DIVIDE AND CONQUER: COMPARISON OF STATISTICAL AND PROBABILISTIC TOOLS FOR RISK ASSESSMENT IN MULTI-STAGE PROCESSES

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Faster decisions imply awareness and acceptance of risks associated with accelerated pharmaceutical development of compounds. Many statistical and probabilistic tools are available for multi-stage processes or multiple unit operations, however it is not well understood how well these tools assess probability of success (or failure) for a drug to meet a specification limit.

Moreover, with limited data a reliable estimate of variation (noise) is out of scope, and transmission of signal could also be biased. In this presentation a risk of failure will be quantified for a hypothetical process with three stages using two approaches: sequential one-variable-at-a-time approach (OVAT), and the DoE approach where signal and noise are estimated from a joint screening/optimization/confirmation study.

NCB conference

June 2017

SIGNAL AND NOISE IN BIOLOGICS FORMULATION DEVELOPMENT

In the past the formulation development is sequential where experiments from the previous stage inform factor levels at a subsequent stage.

Currently, Drug Product Science & Technology in PD has started utilizing DoE approach for ruggedness studies. The choice of formulation is still guided by OVAT-type approach which may not be possible to do with accelerated timelines. The CQA's that are most informative are measured at time points several months on stability, therefore delaying the start of the next study.

An alternative is to do DoE earlier in formulation development for screening and optimization purposes, and only do a few verification runs once the design space is well understood.

In OVAT signal is estimated from these separate experiments, and noise is hardly mentioned. However, a reliable estimate of noise is crucial in fit-for-purpose environment. How much risk are we taking? Is it acceptable given the stage of formulation development?

TYPICAL OVAT APPROACH

Study	x1 PC	x2 pH	x3
S1	-1	0	1
S1	-0.5	0	1
S1	0	0	1
S1	0.5	0	1
S1	1	0	1
S2	0.5	-1	2
S2	0.5	-0.5	2
S2	0.5	0	2
S2	0.5	0.5	2
S2	0.5	1	2
S3	0.5	-0.5	1
S3	0.5	-0.5	1
S3	0.5	-0.5	2
S3	0.5	-0.5	2
S3	0.5	-0.5	2

Three factors in three studies.

Study 1: Protein concentration is varied from low to high with 5 levels. Outcome identifies 0.5 as optimal, used in Studies 2 and 3.

Study 2: pH is varied with 5 levels, then fixed at -0.5 for Study 3.

Study 3: Categorical factor x3 is varied.

A final target formulation with protein conc. of 0.5, pH of -0.5 and level 2 of x3 is replicated 3 times (not usually done in formulation development).

DESIGN FOR DOE APPROACH

Study	x1 PC	x2 pH	x3
DoE	1	1	2
DoE	1	-1	2
DoE	0	0	1
DoE	-1	1	1
DoE	-1	1	2
DoE	0	0	1
DoE	1	1	1
DoE	-1	-1	2
DoE	1	-1	1
DoE	0	0	1
DoE	0	0	1
DoE	-1	-1	1
verification	0.5	-0.5	2
verification	0.5	-0.5	2
verification	0.5	-0.5	2

Three factors studied simultaneously followed by three verification runs.

DoE: Full-Factorial design, 12 runs (4 center point runs)

Verification: 3 runs at the estimated optimum from DoE

SIMULATION STUDY

Compare performance of OVAT and DoE approaches

- Assume that both OVAT and DoE approaches arrive at the same optimal formulation.
  - In reality the DoE approach should be much more powerful to find the optimal formulation.
- Note that both approaches have 15 runs and the same number of replicate runs at the "optimal" formulation.

MODEL AND ASSUMPTIONS FOR SIMULATION

True model

$Y \sim 4.86 + 0.30*x1 + 0.12*x2 + 0*x3 + \varepsilon$ (1)

where $\varepsilon \sim \text{Normal}(0, \sigma^2)$, $\sigma = 0.1$

Specification limit $y < 5$.

- At a target formulation of (x1=0.5, x2=-0.5, x3=2) the predicted response is 4.95 and the risk of meeting the spec is 0.95.

OVAT approach: sigma is estimated from the last 5 experiments in Study 3.

DoE approach: sigma is estimated from all of the 15 runs (DoE + verification).

Nominal risk can be varied by adjusting the intercept in Eq. 1.

Each simulation is carried out 100,000 times.

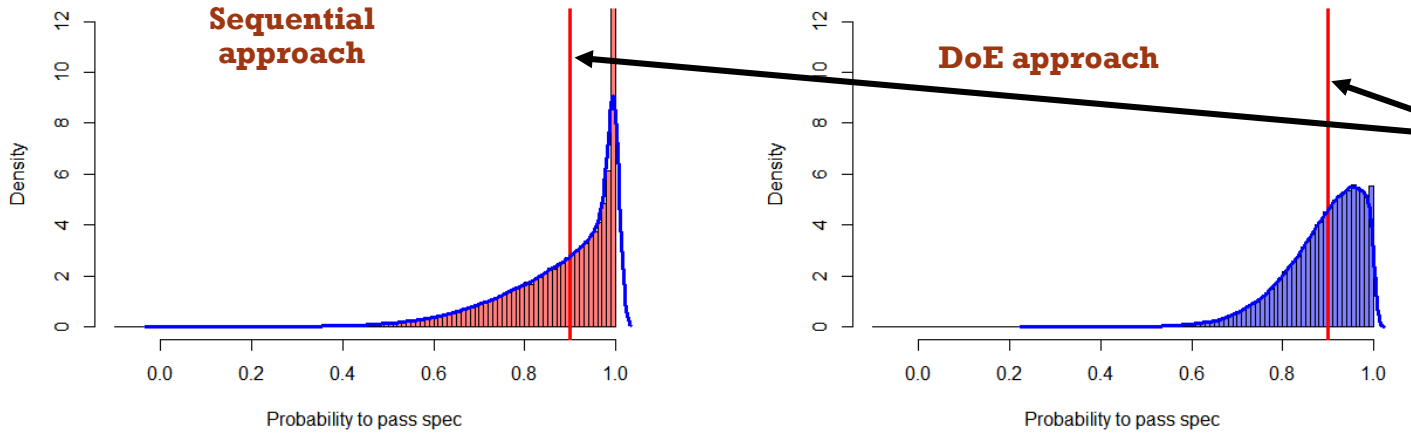
HOW TO DESCRIBE UNCERTAINTY

- For assessing how well the sequential and DoE approaches quantify uncertainty, we'll use the likelihood scale in Table 1.
- Reference: November 2010, "IPCC guidance note for lead authors on the IPCC Fifth assessment report on consistent treatment of uncertainties"
- https://www.ipcc.ch/pdf/supporting-material/uncertainty-guidance-note.pdf

Table 1. Likelihood Scale

Term*	Likelihood of the Outcome
Virtually certain	99-100% probability
Very likely	90-100% probability
Likely	66-100% probability
About as likely as not	33 to 66% probability
Unlikely	0-33% probability
Very unlikely	0-10% probability
Exceptionally unlikely	0-1% probability

CASE 1: A ROBUST PROCESS WITH NOMINAL (TRUE) PROBABILITY OF MEETING THE SPEC AT 0.90



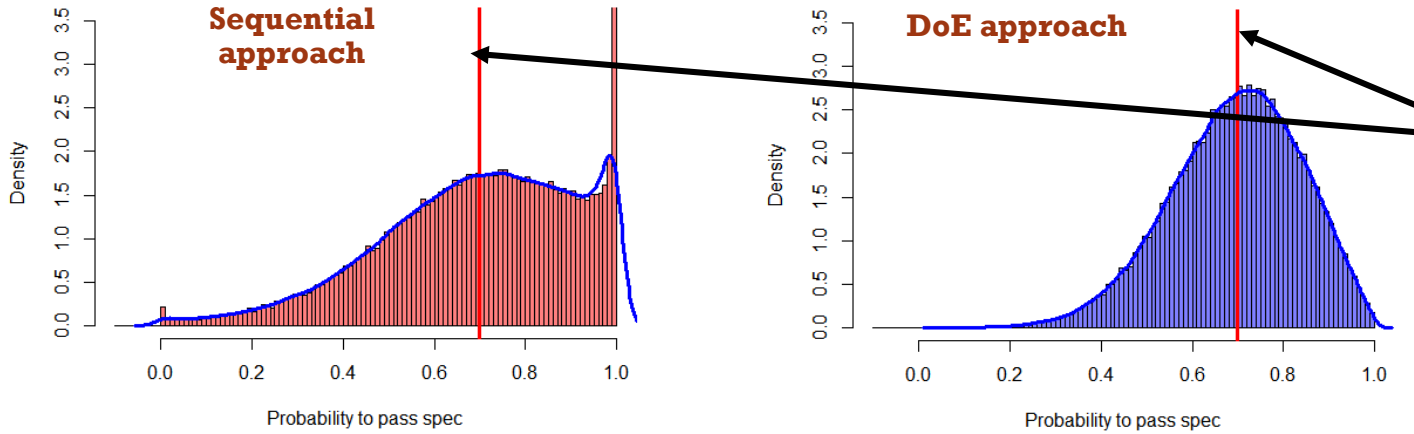
The true probability level is denoted by a red vertical line.

Table 2. Likelihood scale classification with a True Probability of passing the spec at 0.9

Category	Term	Proportion Sequential	Proportion DoE
≥ 0.99	Virtually certain	0.22	0.06
0.9 ≤ p < 0.99	Very likely	**0.35**	**0.47**
0.66 ≤ p < 0.9	Likely	0.37	0.46
0.33 ≤ p < 0.66	About as likely as not	0.06	0.02
0.10 ≤ p < 0.33	Unlikely	0.0023	0.00002
0.01 ≤ p < 0.10	Very unlikely	0.0001	0
< 0.01	Exceptionally unlikely	0.0001	0

Sequential estimates "Virtually Certain" 16% more often then DoE. Hence the level of confidence is higher than it should be more often with the sequential approach.

CASE 2: A PROCESS WITH NOMINAL (TRUE) PROBABILITY OF MEETING THE SPEC AT 0.70



The true probability level is denoted by a red vertical line.

Table 3. Likelihood scale classification with a True Probability of passing the spec at 0.7

Category	Term	Proportion Sequential	Proportion DoE
≥ 0.99	Virtually certain	0.06	0.00
0.9 ≤ p < 0.99	Very likely	0.14	0.06
0.66 ≤ p < 0.9	Likely	**0.40**	**0.55**
0.33 ≤ p < 0.66	About as likely as not	0.34	0.38
0.10 ≤ p < 0.33	Unlikely	0.05	0.01
0.01 ≤ p < 0.10	Very unlikely	0.007	0.0001
< 0.01	Exceptionally unlikely	0.002	0

Sequential estimates "Virtually certain" or "Very likely" 14% more often then DoE. Hence the level of confidence is higher than it should be more often with the sequential approach.

WHAT HAVE WE LEARNED?

- For these two process the sequential approach is overconfident by at least 14%. Also, misclassification to lower likelihood scale (less confident than should be) happens at least 9% more often with the sequential approach.
- This simulation is overly optimistic because the model does not account for a bias in the sequential decisions, and interactions of the control factors (e.g., pH*Protein Concentration) are assumed to be zero. When we introduce the bias and significant two-factor interactions, divergence between the sequential approach and "truth" will be more pronounced.

Conclusion

A case study shows that sequential OVAT approach results in risky decisions more often than the DoE approach despite the same number of runs. The consequences of such decisions are not taking action to improve a formulation when action is needed, or taking extra time and resources when no action is necessary.

Further research

Increase model complexity to mimic real-world scenarios with interactions, non-linear effects, sequential optimization, stability time effect, etc. Evaluate performance of the variance transmission approach which is expected to be better than sequential OVAT but worse than DoE approaches.

REFERENCES

- Montes, Richard O. "Variation Transmission Model for Setting Acceptance Criteria in a Multi-Staged Pharmaceutical Manufacturing Process." *AAPS PharmSciTech* 13.1 (2012): 193–201. *PMC*. Web. 23 May 2017.