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POINT OF VIEW

Requirements of a new allergen regulation

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Rafael Llàtser from Hospital de Santa Tecla de Tarragona, asked Ana Tabar about the convenience of food oral challenges in outpatient clinic in pediatric population. A. Tabar answered that there is a gap among clinical practice, investigation and regulation. Safety is always a priority for practitioners, but it must be a place for off-label practices mainly in investigation in order to prove some hypothesis.

A. Tabar stated that allergists were expecting a final document from AEMPS because allergen immunotherapy is actually a good product, a therapy that in fact, works properly. She wondered if a faster procedure could be possible, considering that new regulation seems to be mandatory. She asked whether a stepwise approach could be considered.

M. Timón clarified that the draft is finished and waiting for publication. The document proposed seems to establish different regulatory routes for different types of allergen products. He commented that regulation is mandatory in this field because it enables the evolution toward new and large clinical trials with better products, but there are some issues that must be elucidated.

Abbreviations: AEMPS, Agencia Española de Medicamentos y Productos Sanitarios; AIT, allergen specific immunotherapy; EMA, European Medicines Agency; NPP, named patient products; MS, mass spectrometry.

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Background: Allergy vaccines are manufactured from natural allergenic sources, which have an intrinsic variability in their protein composition. Exhaustive control-in-process from the early stages and a deep standardization of the manufacturing methods contribute to the consistency of the final product. There is a wide range of products for diagnosis and Allergen-specific Inmmunotherapy (AIT) all around EU. There are great differences regarding manufacturing process, standardization methods and potency between products. These differences make the comparison difficult.

European Medicines Agency (EMA) has been working in a new guideline for allergen extracts. The objective of this new version was to provide the principles and guidance for manufacturing and quality control of allergen products of biological origin, including allergen extracts from natural source materials, which are the current base for the manufacturing of AIT.

In Spain, AIT products are mainly distributed as medicinal products manufactured for an individual patient, called named patient products (NPP). The distribution of these products as NPPs should not be the choice for our most prevalent allergies, such as dust mite or grass pollen allergies. In this context, a proposal by AEMPS has been draft for better vaccines that benefit the patient and improve the AIT prestige.

M. Merino, explained that both industry and clinical practitioners, know the draft from AEMPS. Regarding allergens for in vivo diagnostics, she asked if a specific dossier

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to regulate their quality had been proposed. M. Timón described that AEMPS wants to avoid a very strict regulation, like in Germany, where some dossiers could not be released because of the regulation. He exposed the dossier maintenance is expensive, not only the product authorization. There are some fees that must been paid, as well as keeping the product pharmacovigilance. Sometimes the whole process could be too expensive. Looking for better solutions, AEMPS is studying how to regulate the allergens that would not be profitable but are clinically relevant for diagnosis. Perhaps joining together allergens belonging to the same group of diagnosis under the same umbrella of authorization could be a solution.

S. Vieths described the regulation approach in Germay. They were putting the most frequent allergens in the country as pollen, mites and insect venoms and the demand of authorization. They wanted to be fair with manufacturers and give them the chance to generate data. These data could be the same for the products in Spain that have been in the market a long time, 20 or 30 years. A long transition period was offered to the companies in order to generate data, up to seven years after receiving the deficiency letter. They did a stepwise approach because the intention is not to kill the market. During the first period, when the deficiency letter has been sent with the quality requirements, the product is still on the market.

Jerónimo Carnés, (I+D Department of Leti Laboratories) explained that allergoids are products that offer a challenge for characterization, being very complicated after their chemical modification. Even it is more difficult for minor allergens. Techniques for quantification such as mass spectrometry are currently being developed. How do you see the transition between the current quantification of major allergens from recombinants to mass spectrometry (MS) in an acceptable regulatory way? S. Vieths answered that currently is not possible to switch from recombinant allergens to MS, and it is not the plan. Whether the quantification of peptide of the allergen in allergoid by MS works properly, this fact has to be shown.

J. Carnés wondered how to establish the link between the quantification with monoclonal antibodies with an hypothetical method with MS in the future. He hypothesized that probably, the result in numbers, using those techniques would be different. S. Vieths replied that this question is difficult to answer; because results from these different specific methods to quantify allergens are usually not comparable.

Background: Polymerized allergenic extracts (allergoids) are commonly used in allergen Immunotherapy across EU. Chemical modification is thought to reduce the side effects in AIT while retaining immunogenicity. The resulting allergoid cannot be assessed by common analytical methods like immunoassays, so its analysis was usually limited to demonstrating the reduction in IgE reactivity. Clinical efficacy and safety of some of these modified extracts have been demonstrated. MS has been used as a tool to identify novel allergens or to prove identity and enhance the quality control of recombinant allergens. In addition to identifying proteins, MS may accurately quantify selected proteins.

Recently, allergen sequences have been recognized by mass spectrometry in depigmented and polymerized extracts of house dust mite and Betula, suggesting preservation of major and minor allergens. Nevertheless, publications on allergoid-specific characterization methods are still scarce proportionally to those with native extracts.

José Luis Justícia, Medical Director of Allergy Therapeutics, asked M. Timón about the batch releasing. He described how the releasing batch was performed in Germany, where a permission is needed for each lot. M. Timón answered the there is no plan in Spain to release batch by batch. Finally J.L. Justícia, wanted to know if there is a project to regulate under the same regulatory principles in the all the member states of European Union. M. Timón explained that the regulatory framework in EU remains heterogeneous, but there are quite common bases. Each state adapts its regulation to its current market, so there is no common plan in the short term.

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