The definition of relative potency (RP) requires that the two products are similar, that is, that they have parallel dose-response curves.

This assumption can be violated by biosimilars. If it is then the relative potency does not exist as a single quantity.

The purpose of this poster is to encourage discussion on this important topic by a) reviewing current practice and b) exploring some alternative options in this situation.

A total of 20 Antibody Dependent Cell Cytotoxicity (ADCC) assays comparing the associated activities of Remicade and Remsima.

We fit the dose-response curve with a four-parameter logistic (4PL). The parameters are A (the lower asymptote), B (slope parameter), C (the EC50) and D (the upper asymptote).

There were no systematic differences between the lower asymptotes or the slopes.

However, the upper asymptote was consistently lower for Remsima than for Remicade.

This graph shows an example assay. The difference in upper asymptotes is clearly visible.

One option is to fit a non-parallel model, calculate the EC50 for each line, and report their ratio (relative binding) [1].

What non-parallel model should be used? For a 4PL, can either fit a completely non-parallel model, or constrain some of the parameters (e.g. the asymptotes or the slope) to be equal.

In this example, since we observe no systematic differences for the lower asymptote and the slope, we constrain them to be equal for both lines.

This example shows two lines with the constrained 4PL fits and the EC50.

The ratio of the EC50 is 0.88 with a 95% CI of (0.78, 1.01).

This can be misleading. The EC50s occur at different response levels. Their ratio is not the horizontal distance between the lines.

Separately, report also the ratio (or difference) of the upper asymptotes. The ratio is 1.28 with a 95% CI of (1.19, 1.38).

An alternative is to look at the relative potency over a range of responses [1].

Stage 1: Fit a non-parallel model. As above, we constrain the lower asymptotes and slope parameters to be equal for both lines.

Stage 2: Calculate the relative potency:

Stage 3: Report the RP as a function of response:

This shows the complete behaviour. In this case, can see that the RP is lower at higher responses.

Inconvenient to report a whole graph. Can this information be condensed?

For this example we could report the difference in C parameters (ratio of EC50s) and the difference in D parameters (relative response). These are the only differences between the fits, so contain all the information about the difference between the materials.

– Difference in D parameters is the difference in the upper asymptotes. Intuitively, this is the difference in the maximum effect of the materials.

– But difference in C parameters (ratio of EC50s) can be misleading – see previous box.

Or report ratio of the doses needed to achieve 50% of the maximum reference response; this has the advantage that the same response level is being compared between the lines. In this example the ratio is 0.76 with a 95% CI of (0.66, 0.87).

Alternatively, summarise the behaviour of the RP as a function of response:

"For responses in the range 0.2 – 1.0, the RP is always between 0.57 and 0.82 and the 95% CI for the RP is always between 0.46 and 0.92."

Or convert the behaviour of the RP and its CI over a range of responses into a single mean RP and CI for that range.

"For responses in the range 0.2 – 1.0, the mean RP is 0.74 and the 95% CI is (0.60, 0.92)."

These options are as yet all untested in a regulatory framework.

The usual definition of relative potency may be inappropriate for some biosimilars. We have presented some alternative choices which are more suitable and showed examples of their use. Further work is required to decide the most appropriate approach.

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