51). The major requirement which these specifications have to follow is the *European Pharmacopoeia Monograph on Allergen Products* which was updated by version 6.6 (52) coming into force [for the German translation] by Feb. 1st 2011. This update included several new requirements for analytical testing procedures including the measurements for protein profile and protein content (6). In addition to the AIT therapeutic products these requirements are valid for all diagnostics as well. Without fulfillment of the monograph testing procedures including validation, batch release is no longer possible. The main problems that occurred during the implementation of the requirements was the validation of protein profile and protein content determination as these methods were difficult do adapt and to optimize

[More technical details of the European Pharmacopoeia Monograph on Allergen Products *have already been widely discussed and will not be analyzed here any further* (6)*]*

Protection from parallel imported AIT products

A positive aspect of the institutional batch release obligation was the protection from parallel imported drugs [§ 21, § 73 AMG] for a long time. As the relabeling of the parallel imported AIT drugs represents a manufacturing step, parallel imported drugs would automatically require a national PEI batch release. For a long time this batch release requirement prevented parallel import companies from entering the German market because the technical and analytical hurdles were too high. Finally these hurdles were taken in early 2014 when first AIT parallel import products were placed on the German market after a successful institutional batch release (53).

Reduction of diagnostic offers as a consequence

The PEI took the update in the monograph as a milestone to make the manufacturers aware of the Ph. Eur. requirements (54). As a result of these new requirements, the AIT manufacturers need to update their batch release tests, procedures and documentation to stay in line with the Ph. Eur. 6.6. This is especially the case for the diagnostic products where the marketing authorizations are old and not frequently maintained. In case this was [or even is] impossible or where restricted resources do not allow it, Ph. Eur. requirements lead to a huge wave of sunset clause [according to article 23 of 2001/83/EC] induced marketing authorizations losses or authorization withdrawals (55), (56), (57), (58). It is proven that more than one hundred marketing authorizations for diagnostic AIT products were withdrawn or expired between February 2011 and January 2014 (55), (57). By today only 700 diagnostic marketing authorizations are left (19), (58). These numbers demonstrate how the batch release and validation requirements work as regulating tools. Products that cannot demonstrate a sufficient CMC development status are not compliant with the batch release requirements of the PEI. As a result, these products are no longer marketed and will undergo the sunset clause rule after more than three years of market absence (40). A major reason for this tendency is given by the fact that diagnostic products especially for rare allergens do not promise to have an adequate return for any further investment in method development or validation (56), (59).

Batch release from a meta perspective

Within the pharmaceutical industry there are only few product classes that require an institutional batch release. According to the German legislation (§ 32 AMG) this requirement is limited to vaccines, blood products, immunoglobulin, sera from animals, and allergy products (21). While all other products are of a highly dangerous risk potential under respect of their biological nature, allergy products are undergoing these burden due to their low development status and due to the risk of anaphylactic reactions. The fact that many AIT diagnostic products currently drop off the market because they do not meet the analytical requirements for batch release justifies this part of the legislation. Focusing on increasing AIT product quality the duty of batch release is good practice.

On the other hand, the combination of the Ph. Eur. requirements and the batch release criteria will consequently lead to a consolidation of the diagnostic width in AIT. It will reduce the number of available AIT diagnostics, as the manufactures will not be able to provide the required substantial analytical research data. The serious disproportion of development costs and return on investment leads to an economic market consolidation according to the supply and demand principle. The fact that an industry would ever maintain an unprofitable group of products is an illusion. Allergy organizations and doctors associations are complaining about that and the discrepancy between the number of required diagnostic products and the number of available products will differ more and more in the future (59).

4.3 A NEW ASPECT OF AIT DIAGNOSTICS

Update of the German Drug Law

With the update of the German Drug Law during the revision in 2012, [*2. AMG Änderungs-gesetz*] (21) many changes have been implemented. Most of them are linked to the update of the European pharmacovigilance legislation and affect the whole pharmaceutical industry in the same way. However, update of § 13 (2a) AMG has a unique and special impact on the German AIT companies and their market. To fully understand this impact it has to be considered that products that are manufactured in a pharmacy do not require any kind of marketing authorization [as long as their number is limited to less than 100 units per day according to §21 AMG (2),1] and if they are part of the daily pharmaceutical practice of the acting pharmacy. Apart from the marketing authorization aspect, pharmacies require a pharmacy manufacturing license to perform manufacturing activities for several classes of medicinal products: Sera, test antigens, allergens, and Advanced-therapy Medicinal Products (21).

Within the above mentioned revision of the German Drug Law test allergens for diagnostic purpose have now been excluded from this manufacturing license requirement. As long as it is part of their daily practice, pharmacies are now free to manufacture up to 100 units of diagnostic test allergens without any marketing authorization or manufacturing license.

By this way all the established control mechanisms [MAA obligation, Ph. Eur. requirements, institutional batch release] for AIT diagnostics do not apply any longer. The only control mechanism that would still be in place is the obligation for the pharmacy to test the manufactured allergen products according to the existing monograph. But because of lacking infrastructure and because of the high complexity of the protein quality testing it is not very reasonable that a pharmacy could perform such a test. The tests that the industry has to struggle with would just be transferred to the pharmacy. For a normal operating pharmacy this represents an insuperable hurdle.

Downsides of local manufacturing and intension of the law revision

Under these circumstances the update of § 13 (2a) AMG has to be questioned. A normal acting pharmacy would never benefit from this new regulation as it would not be able to perform the complex controls according to the monograph. From this perception the update of the AMG does not provide any benefit for the supply of allergen diagnostics as long as pharmacies are compliant to their control obligations.

What could indeed turn the balance would be the supply of the pharmaceutical industry. As soon as the industry would supply a dedicated pharmacy with the raw material, the infrastructure [analytical QC equipment], and the required process knowledge, a dedicated pharmacy would be able to manufacture and control AIT diagnostics. This way a pharmacy would become the auxiliary person of the pharmaceutical industry which would bypass the German law. This would prevent the industry from any further dossier maintenance or validation requirements.

Furthermore, it could be possible that pharmacies acquire raw materials from any other source and manufacture diagnostic AIT products of an unknown quality and allergic potential. This is a not negligible risk as the allergic activity of allergic raw material is difficult to describe and difficult to standardize. In this case the patient´s benefit of a wider available diagnostic range must be accurately weighed against the fact that these products are marketed without any controls.

A TAV for diagnostics?

Apart from the diagnostics that may be manufactured in pharmacies [and lack institutional quality controls by this way] some AIT diagnostics are marketed in Germany without an official product status (60). Following the German principal of national re-registration procedure [*Nachzulassung* according to § 141 Abs. 4 AMG] these products are still marketed as long as their MAA [originally initiated before 2008] is pending. This process is comparable to the TAV process for the therapeutic products. But where the TAV has set up a complex regulatory framework which ensures the quality of the products that are under evaluation, this is not the case for the pending diagnostic products. These products are not obliged to undergo any form of institutional batch release or any other kind of quality control as long as the MA assessment is ongoing. This means that there is no institution that requests or monitors the compliance to the Ph. Eur. requirements and to the EMA quality guideline on allergy products. This implicates a potential risk on patient safety after all.

Even if not illegal from the pharmaceutical law perspective, it is obvious that these products show a competitive advantage as they lack or postpone the investments for pharmaceutical development since many years.

4.4 The Clinical and Quality Guidelines on Allergy Products

Basically, there are two EMA documents which give active guidance during the development of allergy products. These are the *Guideline on Allergen Products: Production and Quality Issues* (61) [replacing the older quality guidance of 1996 (36)]and the *Guideline on the Clinical Development of Products for Specific Immunotherapy for the treatment of Allergic Disease* (39).

Guideline on the clinical development

Besides introduction, scope, and legal basis the guideline contains five chapters with the following content: Patient characteristics, co- and rescue-medication, strategy and design of clinical trials, efficacy, and safety.

Chapter 4.3 of the guideline on the clinical development about the strategy and design of clinical trials is the most comprehensive one. It sets up a totally new quality and range of guidance that was unknown in AIT development before. Main criteria are

- DBPC trial requirements and the need to show superiority at least against placebo.
- justified primary and secondary clinical endpoints including a harmonized scale for the symptom scores. All primary endpoints are described in detail and
- a connection between study duration and product indication. Depending on the study duration the product indication may vary as shown in the following table.

Study Duration and Outcome	Indication
Efficacy in the first pollen season or after a few month of treatment for perennial allergies	Treatment of allergic symptoms
Maintenance of the clinical effect for two or three years of treatment	Sustained clinical effect
Long term effect in the post treatment years	Disease modifying effect
Absence of symptoms in the post treatment years	Curing allergy

7

7- Study duration and indication in AIT (39)

The other chapters of the guideline give detailed instructions on patient selection and the use and evaluation of co- and rescue medication. This is even more important as the rescue medication will be depicted by the rescue medications scores that are part of the clinical endpoints beside the symptom scores. Finally, this clinical development guideline is also linked to the S*tandard Pediatric Investigation Plan (PIP) for Specific Immunotherapy* (62) which completes the regulatory framework on the clinical development in AIT.

[The PIP will be deeper discussed in chapter 6 "Children in AIT". The clinical discussion on AIT will be continued there again.]

Quality guideline on allergy products

The *Guideline on Allergen Products: Production and Quality Issues* (61) has already been deeply discussed and the impact of this guideline on the industry has been widely assessed in other literature (6). Because the relevance and content of this guideline has not changed since this last evaluation, these quality topics will only be summarized very briefly. The main content of this guideline is represented by four chapters that guide through

- the introduction of the homologous groups concept and the preparation of allergen mixtures and their comparability
- the manufacturing and control of the active substance
- the preparation of standards and reference material, especially the in house reference preparation (IHRP) and
- the quality and control of the finished product.

Seen in context to the new requirements of the Ph. Eur. 6.6, this guideline provides all information that is needed by the industry for a progressive and sufficient CMC development. Taking into account the German TAV situation, this guideline will enable all AIT manufactures to bring their products through the TAV process from the quality perspective as long as they accept this guideline and follow its recommendations.

5 THE EXTENDED REGULATORY FRAMEWORK

IN ADDITION TO THE RULES AND REQUIREMENTS THAT AFFECT AIT DIRECTLY THERE IS AN EXPANDED REGULATORY FRAMEWORK WHICH SETS UP ADDITIONAL RULES AND REQUIREMENTS. THE FOLLOWING CHAPTER WILL SHOW SOME EXAMPLES, HOW THIS EXTENDED REGULATORY FRAMEWORK AFFECTS AIT.

5.1 HEALTH TECHNOLOGY ASSESSMENT AND BIOSIMILARITY

Health Technology Assessment in Germany

Like in other countries throughout the world (63) German authorities have established a health technology assessment (HTA) called *early value assessment [Frühe Nutzenbewertung]* (EVA). This assessment has been embedded into the German social law [§35 SGB V] (64) and not into the AMG as its main purpose is the modulation of health economic aspects [pricing and reimbursement]. In January 2011, the German HTA of EVA came into force based on the *Verordnung über die Nutzenbewertung von Arzneimitteln nach §35a Abs. 1 SGB V für die Erstattungsvereinbarung nach § 130 SGBV* [AM-NutzenV] (65). This AM-NutzenV was published as one part of the pharma package legislation update that was aimed to rearrange the German pharmaceutical market (AMNOG). The EVA represents the validated national tool to evaluate the benefit of new medicinal products [or new indications of existing drugs] compared to medicinal products that are already well established. The evaluation of the benefit of new medicinal products is a complex process that refers to data from the pivotal clinical trials and to health economic considerations.

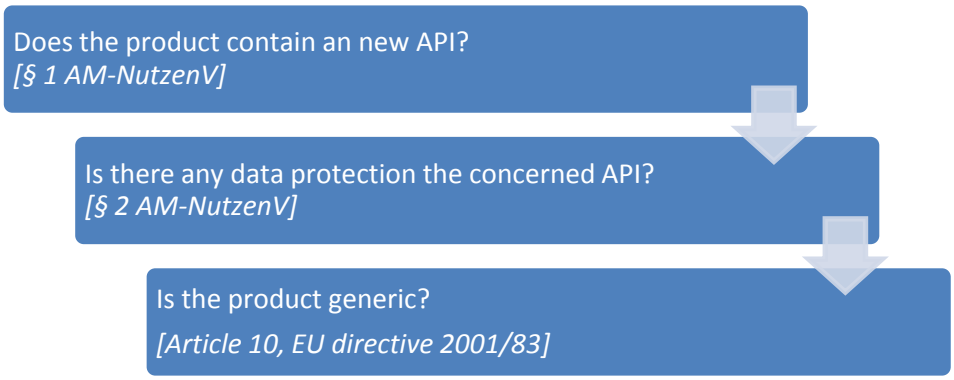
The main parameters that are taken into account for this assessment are the

- Improvement of general health condition
- Shortens of the duration of an illness
- Prolongation of the overall life span
- Reduction of side effects
- Improvement of quality of life (65).

It is the economic purpose of the German EVA as a HTA to translate the evaluated medical benefit for a specific treatment into a monetary value. Even if the prices of newly launched medicinal products in Germany are free of any limitations, the reimbursement, which is covered by the institutional health insurances, is based on the outcome of the EVA and based on how beneficial a new medicinal product is.By this way the early value assessment has been set up as the German standard tool for the negotiation of the product reimbursement price.

This means that even if the product price is free of limitation the new product can only be successful when the reimbursement rate of the national health insurances is high. At best the reimbursement rate is equal to the product price. So the EVA of any new product will answer the question whether a new product will earn good money and whether it will return all the research costs [high additional benefit = high price] or even not [no additional benefit = low price].

As already mentioned, the EVA HTA procedure is only applicable for new products that acquire a new marketing authorization. According to §1 of the AM-NutzenV a new product is defined by a new active pharmaceutical ingredient (API). New APIs in turn are defined [§2 AM-NutzenV] as APIs that are covered by data protection. The term of data protection has been defined by article 10 of the EU Directive 2001/83/EC (40) and was transferred into § 24b of the AMG (21). The data protection term describes the 8 year period which protects new medicinal products from upcoming generic MAAs and the 10 year period before the active marketing of the first generic medicinal product may start. This leads to the following cascade:



8 - Cascade of Questions for HTA Requirements ***[own creation, May 2014]***

In conclusion, the German EVA is not applicable to the open and generic market. This is clear to understand because generic products are relatively cheap [compared to the reference products] as the market regulates the generic product prices by the basic economic rule of offer and request.

EVA for AIT products under TAV?

Keeping an eye on the AIT products that are undergoing the TAV process, one may question whether these products would have to undergo an EVA or not, as the definition of new products is hard to adapt. Anyway, this question is of high interest from the German AIT perspective as the local allergen manufactures have many pending marketing authorization procedures for their products running by the TAV process. Until today it has not officially been stated whether the medicinal products, that will remain at the end of the TAV marketing authorization procedure, are new products or not. This leads to even more new questions:

- Would all AIT companies have to undergo an EVA for their TAV products?
- If yes, would they be able to invest the required resources for EVA dossiers?
- Would indirect comparisons for these EVAs be sufficient as there are no state-of-the-art head-to-head trials available in AIT today?
- Can AIT demonstrate a clear medical benefit compared to symptomatic treatment?

Most German AIT products are marketed for a long time. The therapy principles of AIT are well known. The API compounds of the products that are currently undergoing the TAV are common for a long period of time, too. Even if all TAV products are originally based on NPP compositions, their APIs and the mode of action are not the outcome of new research activities. The latest marketing authorization in the AIT field [granted in 2008] underlines this perception as it did not result into any kind data protection (66). Therefore, natural allergens like the APIs of AIT products, cannot considered being a new active substance. As a result the German AIT products would not be obliged to undergo a national EVA in Germany. This HTA tool would not be applicable to them.

Reference pricing and fixed amount groups

The fact that only products with a new API have to undergo the German EVA as a HTA tool does not automatically grant a free pricing for all other products. Generics and other products that do not undergo a national HTA are included into the German national reference pricing system where applicable (67). This reference pricing system is described in the German social law [§ 35 SGB V] (68) and is functionally based on fixed amount groups. This pricing system includes products

- with the same API
- with comparable APIs that should be small chemical related substance or
- with a comparable therapeutic effect, especially combination products. (69)

It is highly questionable if AIT products, even if they treat allergies against the same kind of allergens, can be represented by any kind of fixed amount group. As a fact, AIT products are not directly comparable among each other as they miss

- a clear characterization of the API [because they are biologics]
- a comparable dosage unit [because manufacturers use individual units]
- a comparability of the clinical effect [as no head to head trials exist].

As a conclusion AIT products cannot be grouped which makes a reference pricing impossible. Again it comes to the conclusion that even if the APIs in AIT products are not new, the standard tools for generic products [and generic product pricing] are not applicable. In principle, AIT products would be more comparable to the traditional herbal medicinal products by their nature. But these again show the exception that they are not covered by the institutional health insurances in most cases (70).

Generics in AIT: A question of biosimilarity?

The question about a generic product status and generic applications in AIT remains and the outcome of this discussion is a factor of economic importance. Why are there no generic AIT products on the market even if the products are not covered by data protection? What is the regulatory framework for potential generic products in AIT?

The main reason for the complexity of this discussion is the fact that AIT products are very different from products that contain small chemical molecules like in other pharmaceutical mass markets. The following table shows some of these differences:

	Small chemical molecules	Biologics (in AIT)
API nature	Single small chemical molecule	Complex mixtures of large proteins
API structure	Defined molecule structure	Tertiary and secondary structure defined. Molecule sequence may differ slightly
Analytical characterization of the API	Clearly to characterize State-of-the-art methods available	Difficult to characterize on molecular level Methods still under development
Reference product	Widely available as soon as data protection expired	Limited in number and quality
Generic MAA criteria	Equivalent qualitative and quantitative API composition Bioequivalence	Biosimilarity

9 - Small Chemical Molecules vs. Biologics ***[own creation, June 2014]***

In conclusion, generic applications for small chemical molecule products are standard applications. Under demonstration of the equivalence of the API and by providing comparable bioavailability [products are deemed *essential similar*] generic applications in accordance to Article 10 of the Directive 2001/83/EC are common practice. (40)

This is different for the biological products in general and applies to AIT products, too. Following the EMA Guideline on *Similar Biologic Medicinal Products* [currently under revision] generic allergen products would need to fulfill the biosimilar criteria to be accepted for a generic MAA. Accordingly the 2005 version of the guideline (71) states the following:

Currently, it seems unlikely that these products [vaccines] *may be thoroughly characterized at a molecular level. Consequently, vaccines have to be considered on a case-by-case basis. Applicants should take appropriate advice from the EU Regulatory Authorities. Allergen products are similarly complex and the same approach should be taken.* (71)

According this 2005 document, there is no general guidance on how to demonstrate biosimilarity in AIT, just because products cannot be characterized in detail. The analytical excellence is the factor of limitation.

Because biologics are developing widely, the 2005 guideline is currently under revision (72). The draft of the revised guideline already states that *the standard generic approach (...) which is applicable to most chemically-derived medicinal products is in principle not appropriate to biological/biotechnology-derived products due their complexity* (72). Additional or more precise information on allergen products cannot be found in this guideline draft. So the new version of the guidance will turn out very general. Furthermore product-specific biosimilar guidelines exist for a limited number of products. (73) But this is not the case for AIT products which are not covered by any product specific guidance. Thus it is not defined how biosimilarity for allergen products can be demonstrated and how the biosimilarity criteria in AIT can be reached. Even if this does not explicitly exclude the generic MAA approach, this approach is very difficult because it is not described how to proceed.

As a last point the number of available reference products would be very small, because many of the AIT products that can show up with a marketing authorization cannot provide an adequate dossier quality or evidence.

5.2 FINANCIAL IMPLICATIONS OF THE GERMAN LAW

The EVA as a HTA in Germany as described before is only one of the provisions that were taken by the German government to reduce the costs of the local healthcare system. Another key brick in the cost puzzle is the use of mandatory rebates. According to German law all pharmaceutical companies have to grant a mandatory rebate to the health insurances during the reimbursement process. In an indirect way this rebate reduces the price of the medicinal products which a company is selling. In parallel to the German EVA the legislation about mandatory rebates has been integrated into the German SGB V, too. It was updated by August 2010 by revision process of "the Gesetzliche-Krankenkassen-Änderungsgesetz" (GKV-ÄndG) (74). With this update the mandatory rebate was raised from 6 % to 16% of the product price (ex lab price without taxes) until the end of December 2013. By this way the GKV-ÄndG has saved 2.7 billion € for the national institutional health insurances 2013 (75). By January 2014 the rebate has been reduced from 16% to 6% and was raised to 7% again by April 2014 (75).

Away from this general consideration back to AIT it is clear that German AIT companies lost 10% of their turnover by 2010 overnight. This loss of money fell into a time, where companies had to take difficult decisions for their future as they had to plan their whole clinical development for the TAV and had to invest into analytical product development to comply with the pharmacopeia. The reduced turnover had great influence on these considerations because of the reduced R&D budgets. In conclusion, the German AIT companies are facing high investments to maintain their product portfolio or to bring it into the right regulatory shape. But the financial resources to handle these projects were and are still limited because the German legislation puts a lot of financial pressure on the pharmaceutical industry by increasing the mandatory rebate by 10%. This way the mandatory rebate disabled the AIT companies to fulfill their development obligations. While quality considerations have to be taken into account and because concerns to public health need to be avoided by all means this may lead to reduced product availability due to limited resources.

One German AIT company brought this case to court and challenged the mandatory rebate in conflict to their financial situation [because of their development obligations defined by the TAV] under consideration of the *Transparency Directive* 89/105/EWG (76).

During the first instance this approach was successful and the rebate was reduced to a lower burden for this company again. But in second instance the case got lost which was justified by the fact that the complaining company was only a local distribution organization of a global company. Development costs which were originally compared against the German mandatory rebate should have to be clearly outlined as costs of the whole company but not as costs of the German affiliate only (77).

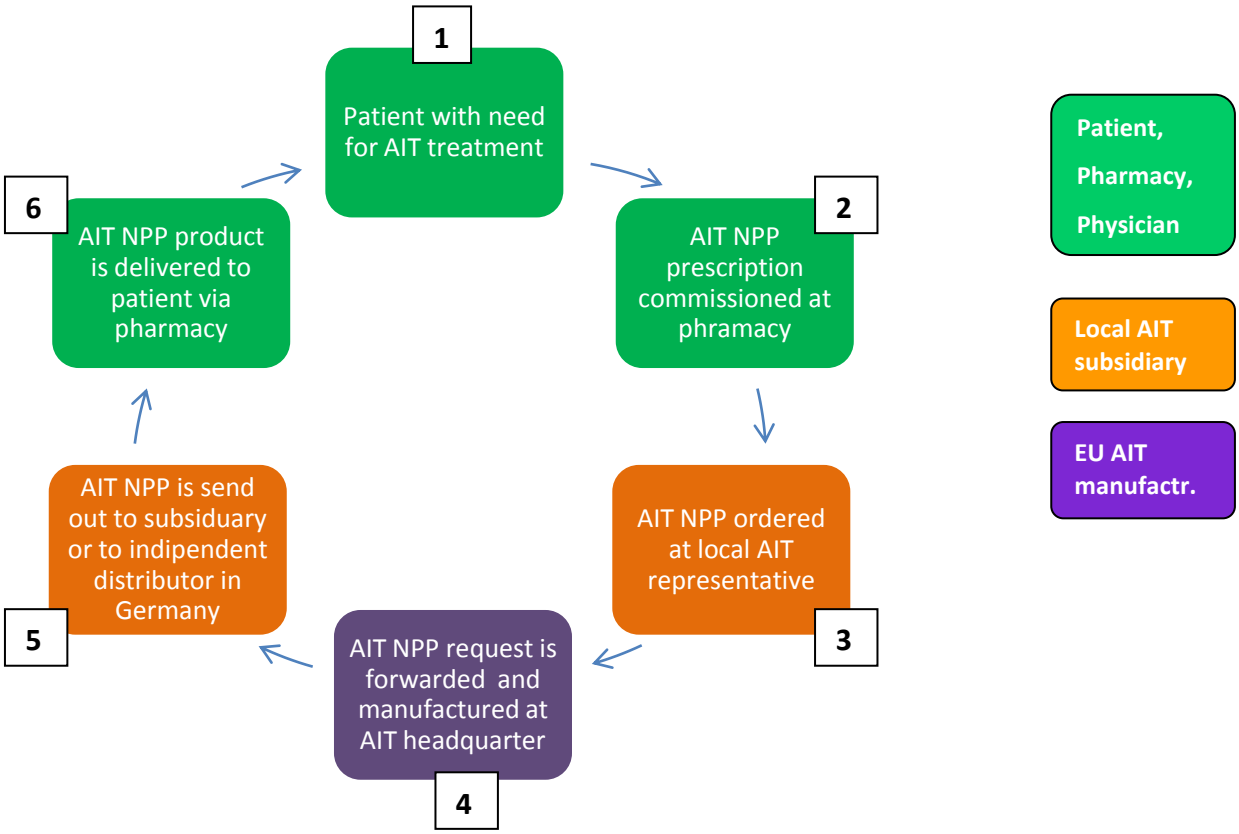
5.3 THE 2013 REVISION OF THE GDP GUIDELINE

The development and manufacturing of medicinal products underlies the general principle of Good Manufacturing Practice (GMP) and its quality framework. In Germany the GMP framework is mainly described by the international ICH Q guidelines (78), the AMG (21), and the *German decree on drug product and API manufacturing* (AMWHV) (79). Within AIT the local German companies are mostly purely national distribution organizations or local representatives of international companies. These local subsidiaries are not involved into any kind of CMC activities. They receive the finished medicinal products exclusively from their headquarters or holding companies (23). Some of them do not even have physical contact to their medicinal products as they use wholesalers and distributors for the product handling (80). Thus the GMP quality framework is mainly not applicable to these companies because they do not perform any kind of manufacturing-related activities on product level.

Apart from GMP, the Good Distribution Practice (GDP) represents the reasonable regulatory framework here. The basic GDP principles and requirements are based on the German Drug Law §§ 4, 43, 47, 52a, 63a, and 74a (21). As the AMG represents the highest level of national legislation it represents the necessity that all German AIT companies need to have a wholesaler license. In second line, the AMG is amended by the *decree for pharmaceutical wholesalers* (AM-HandelsV) (81) and the German *decree on drug product and API manufacturing* (AMWHV) (79) . The latest and most detailed guidance is given by the European wide accepted *Guidelines of 7 March 2013 on Good Distribution Practice of Medicinal Products for Human Use* (82) about product distribution and product handling.

This guidance is empowered by the article 84 of Directive 2001/83/EC, which brings it up to the highest regulatory level and makes it mandatory for the industry. It gives latest and most detailed guidance on product distribution and product handling.

The latest revision of the EU GPD Guideline in 2013 brought massive implications and consequences to the industry as it was extensively revised, detailed and expanded. By today the new GDP guideline is the most detailed GDP framework in Europe and a new benchmark for all pharmaceutical companies that are involved in logistic activities. It affects all kinds of pharmaceutical companies that are part of the logistic product distribution chain from first customer contact and order entry until final product delivery. This includes the German AIT companies that are mainly distribution organizations as explained. Especially the handling of the complex NPP order process [in which each product is based on an individual patient prescription] requires a sophisticated logistic organization.



10 - NPP Distribution Cycle

[own creation, May 2014]

The NPP distribution cycle above demonstrates that the AIT NPP distribution relies on a defined interaction between the local AIT distribution organization, the corporate manufacturer, and the customers. The 2013 revisions of the GDP guideline have a strong impact on this distribution cycle. The main changes and the facts with the biggest impact are listed below (82):

- The responsible person for GDP

  The responsible person for GDP [reflects the German responsible person according to § 52a AMG] is established. The responsibilities are clearly described [12 dedicated topics]. Some activities need to be executed by the responsible person exclusively and cannot be delegated. This implies that the responsible person is qualified properly and actively involved into management activities.

- Training obligations

  The new GDP guideline adds mandatory training obligations. This includes special training that enables the personnel to identify falsified medicines.

- Equipment

  Complex equipment now requires qualification and validation. This includes computerized systems which should now be validated. This validation is identical to the GMP validation that is mainly based on the US code of federal regulation 21 / 11.

- Storage

  Storage areas (apart from room temperature) now require a temperature mapping and a justification to argue the adequate storage for the medicinal product. Furthermore a risk management tool (to discuss changes in the storage areas) needs to be in place. In addition the FIFO (first in, first out) principle has been replaced by the FEFO (first expire, first out) principle.

- Good Documentation Practice

  Good documentation practice now needs to be established over the whole logistic process wherever products are involved.

- Contracts and 3rd parties

  Suppliers, subcontractors and customers need to be qualified if they are allowed either to supply, distribute, manage or receive medicinal products. Every company is responsible to clearly monitor, describe and if possible to validate third party responsibilities and activities. Contracts need to be in place.

- Transportation

  Transport now has to be performed under maintenance of the storage conditions.
  A transport validation should be available. If the transport conditions differ from the storage conditions an extensive risk analysis has to be performed and justified.

To summarize all these revised and additional requirements in GDP it can be stated that the main principles and guidance of GMP have been extended to all pharmaceutical logistic workflows. GDP has been adjusted to the existing GMP and both frameworks are now in line. Even if the German AIT subsidiaries were hardly affected by the original GMP framework they are now fully affected by the GDP guideline and its requirements. Wholesalers and distributors that were not covered by GMP until then are now facing the massive regulatory impact of GDP. This implicates a lot of additional workload and a new requirement for additional resources. New procedures and work flows need to be designed and implemented. The requirements for the responsible person, the training of personal, the right transportation [under storage conditions], and the validation of computerized systems are the key points of the GDP requirement increase.

5.4 THE PHARMA PACKAGE AND PHARMACOVIGILANCE

The latest pharmacovigilance legislation updates of the EU Regulation 726/2004 [amended by regulation EU/1235/20010] and the Directive 2001/83/EC [amended by 2010/84/EC] have been implemented in Germany with the update for the EU pharma package in the AMG in 2012. Furthermore, the acting EU Regulation 520/2012 was published and came into force by July 2012.

Directly binding in all EU member states, the eight chapters of the acting regulation aim to

- Implement a pharmacovigilance system master file (PSMF) at industry level
- set minimum requirements for a pharmacovigilance quality system
- set minimum authority requirements for Eudravigilance database surveillance
- state norms and formats
- increase speed and quality of spontaneous case reporting
- inure risk management planning
- update the handling of Periodic Safety Update Reports (PSUR) and
- update the handling of a Post Authorization Safety Studies (PASS)
  (83)

This new legislation is of high relevance for the whole pharmaceutical industry, including AIT. The implementation of tools and processes, to fulfill the listed requirements, will cost a lot of additional resources. Depending on the number of [especially diagnostic] marketing authorizations [which may exceed more than 100 MAs per company in AIT] the costs for the preparation and submission of PSURs are not negligible at all. These costs might even increase dramatically if the EMA follows their planning to raise the costs for PSUR management (59). As a second point the documentation PASS studies will require more resources, too. Furthermore, the number of DBPC trials in AIT is still small and the number of patients per DBPC trial does rarely exceed a hundred patients per study arm (84), (85), (86). This leads to the conclusion that the safety considerations of AIT products are built on comparatively small patient populations. In conclusion, PASS is really needed to research and observe the safety and tolerability of AIT products under real life conditions. In daily practice severe adverse reactions are rare and the number of systemic reactions only affects between 0.1 % and 0.01 % of all patients (14). Cases with fatal outcome have been reported for SCIT in the US between 2001 and 2008 with a ratio of one single fatal case per two million injection visits. (87)

6 CHILDREN IN AIT

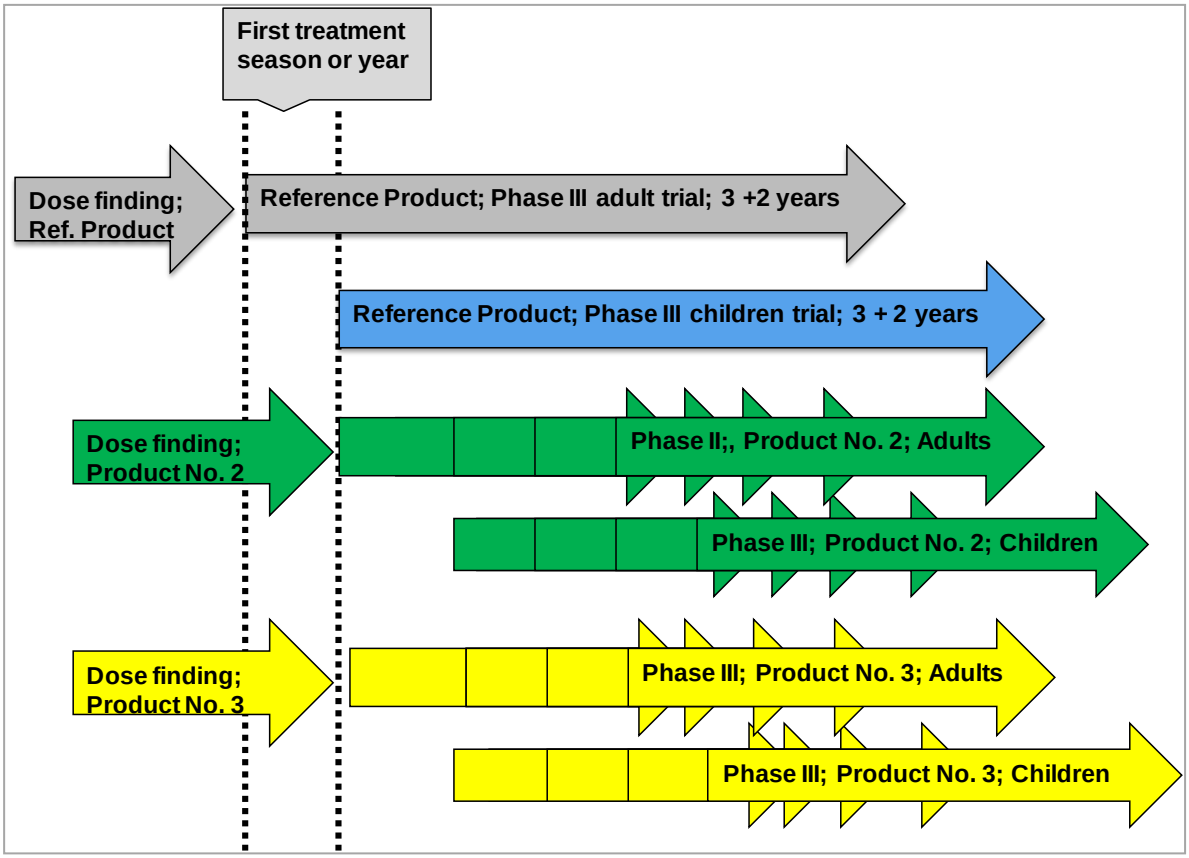
EVEN IF THE EFFECTIVENESS OF AIT HAS BEEN PROVEN, OVER ALL AGE GROUPS CHILDREN ARE THE MOST IMPORTANT PATIENT SUBGROUP. THE EMA STANDARD PIP ON ALLERGY PRODUCTS STATES THAT *CHILDREN ARE BELIEVED TO DERIVE POTENTIALLY GREATER BENEFIT FROM IMMUNOTHERAPY TO INHALANT ALLERGENS* (88) AS *THE EFFECT STARTS EARLIER* AND HOLDS ON FOR A LONGER LIFE SPAN. OPPOSED TO THIS FACT THE DIMENSION OF CLINICAL EVIDENCE OF AIT IN CHILDREN IS LOWER COMPARED THOSE IN ADULTS. AS THE IMPORTANCE OF THE CHILDREN SUBGROUP COMPARED TO THE AVAILABLE CLINICAL EVIDENCE IS NOT IN LINE, THE FOLLOWING CHAPTER WILL DISCUSS THE ROLE OF CHILDREN IN AIT FROM DIFFERENT PERSPECTIVES.

6.1 PEDIATRIC INVESTIGATION PLAN (PIP)

Following the pediatric regulation 1901/2001/EC (89) all new MAAs need to include considerations and clinical evaluations for children aiming for a children indication wherever possible. With the initiation of the EMA/PDCO Standard Pediatric Investigation Plan for Allergen Products for Specific Immunotherapy (62) the EMA has followed this path. The key element of this standard PIP is the duty to develop at least one representative allergen of a manufacturer's portfolio for a long term children indication (3 of treatment +2 years of additional observation). The PIP has been developed continuously to the current revision III. The main questions that were discussed over the revisions were considerations about the requirements for children studies and where (when) these trials should be placed into the overall development of an AIT product. Especially the implementation of revision III has facilitated the conduction of the PIP related studies as these could now be started earlier in the development process. According to the standard PIP pediatric trials with the selected product should be initiated as soon as the following requirements in adults are met:

- A tolerated dose range is declared by a completed dose finding study
- dose-response relationship for clinical efficacy is proofed
- short-term efficacy was demonstrated (over one year / one pollen season) and
- safety data demonstrate no increased risk of anaphylactic reactions from adult trials (possibly including adolescents).

The details of the positioning of the required children trials for the fulfillment of the standard PIP is a critical point in the AIT product development. Once a reference product has been chosen, this product requires intensive long term development. The advantage of the PIP revision III is that children trials can be initiated earlier, right after the results of the first interim analysis in adults are available. The new situation is shown below.



11 - Children Trials according to PIP ***[Based on* (46), (62)*; own visualization]***

The PIP in Conjunction with the German TAV

The pediatric regulation as well as the standard PIP on allergy products, are both completely applicable to any AIT development. This means that all products that are currently undergoing the German TAV MAA process have to fulfill the requirements of the standard PIP on allergy products. In conclusion, the full 3+2 year study program for a long term indication has to be fulfilled for adults and children at least for one reference product of each manufacturer. For all other products the chosen study length may depend on the planned indication as described in table No. 7 *Study duration and indication in AIT.*

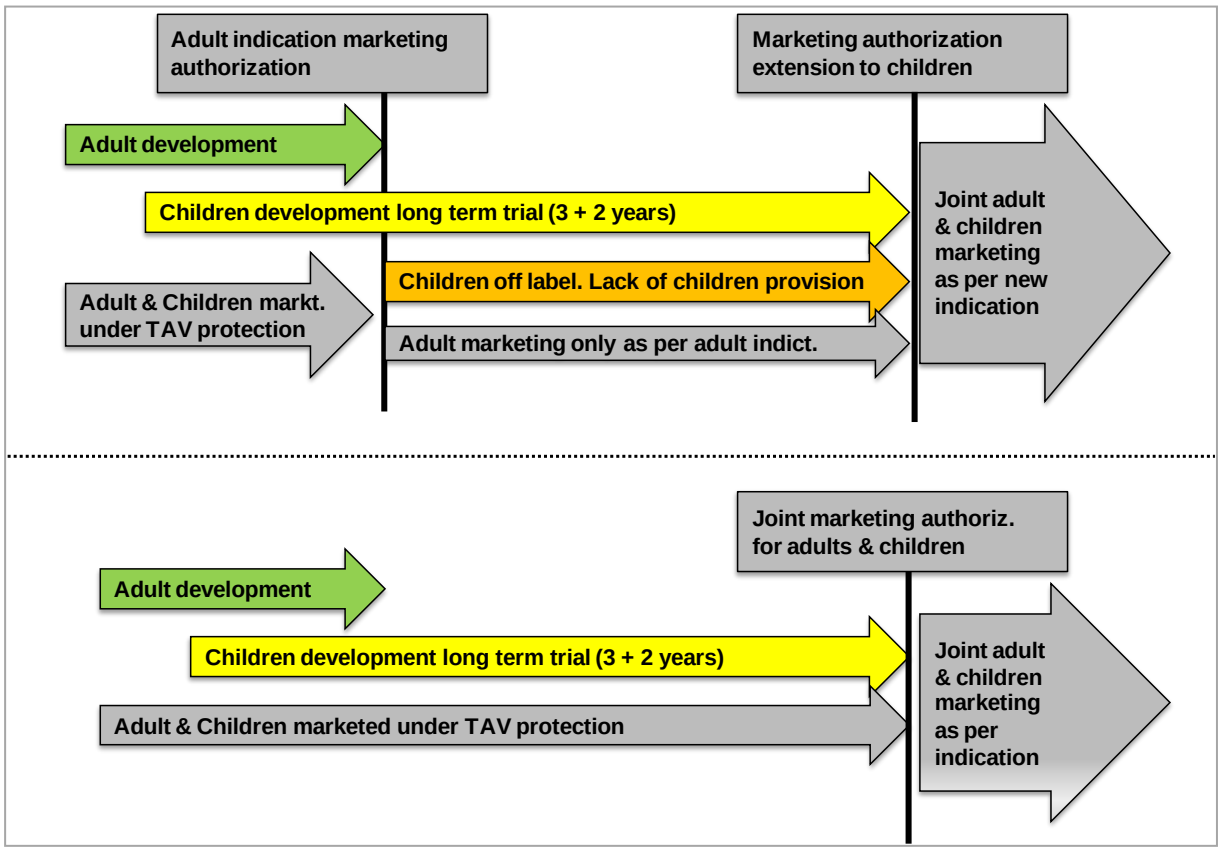
Keeping in mind that originally nine different manufacturers had announced 123 TAV MAAs this would lead to an enormous number of new clinical trials. The applications should include at least 18 long term studies [nine for adults and nine for children]. Furthermore, all other allergen products that could not participate from homologous group considerations [according to the AIT clinical development guideline (39)] would require additional clinical trials. These studies might of course be shorter than the PIP reference product depending on the planned indication (62).

By May 2014, 30 months after the start of the TAV 111, PIP decisions for AIT products were listed on the EMA website (90). 100 of these PIP decisions were taken between November 2010 and February 2011 which clearly indicates them as a result of the TAV applications and the related PIP implications. The EMA revisions of the standard PIP are hardly represented and the PIP applicants do not seem to follow these modifications regularly. Since the implementation of the standard PIP only 6 revised opinions are reported. Comparing the 111 PIP applications on the EMA side against 22 [30 studies in total minus 8 dose finding studies] potentially pivotal clinical trial applications at the PEI (47) the chance of full PIP compliance for all AIT companies is low and not plausible. This is even the case considering the fact that children trials will always require an adult counterpart first and will always be delayed compared to the adult trial program. Restarting the discussion of chapter 4.4 in conjunction with the TAV it can be judged that not all of the outstanding 96 MAA will reach a good ending. The fact how applicants submit clinical trial applications to the PEI and how they maintain their PIPs underlines this perception.

What' first, what's next: Adults vs. children

As already explained and as a consequence of the PIP structure, adult trials will always be at least one year or season ahead compared to their children counterparts [*figure 10]*. This leads to a constellation where an adult indication might already be approved while the corresponding children study program is still running. But how can a children treatment be continued as soon as only an adult indication for the product is approved?

Today the SmPCs for most TAV products are not very specific and the patient age groups are not clearly specified. This means that the indication is not separated between adults and children. In conclusion adults and children are both tolerated equally as patients. As soon as the adult indication of an AIT product gets approved this specific TAV product would become an *adults only* product. This is the case as the approved adult indication would immediately block any further supply for children. Unfortunately the TAV legislation does not cover that point. The marketing protection rights of the TAV would not be effective in such a case even if the MAA trial in children is still running. In conclusion, products that are available for adults and children in parallel during the TAV would be limited to adults upon approval only because of the time shift between the adults and the children [which is caused by the PIP trial requirements]. In principal this would lead to an off label treatment period for children.



12 - PIP Children Gap ***[Own creation; May 2014]***

The second of the two figures above demonstrate how to avoid this scenario and how to continue children supply without any risk of off label therapy. Basically an agreed delay of the adult authorization can lead to the advantage of a joint marketing authorization.

Adults and children would be approved in parallel then. This joint marketing authorization may protect AIT manufacturers from a potential children gap. Furthermore, these considerations are not only valid for the reference product and the long term indication but may also be taken into account for all the other TAV applications [e.g. treatment effect after first season or year]. The rule that still needs to be followed anyway is the maximum TAV bridging period of seven years after answering the first clinical deficiency report. This period may not be exceeded without losing the TAV protection rights for marketing.

6.2 SmPC Review. A Question of Indication?

When talking about AIT products many key points of differentiation need to be considered. As already discussed, there are huge differences in the nature of the product [natural allergen or modified allergoid], route of administration [SCIT or SLIT], indication [treatment, sustained effect, disease modifying effect], and target population [adults or children].

The AIT products that are marketed today [excluding the NPPs for rare allergens] are either charged under TAV protection or have an active marketing authorization which was mostly acquired during the early 1990s. New products are very rare. The SmPCs of the TAV products are still based on the NPP products they originally referred to. As these NPP SmPCs were free of any authority control and as their basic core information are more than 20 years old they show only very general characteristics and information. Products that received their marketing authorization during the last few years past [this is especially the case for two oral grass tablets that underwent their renewal procedures in 2011 and 2013] show a more adequate description of indication, contra indication and target population as requested by the current EMA Quality Review Document (QRD) convention.

The *table 12* in *APPENDIX I* shows seven of the most frequently use AIT products based on prescriptions in the grass pollen sector in 2013 (53). Among them there are natural allergen product and allergoids. Both routes of administration [SCIT and SLIT] are reflected as well. There are products with relatively new marketing authorizations, those with old marketing authorizations, and those without marketing authorizations, currently running the TAV. In conclusion the table reflects the German AIT grass pollen market on a realistic landscape.

It is demonstrated that products that are marketed under NPP provisions without marketing authorization [under TAV] show the widest indication and the lowest regulation for the patient populations. Products with the most recent marketing authorization status and higher evidence [given by the number of conducted DBPCTs] show hard limitations [in terms of population and indication], instead.

This paradox situation demonstrates that the TAV process needs to proceed with high urgency. It is really needed to harmonize the SmPCs of the different AIT products and to bring more results of highest evidence into this indication where many products that are currently marketed without any substantial clinical data [demonstrated by DBPC trials]. Furthermore, the effect on children and the inclusion / exclusion of asthma needs to be specified by clear criteria. The high freedom in indication, age group and tolerance of asthmatic patients seems to be disproportional to the very low level of evidence for the NPP products. The fact that products without any defendable clinical evidence are used in the most sensitive patient populations is not acceptable. Products which indicate [according to SmPC] that *for children over 5 years, only few clinical data are available which are not sufficient for a proof of efficacy* (91) should not be used as long as dedicated alternatives exist!

6.3 AIT IN CHILDREN AND OFF LABEL USE?

Assuming that about 20 to 30 million people in Germany are sensitized towards any kind of allergen and assuming that 20% of the whole German population is allergic (8), (11) raises the question of treatment and its coverage. According to latest available data, only between 12% (92) and 25% (93) of allergic patients receive an AIT treatment. Even if there is a high awareness of the availability and possibilities of AIT, many allergic people avoid AIT as a first line therapy assuming their symptoms are too mild. In contrast to this perception it is proved that children benefit most from AIT (88) and should start their therapy as early as possible. In contrast, children that are treated do often not receive a proper medication. A survey based on German prescription data of 2012 illustrates that only 26% of all treated children with grass pollen related allergic rhinitis received a medicinal product with an explicit indication for children. (94)

This fact is not surprising resuming *table 12* in *Appendix I* amended by the information that out of the 19 German AIT grass pollen products

- only 17 [out of 19] products are available for children
- only 8 [out of 17] products have some kind of marketing authorization
  [while 9 are running the TAV procedure]
- only 5 [out of 8] products show clinical trials according to modified WAO criteria (95)
- only 3 [out of 5] include children trials in their pivotal clinical research and finally
- only 2 [out of 3] have an explicit children indication and not a general indication
  (19), (96), (84), (86), (85), (94)

In conclusion, about three out of four children [26%] are not treated properly when receiving an AIT. Physicians frequently prescribe products that are not based on highest clinical evidence according to the (modified) World Allergy Organization (WAO) criteria (95) or/and cannot show a valid marketing authorization. This kind of prescription behavior is incomprehensible and not in line with any expert opinion. As a consequence, the national guidance [dated 2009] on the prescription of AIT products (97) is going to be revised very soon. The new version of this guidance will provide more details and will evaluate specific products according to criteria like

- use of standardized allergen extract and major allergen content
- DBPC trials, their scores and significance of results and
- marketing authorization status.
  (98)

Furthermore the cascade above demonstrates that off label use is a big problem within AIT [as in many other indications, too]. According to Annex I of the EMA GVP Guideline off label use is defined as a *situation where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information* (99). Even if many AIT products deem children to be included in their overall patient population without any differentiation between adults and children it can be argued whether a documented missing proof of efficacy [as described in chapter 6.2] can be evaluated as an off label use criteria.

7 FINAL CONCLUSION AND FUTURE PROSPECTS

IS THE REGULATORY BURDEN STILL ADEQUATE TO AIT? THIS SIMPLE QUESTION CANNOT BE ANSWERED WITH A SINGLE YES OR NO. IT CLEARLY DEPENDS ON THE POINT OF VIEW AND ON REQUESTED INTENTION. IN FACT THE GERMAN AIT IS MOVING AND UNDERGOING LOTS OF CHANGES.

7.1 FINAL CONCLUSION

The authority perspective

With the implementation of the TAV the former unclear regulatory status of AIT products is now defined in detail. From a national lawgiver´s and authority´s perspective this legislation is really required as it gives guidance and certainty for the marketing of these products to all concerned AIT companies. Even more the current legislation forces the AIT companies to catch-up their backlogs in CMC compliance and on clinical evidence. As explained by the PIP, this is especially important for the children subgroup where many deficits can be detected.

On the other hand, the national authority PEI has to defend the national approach against other individual regulatory AIT concepts throughout Europe. As a joint European regulatory approach on AIT is still missing and will not be available very soon this may lead to conflicts and misunderstandings between the EU countries.

The industry perspective

From the industry perspective AIT is facing a challenging time. The regularizations which big pharmaceutical companies in other mass indications were facing 20 years ago [during the time of national re-registration procedures] are now struggling with AIT in a comparable way. The combination of costs and efforts to succeed in the TAV [including the PIP] are in conflict to a decreasing overall market as well as to the mandatory rebates which lead to a reduction of the available R&D budget for years. Other challenges like the implementation of the new GDP guideline, the fulfillment of GVP requirements, and the acceptance of the pharmacopeia to participate in the institutional batch release reflect multiple additional burdens for the AIT industry.

The rapid development of the regulatory framework and the fact that so many challenges and requirements came up in parallel can be described as a real burden. The estimated resources to those hurdles cannot be earned in a decreasing market burdened with additional mandatory rebates.

From a quality and evidence perspective the high regulatory burden should be weight positively as the new framework will lead to a higher level of quality, safety and efficacy for AIT products. The TAV process in combination with the PIP and new PV legislation will raise the level of clinical evidence and safety. Thus more and more clinical studies will lead to new and state-of-the-art marketing authorizations in AIT.

Other potential challenges and potential conflicts will pass the AIT manufacturers. Due to the reason that the APIs of AIT products cannot considered to be new, TAV products will not need to undergo the German EVA as a national HTA. Furthermore, AIT products are most likely not applicable to reference pricing as well. In conjunction to this it is visible that AIT products will not become generic soon. The absence of a specific guideline [which would be required to define biosimilarity criteria] and missing appropriate reference products make it very difficult for any potential generic application attempt.

<u>The patient and prescribers perspective</u>

Prescribers and patients [especially children] will benefit from this general development. Most of the regulating processes are highly appreciated to enable AIT to take its role as the only causal treatment for allergic rhinitis and to improve the rate of patient provision. The increase of research activities and new published data will lead to a new level of quality, safety and efficacy for AIT products and will come up to their convenience. On the other hand the reduction of the diagnostic width and the loss of many diagnostic marketing authorizations by sunset clause regulation is a real downside of the current challenges. This effect has been observed by the industry, the PEI, and especially by doctors associations and prescribers. But this development is hardly stoppable soon because the update of the §13 AMG is not able to counter this effect; the well-intentioned idea of this law could not be transferred into an acceptable daily practice.

Additional AIT diagnostic marketing authorizations will fall victim to this process as these medicinal products need to comply with standard regulatory requirements but do not promise an adequate return on investment. Specialized doctors or allergy centers and patients that require a wide diagnostic portfolio [of rare allergens] will suffer most from the fact that the current level off supply cannot be maintained for economic reasons.

7.2 FUTURE PROSPECTS

Compared to the pharmaceutical mass markets of other wide spread indications [like diabetes or cancer] the field of AIT is years behind in terms of experience, standards, and infrastructure. Even if the regulatory framework and the environment of AIT have changed rapidly during the last years the AIT industry still has to grow and to adapt. From the German perspective this means that the TAV will impact AIT over the next eight to ten years [until the completion of the clinical research]. The majority of applied products will not pass the TAV procedure but fail due to a lack of resources or internal company priorities. Some may even fail because of clinical trial results that turn not out satisfactory [because of missing efficacy]. SmPCs will be harmonized in future according to the QRD template and will clearly illustrate indications, patient populations, as well as in- and exclusion of asthma. When handling SmPCs, subgroups like children, pregnant women, and elderly people will become more important and more attention will be paid based on new clinical research.

Besides all this, hope remains that upon a certain time a harmonized legislation for the regulation of AIT products within the EU will be available. With the progression of AIT development [in regards to the homologues group and lead allergen principle] and with the rising number of new marketing authorizations NPPs will become less important then. Standardization and process improvement as well as the implementation of biomarker research and progressive IgE testing [to replace skin prick testing] will move AIT into a direction which is led by the allied biologics and biosimilars today.

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AFFIREMATION

Ich erkläre hiermit an Eides statt, die vorliegende Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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APPENDIX I

Product	Oralair	Grazax	Puretal	ALK Depot SQ	Allergovit	Slit One Ultra	Depigoid
Marketing authorization	Yes	Yes	Yes	Yes	Yes	No	No
	2008	2006	1993	1990	1992	(TAV)	(TAV)
Available evidence *	3 adult trials	4 adult trials	0 trials	3 adult trials	1 adult trial	0 trials	1 adult trial
	1 children trial	2 children trials		1 children trial in Asthma			
Product nature	Natural Allergen	Natural Allergen	Natural Allergen	Natural Allergen	Chem. Modified Allegoid	Natural Allergen	Chem. Modified Allegoid
API	5 Grasses Mixture	Timothy Grass	10 Grasses Mixture	6 Grasses Mixture	6 Grasses Mixture	Pollen (NPP)	Pollen (NPP)
Route of Application	SLIT	SLIT	SCIT	SCIT	SCIT	SLIT	SCIT
Indication	Treatment of …	Desease modifiing effect for …	Treatment of …	Causal treatment of …	Causal treatment of …	Treatment of …	Treatment of …
Asthma inclusion	None	None	Incl. Asthma Bronchiale	Incl. Asthma Bronchiale and Asthma prevention	Incl. Asthma Bronchiale	Incl.light to medium concurrent Asthma	Incl. Asthma Bronchiale
Target population	Adults	Adults					
	Children (starting at 5 years)	Children (starting at 5 years)	Patients in general	Patients in general	Patients in general	Patients in general	*No information*
Exclusion criteria	Children below 5 years.	Children below 5 years.	Children below 5 years.	Children below 5 years.	Children below 5 years.	Children below 5 years.	Children below 5 years.
Further information			For children over 5 years, only few clinical data are available which are not sufficient for a proof of efficacy. However, data on the safety do not show any greater risk than for adults.	For children over 5 years, only few clinical data are available which are not sufficient for a proof of efficacy. However, data on the safety do not show any greater risk than for adults.	For children over 5 years, only few clinical data are available which are not sufficient for a proof of efficacy. However, data on the safety do not show any greater risk than for adults.		

* "Evidence" is described by the availability of an active marketing authorization and the listed number of BDPC trials with a statistic siginificant result of at last 20 % efficacy against placebo.

13 – SmPC Review (19), (96), (84), (86), (85), (18), (100)