Statistical approaches for reporting potency of biosimilars – what to do with non-parallel curves?

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Introduction

- 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.
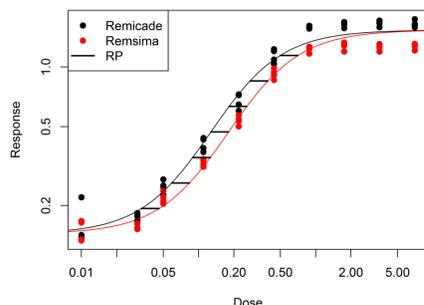
Example

- 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 EC_{50}) 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.**
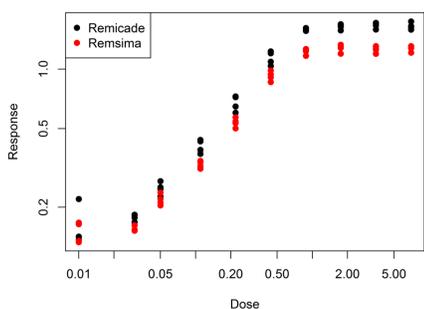
Current practice: use the RP anyway?

- It is tempting to ignore the difference in the upper asymptotes and calculate the RP anyway.

- Fit a parallel model.

- The RP is the horizontal distance between the curves.

- In this example the RP is 0.71 with a 95% confidence interval (CI) of (0.60,0.83).

- **This is not recommended**. The RP should be the amount by which a material has to be diluted so that it behaves in the same way as the reference material. If the dose-response curves are non-parallel, there is no dilution which will make them the same.

- Furthermore, the model will be a poor fit. This will lead to inaccurate estimates of the CIs.

- If the amount of non-parallelism is large, it cannot be ignored. A non-parallel model should be used. What can be extracted from it?

Current practice: ratio of EC_{50}s

- One option is to fit a non-parallel model, calculate the EC_{50} 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 EC_{50} s.
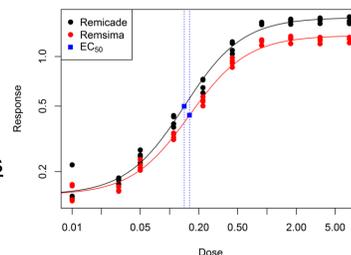
- The ratio of the EC_{50}s is 0.88 with a 95% CI of (0.78, 1.01).

- **This can be misleading**. The EC_{50}s 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).
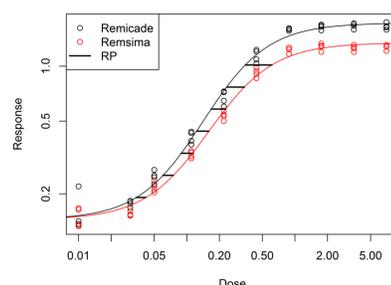
Alternative option: RP over a range of responses

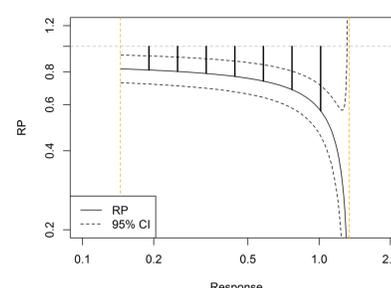- An alternative is to look at the relative potency over a range of responses [1].

- Stage 1: Fit a non-parallel model. As above, we constrain the lower asymptotes and slope parameters to be equal for both lines.
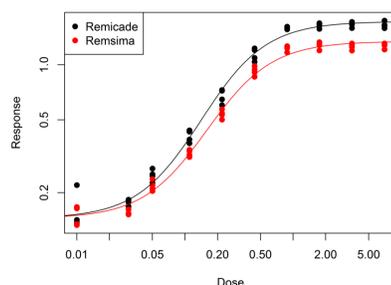
- Stage 2: Calculate the relative potency:

- 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?**

Options for reportable values

- For this example we could report the difference in C parameters (**ratio of EC_{50}s**) **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 EC_{50}s) 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.

Conclusions

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.

Acknowledgements

References

[1] Dinse G.E. and Umbach D.M. 2011. Characterizing non-constant relative potency. *Regulatory Toxicology and Pharmacology* 60 342–353.

About the authors

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