Transfer of a receptor occupancy assay in phase I: a sponsor's perspective

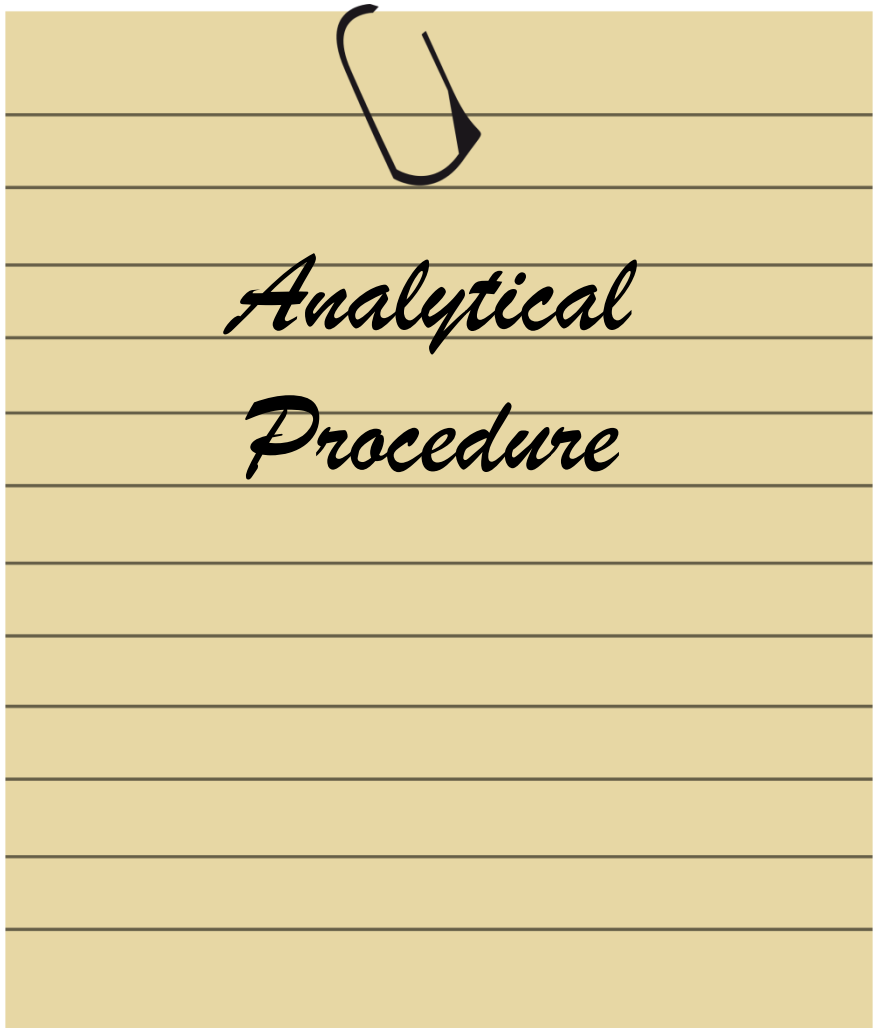
Hervé Farine

Department of Translational Science – 15 Nov 2017

Table of content

- What to transfer?
- Method transfer process
- Case study
- Points to consider to fly with flow in phase I

What to transfer?



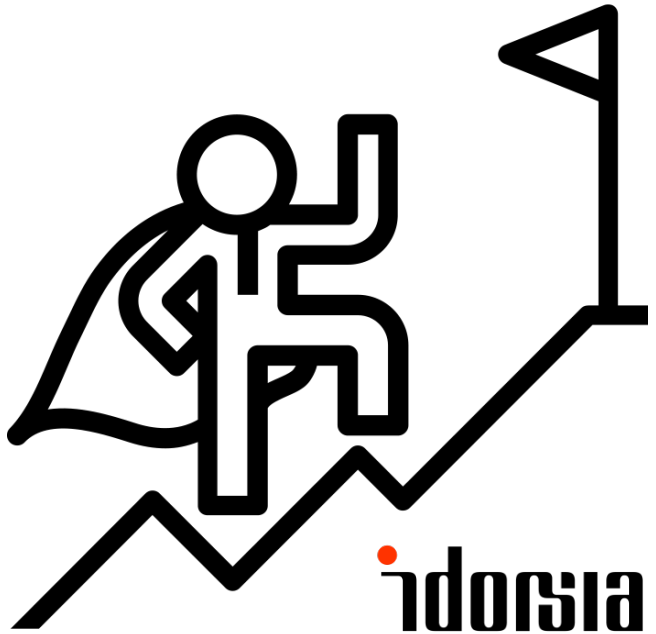
What should be transferred in addition to the method?

Knowledge

Skills

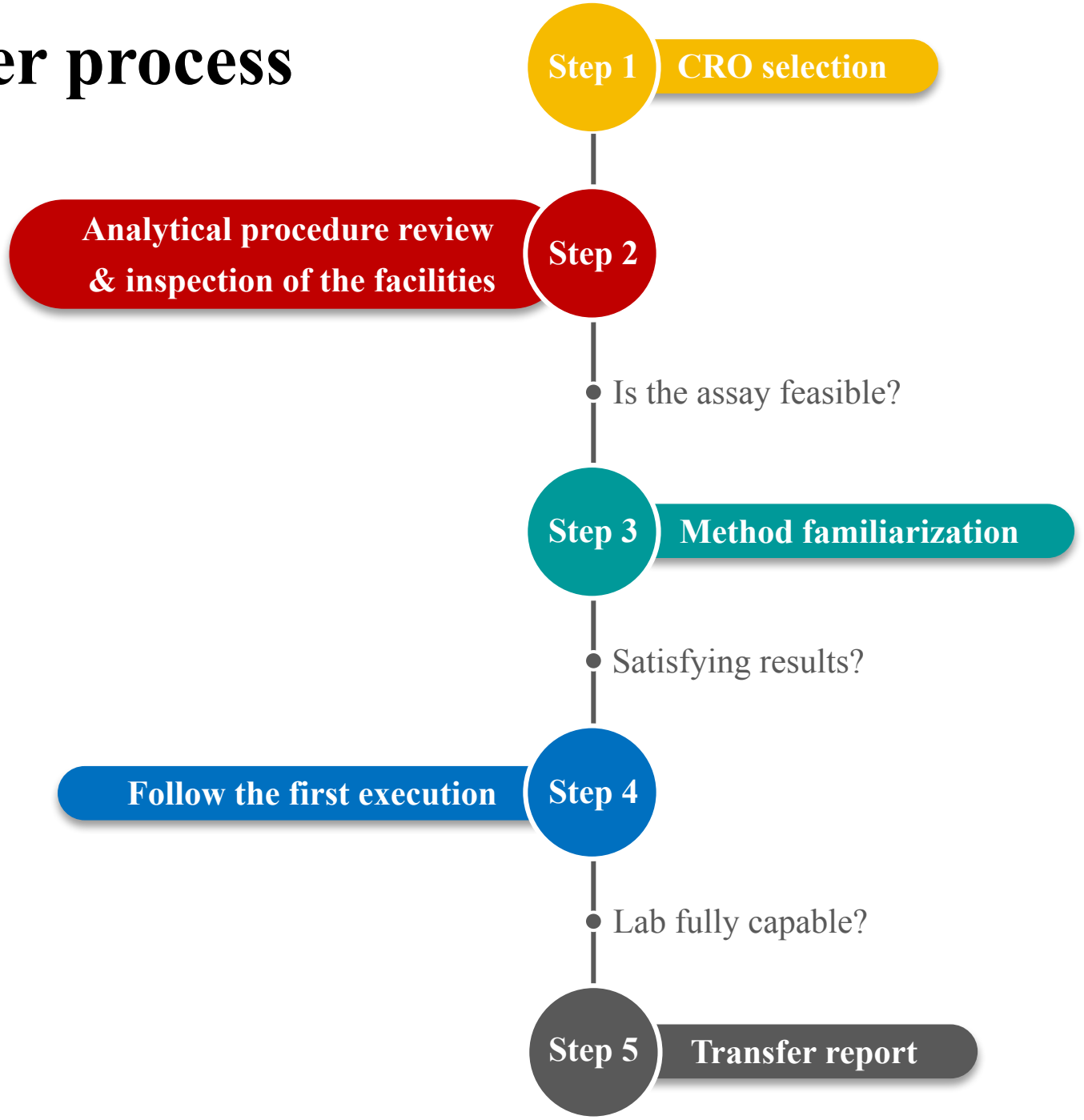
Method transfer and the associated challenges

- Different laboratory cultures / practices
- Different languages / countries
- Different parts of the analysis may be performed at different sites
- Distance / travel / cost
- Personnel changes
- Different interpretation of guidance



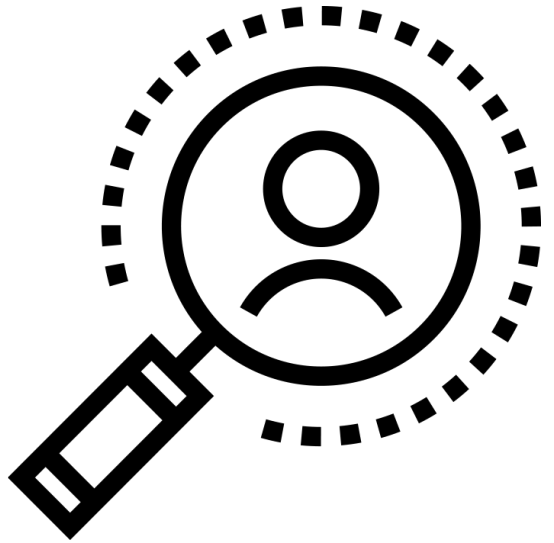
Adapted from Galen Radebaugh 2010

Method transfer process

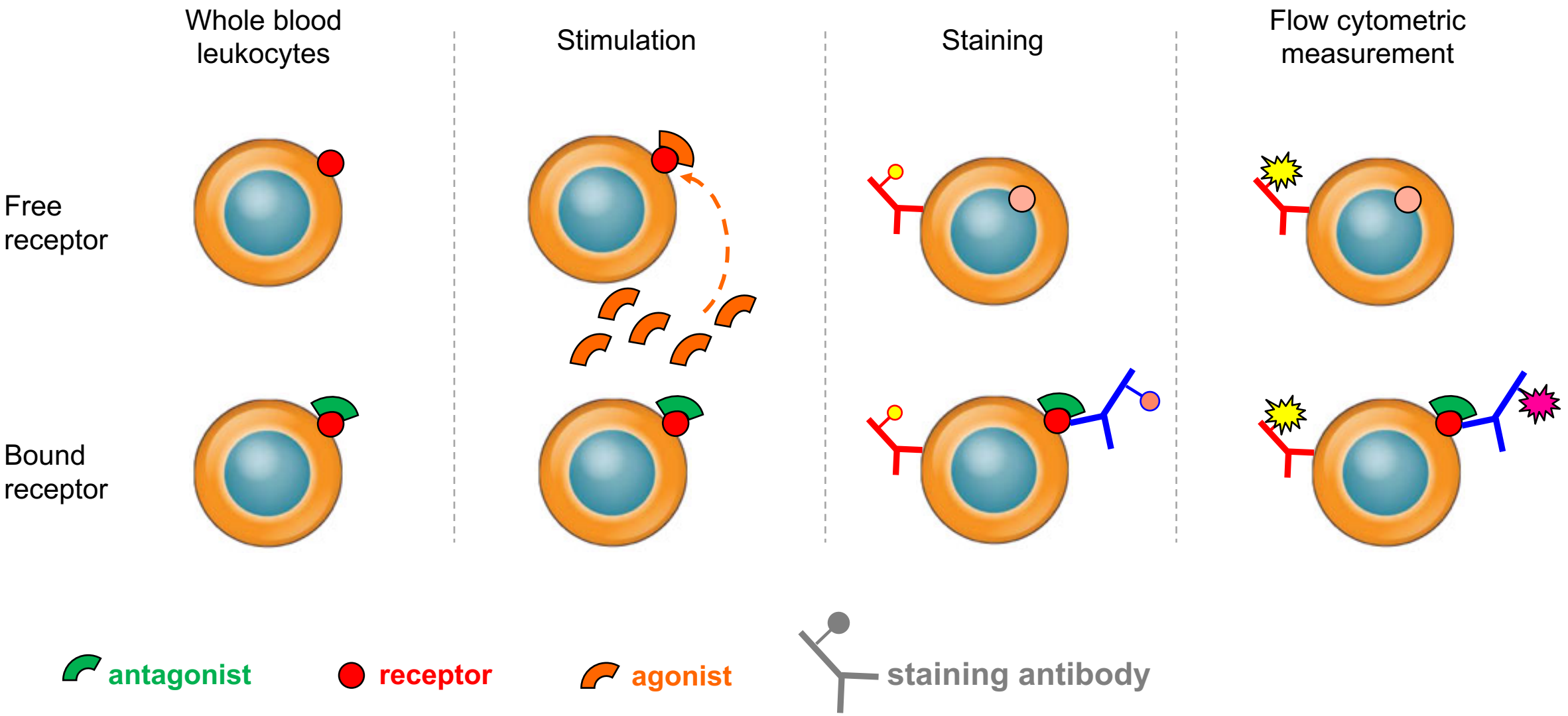


Case study

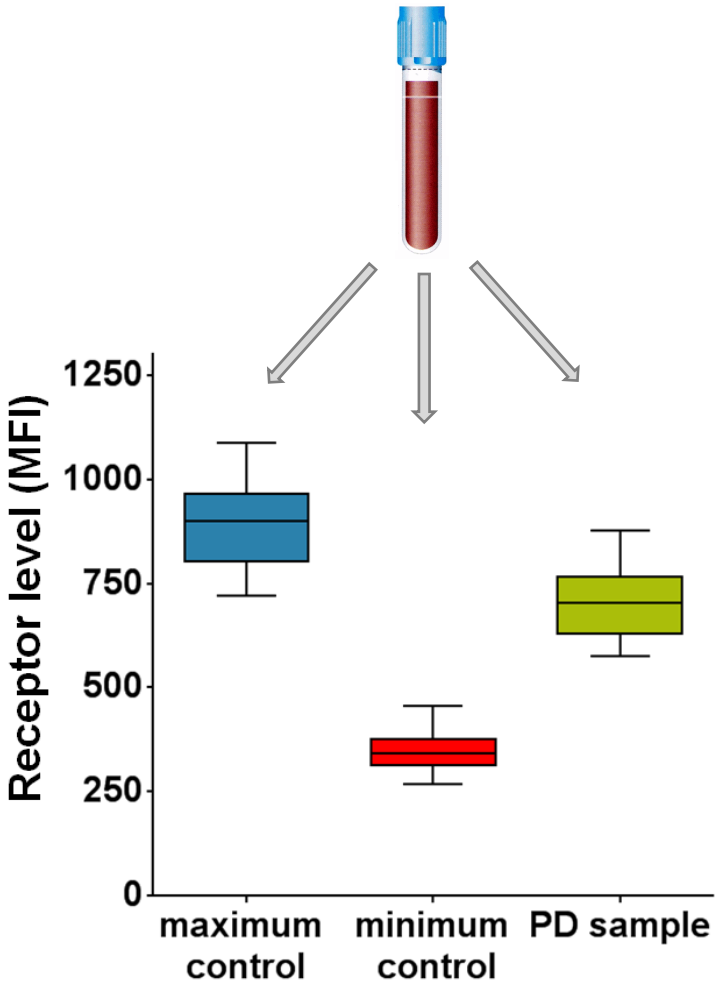
Entry into man study using a receptor occupancy (RO) assay to assess PD effect



RO assay principle



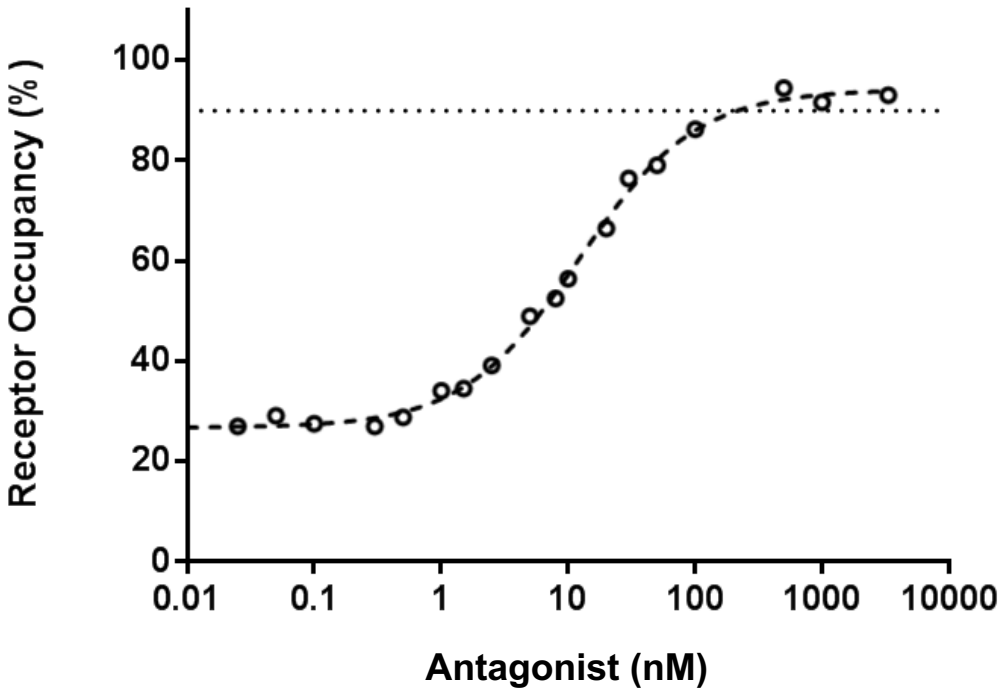
Data normalization



normalization

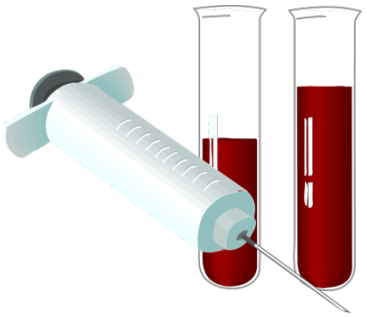
$$RO\ (\%) = \frac{PD - min}{max - min}$$

Pharmacodynamic (PD) effect



RO in the phase I clinical trial

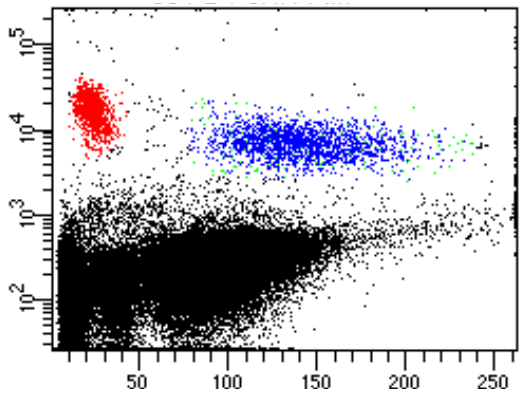
Clinical site	Flow cytometry facilities



Sampling

Sample preparation

Storage and shipment



Sample measurement

max 24 hrs

Method familiarization

1

Presentation

- assay protocol
- results obtained
- system suitability criteria
- highlight the critical steps

2

Training session in the lab

- 2 fresh EDTA blood samples
- 2 to 3 antagonist concentrations
- 1 vehicle

Team

- 5 technicians for the clinical site
- 2 technicians for the flow cytometry facilities
- 2 lab managers

Results of the training session I

RO (%)	Expected values	Technician 1	Technician 2	Technician 3	Technician 4	Technician 5
Control	25-35	33.4	No value *	36.0	33.7	176.1
1 nM antagonist	30-40	37.7	54.2	90.4**	44.6	71.4
10 nM antagonist	60-70	73.0	353.1	64.0	79.5	154.1
100 nM antagonist	90-100	88.7	34.9	40.2**	99.6	61.1

Values far from the target values

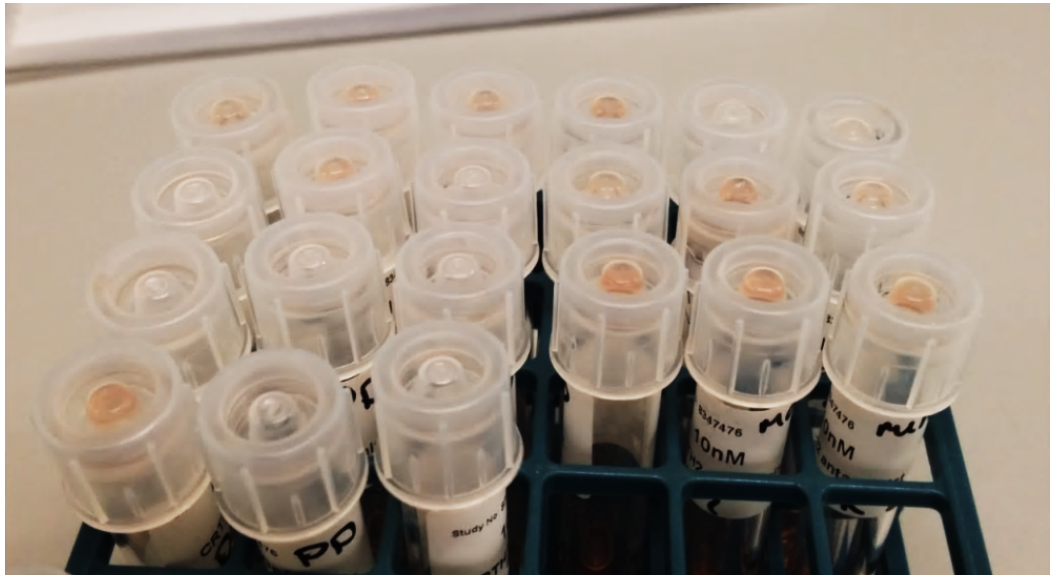
* No values due to lack of precision for the dispensing of the 20 µl of staining reagent

** tube identity mixed up

High heterogeneity in the PD effect measurement

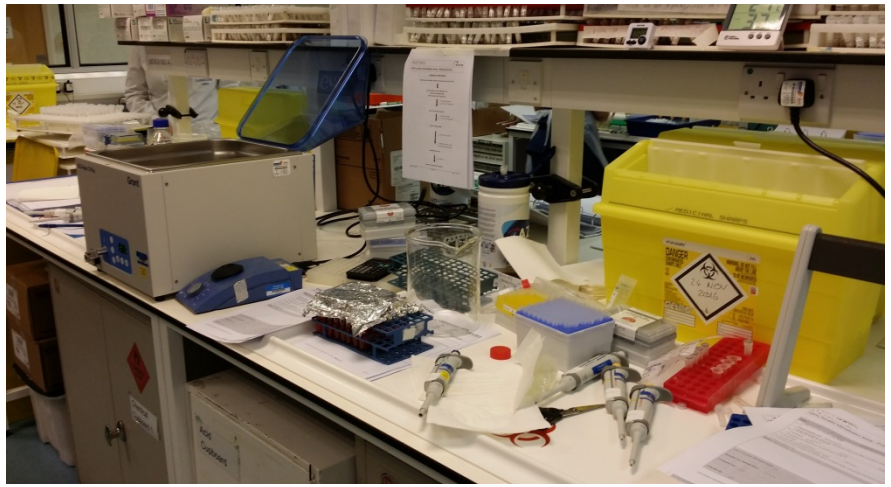
Cause of the problems

- Difficulties in dispensing small volume accurately due to inappropriate pipetting device
- Not enough focused on the work
- Shaking during the transport



Corrective actions

Before



After

Results of the training session II

RO (%)	Expected values	Technician 1	Technician 2	Technician 3	Technician 4	Technician 5
Control	25-35	27.8	36.6	31.3	32.1	42.6
10 nM compound	60-70	77.4	66.7	60.3	69.9	88.9
100 nM compound	90-100	107.5	91.8	93.5	93.5	81.3

Entire phase I

- 213 samples performed (639 tubes)
- No missing point
- 4 re-measurements (due to uncertainty or pipetting mistake)

Points to consider to fly with flow in phase I

Sponsor's tasks

- Know your assay
- Good SST
- Be on site
- QC of the critical reagent
- Use of IVD reagent
- Offer post-transfer support

@ the CRO site

- Laboratory equipment
- Efficient documentation systems
- User friendly features
- System to double check the tube ID

Team work

- Avoid extra outsourcing
- Face to face meetings are preferable over teleconferences
- Proactive collaboration
- Minimize the number of operators

Thank you!

Acknowledgment

Drug Discovery

Daniel Strasser

Peter Groenen

Clinical Development

Jasper Dingemanse

Martine Gehin

Milena Issac