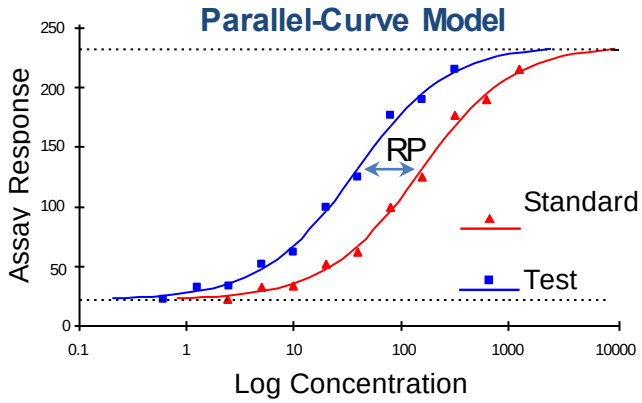
The UCB statistical department for Chemical, Manufacturing and Control is looking for a Master student in statistics who can support our team in the development of a new methodology. We propose 3-5 months unpaid internship at UCB. During the internship the student will work on a statistical methodology for bioassay development. Results of the project could be used by the student for a master project. We would hope to begin the internship as soon as possible.

Description of the problem.

Potency is a critical quality attribute to support development and release of biopharmaceutical products. Protein-drug potencies are assessed by using biological assays which mimic a product's known mechanism of action. Because of the inherent variability of biological assays, potency is not an absolute measure. Rather, it is calculated by comparing the test results with a reference standard (relative potency, RP).

The comparison methodology is based on the assumption that test and standard behave similarly in a bioassay because they contain the same effective analyte. (1) Consequently, the test and standard dose response function curves should share common functional parameters and differ only in a horizontal displacement, see Figure 1.

Figure 1: Parallel-curve Model



Testing for parallelism is a fundamental requirement for assessing the validity of bioassay data used in relative potency calculation.

Typically, the 4-parameter logistic (4PL) function is adequate to describe the non-linear response curve of a bioassay.

$$Y = \frac{(A - D)}{\left(1 + \left(\frac{x}{C}\right)^{B}\right)} + D$$

Where Y is the assay response, A is the response at zero analyte concentration, D is the response at infinite analyte concentration, C is the inflection point (also known as EC50), B is the hill-slope (steepness) of the curve and x is the analyte log(concentration).Relative Potency (RP) is a measure obtained from a comparison of the dose-response relationships of test and standard drug preparations. RP = Horizontal distance between test and standard dose-responses if and only if they are similar.

For a 4PL modelisation of the curves, the relative potency is

$$RP = \frac{C_{standard}}{C_{test}} = \frac{EC50_{standard}}{EC50_{test}}$$

United States Pharmacopeia (USP) (2) suggests testing parallelism using an equivalence method. One way of conducting the equivalence testing is by using an intersection union test (IUT) (3, 4). The objective is practical implementation of the IUT approach. The approach consists of an evaluation of the parameters ratios of the dose-response curves.

A reparametrization is used:

$$\mathrm{f_i} = \mathrm{d_i} - \mathrm{a_i}, \qquad \mathrm{s_i} = -\frac{(\mathrm{d_i} - \mathrm{a_i})\mathrm{b_i}}{4},$$

Then the ratios of interest are

$$\mathrm{r_1} = \mathrm{a_1}/\mathrm{a_2}, \qquad \mathrm{r_2} = \mathrm{f_1}/\mathrm{f_2}, \qquad \mathrm{r_3} = \mathrm{s_1}/\mathrm{s_2}$$

In the framework of the IUT practical application we need to set equivalence limits for each ratio and study the impact of their mutual variations on the parallelism detection. The second problem is practical calculation of one-sided tolerance limits

for the upper confidence limits of the parameters ratios. This method takes into account the precision with which each ratio is generated.

1. Bortolotto E, et al. (2015) - Assessing similarity with parallel-line and parallel curve models . Implementing the USP development/validation approach to a relative potency assay. *BioProcess Technical*, June 2015, 13(6).
2. USP Chapter <1032> *Design and Development of Biological Assays.* USP Pharmacopeial Convention: Rockville, MD, 2013.
3. Jonkman J. and Sidik K. (2009) - Equivalence Testing for Parallelism in the Four-Parameter Logistic Model. *Journal of Biopharmaceutical Statistics*, 19:5, 818-837
4. Yang H, et al. (2012) - Implementation of Parallelism Testing for Four Logistic Model in Bioassays. *PDA J. Pharm. Sci. Technol.* 66, 262–269