

Letter to the Editor

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Establishing objective analytical quality requirements in the IgE specific assay: a message in a bottle

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To the Editor,

The determination of the “allowable total error” in Laboratory Medicine is the first step in the evaluation of the analytical performance of a method and in establishing internal quality control requirements.

A hierarchical list of the strategies to set quality specifications were proposed by Fraser [1] and established at the “Stockholm Conference” in 1999 [2] and, in order of relevance, include criteria based on the clinical outcome, on the biological variability, the professional recommendations, the regulation bodies or EQA schemes and the current state-of-the-art.

The specifications based on the effect of laboratory data on clinical decisions are considered the most relevant and therefore the best theoretical approach for the determination of quality specifications. Unfortunately, it is an approach difficult to apply, as it can be often subjective and there are only a few scenarios where standardized medical strategies are applied. Consequently, this approach is very rarely employed and, despite numerous attempts of different proposals [3], the strategies based on the biological variability are still the most widely used to determine the performance limits of a method.

However, there are cases in which it is not possible to obtain reliable data on the biological variation according to standardized procedures. As for the tests for the

determination of specific IgE, it is unlikely to hypothesize an homeostatic control and moreover in normal situations the concentrations are almost undetectable.

In the CLSI I/LA20-A2 guideline, dedicated to the IgE immunological assays [4], some quality recommendations for manufacturers are outlined, but they seem mainly based on established habits and state-of-the-art criteria.

Years ago, models were proposed in which the concentrations of IgE were put in relation with the probability of presenting clinical symptoms of allergy [5–7]. These were experimental approaches, which showed a trend toward an increase of the probability of clinical evidence of disease with the increase of specific IgE levels, particularly for inhalant allergens. The information are quite heterogeneous, depending on the type of allergen considered, and so far has had a rather theoretical use.

However, the curves established in these past models and their confidence interval (CI) could be used to obtain ranges of IgE concentrations that provide the same probability to find allergic symptoms in a subject (Figure 1).

As an example of this graphical approach, the curve described in Söderstrom et al. [8] has been used. It showed the relationship between concentrations of IgE for *Dermatophagoides pteronyssinus* (D1) and allergen specific diagnosis, and was chosen by the authors, among those previously published [7], to illustrate the confidence interval of the probability of symptoms for each concentration of specific IgE. On the basis of the above mentioned curve, three ranges that cannot be considered significantly different from the clinical point of view have been graphically extrapolated, according to the method outlined in the Figure 1 legend, starting from 0.2 kU/L (the minimum value represented in the graphic). These approximated concentrations and the percentages of allowable total error (ATE) are given in Table 1.

These parameters were applied to the data obtained in our laboratory for the allergen D1, measured using Immuno-CAP250 analytical platform (Thermo Fisher Scientific). The bias (+4%) was derived from the 2013

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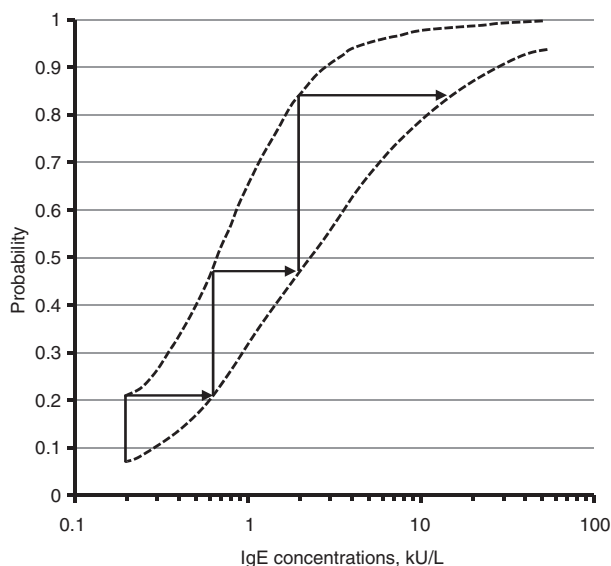


Figure 1: Example of a possible relationship between specific IgE concentrations and the probability of clinical symptoms. The dotted curves represent the 95% confidence intervals. The vertical bars represent the range of probability of symptoms at a given concentration. The highest concentrations that show overlap of probability with respect to the previously identified level are pointed out by the arrows. All the levels between these two concentrations (the range is represented by the same horizontal arrows) cannot be considered significantly different from the clinical point of view.

Table 1: Determination of the allowable total error (ATE), expressed as percentage of the deviation of the ranges of the “clinically equivalent” values with respect to the mean.

Range of IgE concentrations, kU/L	Mean of concentrations, kU/L	ATE, %
0.2–0.6	0.4	50
0.6–2.0	1.3	53.8
2.0–17.0	9.5	78.9

results of the External Quality Assessment *OneWorld-Accuracy*. The imprecision was derived from an evaluation of a serum pool (31 determinations for each level over a period of 2 months with two calibration runs), and the coefficient of variations were 9.1% (mean 0.36 kU/L), 7.9% (mean 2.54 kU/L) and 8.13% (mean 23.6 kU/L).

Using the smallest value of ATE (50%) and the imprecision estimated close to the corresponding levels of IgE (9.1%), we are able to calculate the minimum value of sigma metric ($\sigma = (\text{ATE} - \text{bias}) / \text{imprecision}$) obtaining a sigma value of 5.05.

This is a proposed example of a possible approach for the determination of the quality specifications in the measurement of specific IgE. This example is based

on published data concerning the clinical utility of the method, the best approach from the proposed strategies, and developed with objective criteria. As the assay of specific IgE refers to the same standard curve, it is reasonable to attribute the same value of ATE for different allergens.

Of course, besides the fact that the practical example here presented is simply a graphical approximation, this model has some limitations.

The probability data and CI so far available should be updated. Ideally, the previously described curves should be produced center by center or at least within small geographical areas, although the construction itself of the curves is not easy.

Another limitation is that the curves concerning various allergens are very different, and even within the same allergen they probably cannot be transferred from one clinical setting to another one. However, an alternative approach could be the use of homogeneous groups of allergens, adding together the results, as proposed by Wickman et al. [9].

It is also true that the confidence intervals may be narrower if a great number of homogeneous cases would be included in the analysis. However, in this case it would mean that the clinical significance of the IgE specific determination would be stronger, and then it would be reasonable to request for more stringent quality specifications.

Despite the limitations outlined above, it may be worth trying to use this strategy to ensure the establishment of objective analytical quality requirements for the determination of specific IgE assays, especially in the challenging scenario of the increasingly emerging “component resolved diagnosis”.

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