# A workflow for comparing drug candidates based on Probability of Pharmacological Success (PoPS)

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## Objective

To efficiently compare candidate drugs in early-stage drug development by introducing the concept of cumulative PoPS as an extension to the previously developed framework [1, 2].

## Conclusion

The extended PoPS concept is useful in informing early-stage drug-development decisions. The established workflow offers meaningful gains in terms of efficiency, quality control and accessibility.

## The case study : dual agonists for Neuropathic Pain

Three candidate molecules (ABC001, ABC002 & AC003) are developed with affinity for two different targets T1 and T2.

Target engagement of T1 ≥ 90% is aimed as the efficacy criteria while modest activation of T2 (20-40%) appears to potentiate the primary pain relief effect of T1 activation.

Potency studies have been conducted in mice as well as in vitro. ABC001 is full T1 and T2 agonist while ABC002 and ABC003 are full T1 and partial T2 agonists (with negative cooperativity for the latter candidate).

PK and toxicology have been analyzed in three animal species and revealed average plasma concentration as the relevant exposure metric ($C_{ss,av}$). The No Observable Adverse Effect Level (NOAEL) for $AUC_{ss}$ ($C_{ss,av} = AUC_{ss}/\tau$) in the most sensitive species is dose limiting.

## Data and methods

The template workflow was developed for RStudio and Quarto, including these steps:

**Input data**

Standard defined & optional GUI for data entry.

Ability to handle any combination of assets and endpoints.

Information is split:

- Parameter input file: PK (e.g. CL & Vc) and PD (e.g. $EC_{50}$ & $E_{MAX}$) parameters with the flexibility regarding inclusion of between subject variability and parameter uncertainty.
- Criteria input file: Criteria defining dose and exposure ranges (see case-study example below) + doses assessed as a range or as discrete values of interest.

| | | Individual target criteria | Population success criteria |
|---|---|---|---|
| *Efficacy* | T1 | Engagement ≥90% | ≥50% of population within individual target |
| | T2 | Engagement ≥20% & <40% | |
| *Safety* | Exposure | $C_{ss,av}$ < NOAEL | ≥90% of the pop. < NOAEL |

**Exposure-response and dose-exposure models**

Relationships are user defined by referencing parameters from the parameter input file. The template includes illustrative examples of how this is done.

The rest of the template section is generic but customizable: it automatically generates simulations, plots and text output based on the above user defined information (e.g. figure 1).

**Dose-response**

Generic output based on the input in the above sections illustrating between subject variability as well as uncertainty (View example output with the QR code).

**Probability of Pharmacological Success**

For each dose, simulated response and exposure are compared with their respective individual targets criteria.

Proportion of individuals meeting the criteria is then derived and evaluated against the population-level criteria (view example output with the QR code).

PoPS is the probability to jointly meet all population success criteria (see figure 2). The cumulative PoPS is the probability that a particular dose or any lower dose fulfils all the criteria (see figure 3).

The cumulative PoPS can also be derived for a limited number of district doses of interest (e.g. doses for a planned study).

## Results

The Quarto document can be rendered as an html or pdf output.

Click to see complete example output in web format

### Selected extracts of the output

Figures based on 200 sampled populations of 200 individuals each.

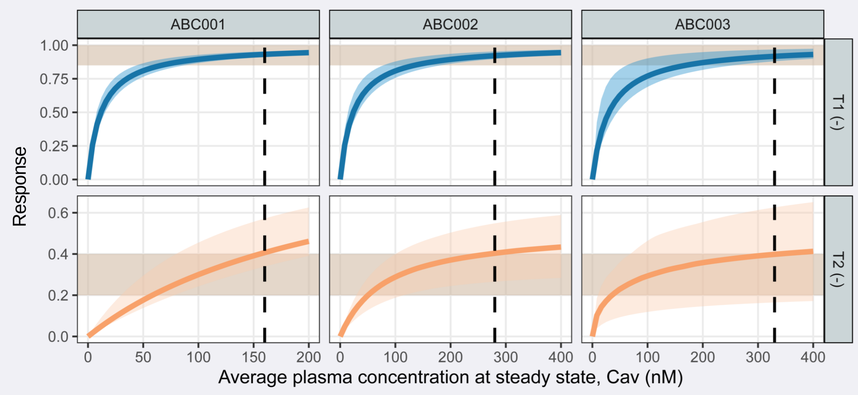


Figure 1. Concentration-response relationships presented with the median prediction (thick colored line) and a 95% confidence interval (shaded area). The target response ranges are indicated with shaded brown areas. The upper exposure limit (NOAEL) is indicated by vertical dashed lines.

Assets ABC001 and ABC002 were found to have relatively similar maximum PoPS for their most likely therapeutic dose (48% vs 44%) outperforming ABC003 (28%).

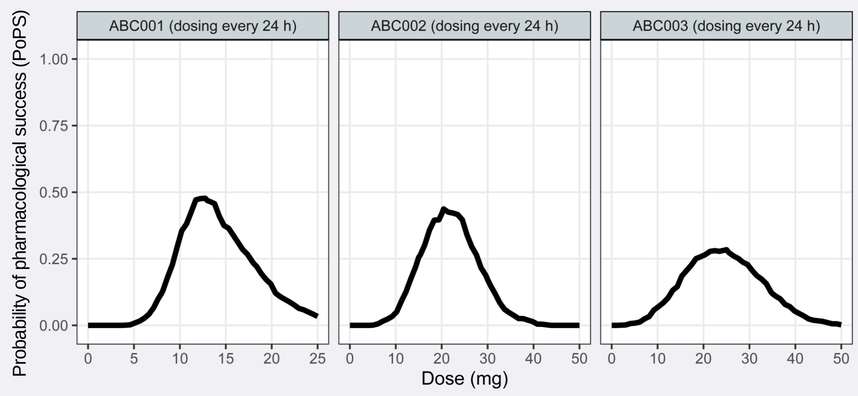


Figure 2. Relationships between dose and the composite probability of pharmacological success (PoPS). The maximum PoPS for each respective asset is 48% at 12.8 mg for ABC001, 44% at 20.4 mg for ABC002 and 28% at 25 mg for ABC003.

However, ABC001 demonstrated a clear benefit in terms of cumulative PoPS across a wider dose range (98% vs. 87% and 63%).

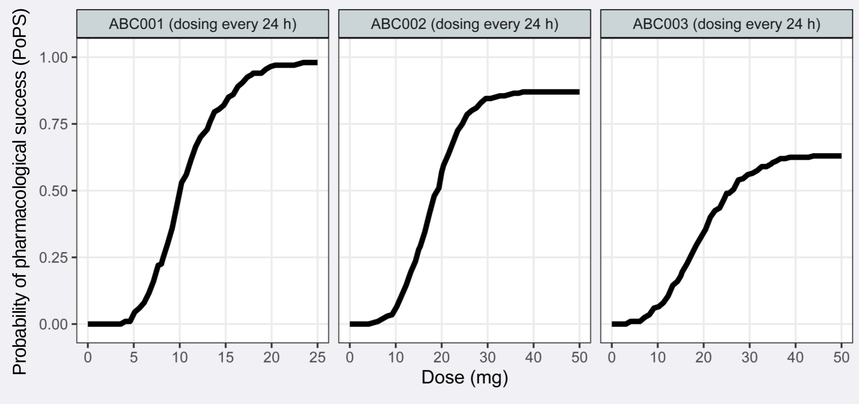


Figure 3. Cumulative composite probability of pharmacological success (PoPS) with ascending dose levels. The cumulative PoPS over the full explored dose range is 98%, 87% and 63% for ABC001, ABC002 and ABC003 respectively.

The PoPS over selected doses of interest is 83.5%, 65% and 40.5% for ABC001 (8, 13, 18 mg), ABC002 (15, 20, 30 mg) and ABC003 (15, 25, 35 mg), respectively.

## Useful applications of the PoPS workflow

Inform about the most likely successful therapeutic dose for a specific asset given multi endpoint success criteria.

Select a dose-range of interest for first-in-human studies and/or Phase 2b studies.

Prioritize between candidate drugs based on cumulative PoPS.

## References

1. Zhou X, Graff O, Chen C. Quantifying the probability of pharmacological success to inform compound progression decisions. PLoS 12;15(10):e0240234.
2. Chen C, Zhou X, Lavezzi SM, Arshad U, Sharma R. Concept and application of the probability of pharmacological success (PoPS) as in drug development: a position paper. J Transl Med. 2023 Jan 11;21(1):17

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