Impact Ratio - An integral part of Roche's synthetic molecule drug substance technical development

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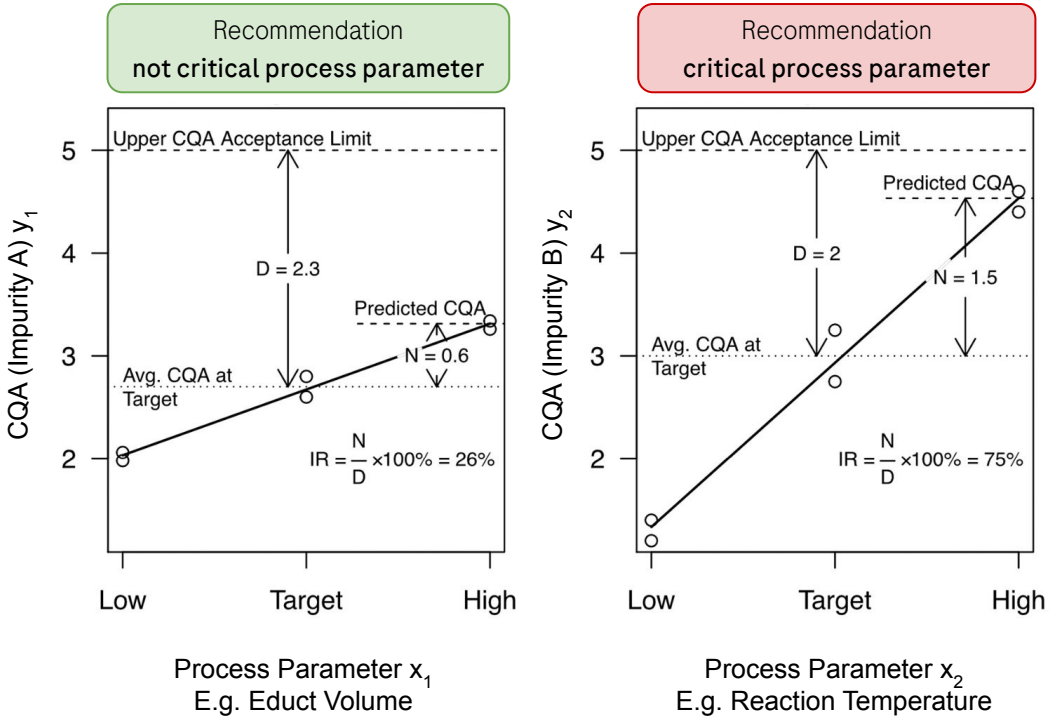
Impact Ratio Introduction

Quantification of practical significance



The impact ratio (IR) quantifies the **practical significance** of a process parameter's main effect on a CQA relative to the CQA's acceptance limit.

We use the magnitude of the impact ratio to provide an **initial, objective recommendation for the criticality of a PP** in process characterization.

CQA = Critical Quality Attribute

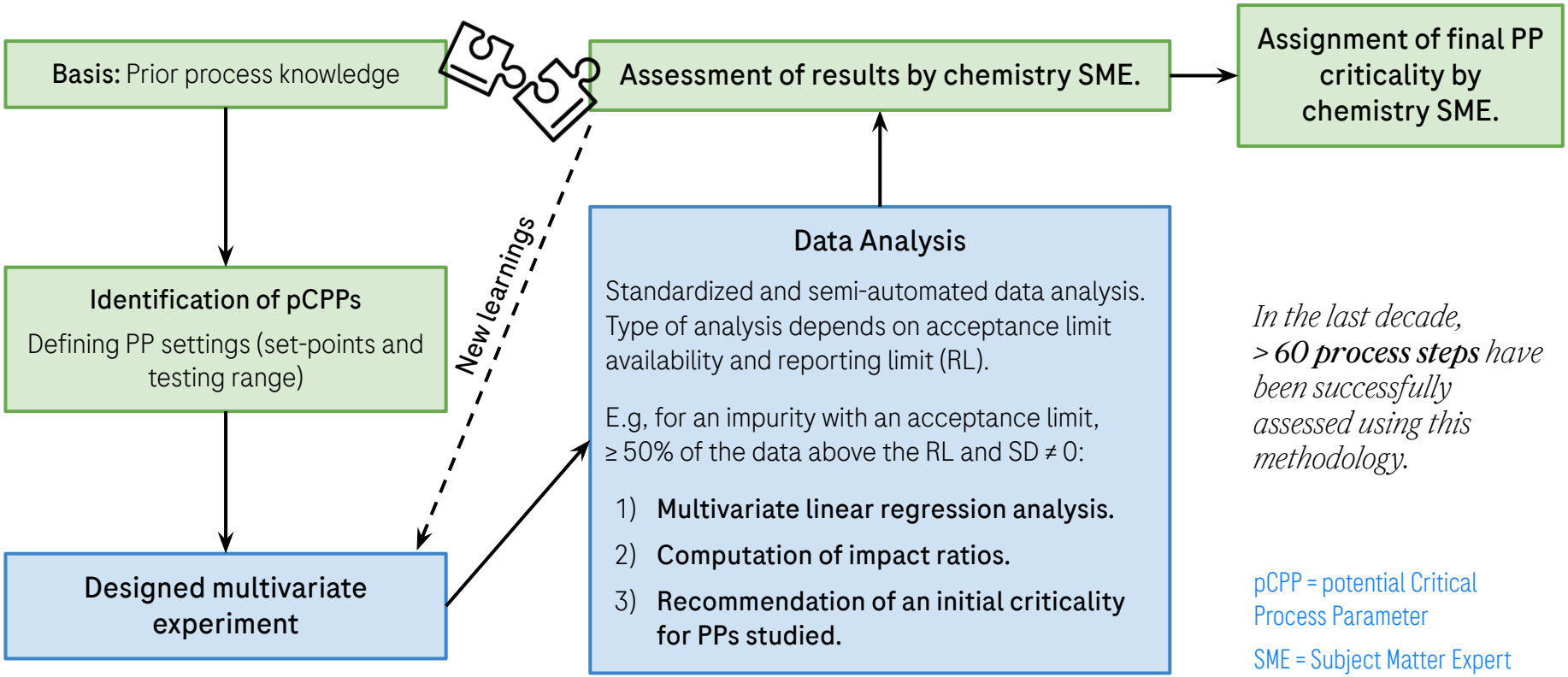
PP = Process Parameter

Lamerz, J., Danila, O.M., Schuster, A., Burren, J., Moessner, C., Göhring, W., Rege, P., Stahr, H., Hildbrand, S. and Coleman, D., 2022. An improved impact ratio for identifying critical process parameters in pharmaceutical manufacturing processes. PDA Journal of Pharmaceutical Science and Technology, 76(6), pp.497-508.

Impact Ratio in Synthetic Molecule Drug Substance

Process Characterization

Workflow for one drug substance manufacturing step



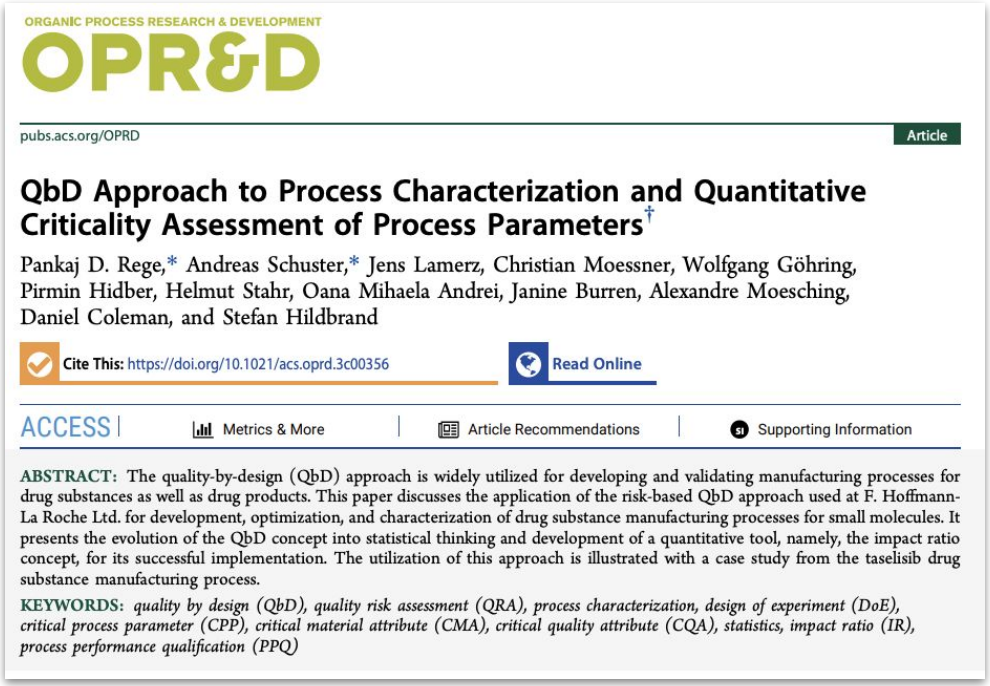
*In the last decade, **> 60 process steps** have been successfully assessed using this methodology.*

pCPP = potential Critical Process Parameter

SME = Subject Matter Expert

More Details in the Publication

Impact ratio in synthetic molecule drug substance technical development



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QbD Approach to Process Characterization and Quantitative Criticality Assessment of Process Parameters†

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ABSTRACT: The quality-by-design (QbD) approach is widely utilized for developing and validating manufacturing processes for drug substances as well as drug products. This paper discusses the application of the risk-based QbD approach used at F. Hoffmann-La Roche Ltd. for development, optimization, and characterization of drug substance manufacturing processes for small molecules. It presents the evolution of the QbD concept into statistical thinking and development of a quantitative tool, namely, the impact ratio concept, for its successful implementation. The utilization of this approach is illustrated with a case study from the taselisib drug substance manufacturing process.

KEYWORDS: *quality by design (QbD), quality risk assessment (QRA), process characterization, design of experiment (DoE), critical process parameter (CPP), critical material attribute (CMA), critical quality attribute (CQA), statistics, impact ratio (IR), process performance qualification (PPQ)*

Rege, P.D., Schuster, A., Lamerz, J., Moessner, C., Göhring, W., Hidber, P., Stahr, H., Andrei, O.M., Burren, J., Moesching, A., Coleman, D. and Hildbrand, S., 2024. QbD Approach to Process Characterization and Quantitative Criticality Assessment of Process Parameters. Organic Process Research & Development 28(4), pp.1003–1017.

Improvement Opportunities

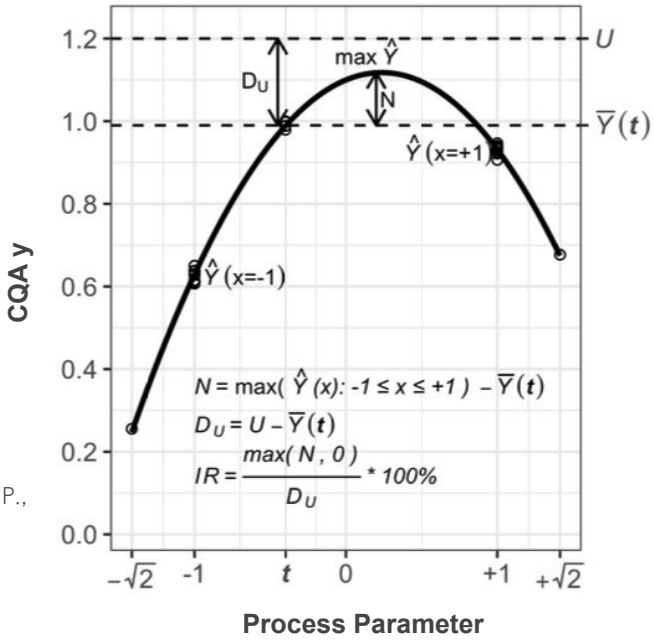
Comments are welcome

- **Impact ratios are point estimates.**

  → Uncertainty quantification by considering process variability, analytical variability and sample size.

- **Relationship between PP and CQA is not monotonic within testing range and the maximum (or minimum) of $\hat{Y}$ is not at target setting t. In this case, IR will fall short to report a potential criticality of PP for the given CQA.**

  → Instead of using $\hat{Y}(x = 1)$ and $\hat{Y}(x = -1)$ for IR computation one could use $\max\{\hat{Y}(x): -1 \le x \le 1\}$. However, an appropriate experimental design and a good predicting model is required for this approach.



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