

Correspondence

Reply

To the Editor:

Reviewing such a broad topic is formidable given many differences in extracts, manufacturing, clinical diagnoses, treatments, and regulation of new product development.¹ In our attempt to present a concise review of differences between continents, we did not intend to minimize the role of the US Food and Drug Administration (FDA) in assuring quality, safety, effectiveness, and labeling of allergen products, as suggested in the correspondence by Rabin et al.²

Our descriptions of FDA regulations included approaches to evaluate older nonstandardized products as well as recent published reviews. We cited an FDA report of internal and external reviews of nonstandardized extracts.³ Efforts undertaken by an expert panel from 1972 to 1979 led to the assignment of these products to aforementioned categories (see 21 CFR 601.25), with most classified as IIIA (ie, favorable risk/benefit ratio). A second panel convened (see 21 CFR 601.26) in the 1980s to review IIIA products, but recommendations were not published. Our oversight was not to mention in detail the current reclassification proposal, yet to be completely implemented.

In 2011, the Allergenic Product Advisory Committee advising the FDA was convened to update the first panel's classification into 5 tables.⁴ Tables 1-3 listed approved extracts. Extracts in Table 5 were considered potentially unsafe. We regret that we failed to mention subsequent revocation of licenses of 15 products in Table 5.

Our review did not intend to imply that the FDA does not provide consistent advice to manufacturers but only that there is no single guidance document outlining the regulatory pathways for approval of new allergens in parallel to the formally developed European Medicines Agency (EMA) guidelines. We agree with Rabin et al that the FDA provides valuable pre- and post-licensure advice to manufacturers. We also recognize that the FDA has guidance documents that describe FDA's current thinking on a range of regulatory topics (see <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/international-council-harmonisation-ich-guidance-documents>).⁵ Nevertheless, our review was accurate in stating that each product under development in the United States is considered separately by the Center for Biologics Evaluation and Research (CBER) because FDA guidance documents allow for the use of alternative approaches provided these comply with applicable laws and regulations.⁵ We appreciate that International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance documents are also considered as part of FDA's guidance.

Our description of new product development (Fig 1, A) shows a recent US sublingual immunotherapy tablet development program where non-US phase II studies were evaluated along with US-generated data; it does not imply that the FDA generally requires non-US phase II data. We appreciate that the FDA accepts US phase I, II, and III data. Even though US and European Union (EU) regulations have evolved independently, we believe that many aspects of allergen product approval processes are similar.

Finally, we regret the implication that quality, safety, and efficacy for authorization of EU allergen products were not also included in the US section. The criteria for new allergen products in the US entail comparable requirements for quality, safety, and

effectiveness. We agree that a positive benefit/risk ratio is also an essential requirement for US licensure.

Overall, we think our review offered an accurate view of the practice of immunotherapy in the 2 continents. We agree with Rabin et al, FDA, on some points and think we have clarified those here.

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