Promotion of the Quality by Design principles in the pharmaceutical industry via the Robustness Index initiative

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ABSTRACT

Quality by Design promotes a science- and risk-based approach to the development, manufacturing and control of pharmaceutical products. The application of these principles, together with scientific rigor and data-driven approach are key to the successful execution of development and delivery of high-quality medicines to patients in need.

To promote Quality by Design principles in the pharmaceutical industry, Janssen has specifically developed the Robustness Index (RI). This index aims at objectively measuring performance and robustness of products and processes under development. As such, the RI acceptance criteria are a quantitative reflection of the development goals and deliverables.

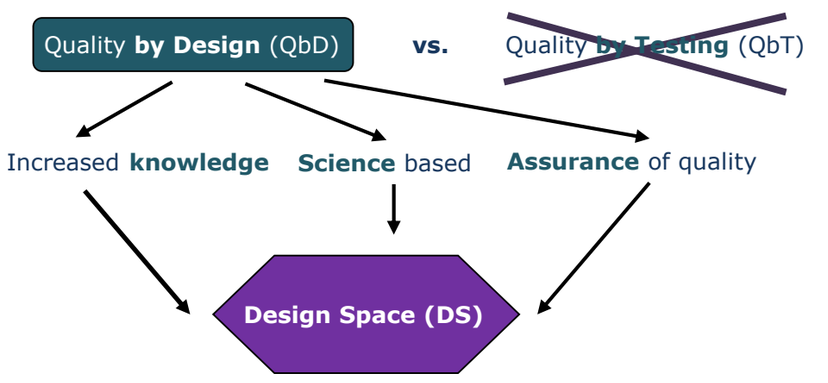
The success criteria of the Robustness Index have been specifically designed to lead the teams towards Quality by Design and data-driven approaches at all stages of the development process. The RI includes, but is not limited to, a focus on measurement system and process capability, long term process performance predictions, and design space analyses.

The Robustness Index methodology has been applied in several development projects. The results of the statistical analyses performed together with their impact on the business choices will be presented. The knowledge acquired from these statistical analyses can contribute to proactively adjust and fine tune ongoing development programs and to drive the teams towards a better application of the Quality by Design principles.

BACKGROUND

Currently, regulatory agencies have greater expectation towards pharmaceutical companies demonstrating a comprehensive understanding of their processes and adopting a risk-based approach. On the other hand, companies are aggressively seeking for higher performance in terms of yield, cycle time, reliability and right-the-first-time manufacturing and control.

Use **modern tools**, to facilitate the implementation of **robust** manufacturing processes that **reliably** produce pharmaceuticals of high quality and that **accommodate** process change to support **continuous process improvement**.
Pharmaceutical cGMPs for the 21st Century – a Risk-Based Approach (FDA, 2004)



According to the PQRI white paper, for successful implementation of a QbD strategy, major components are
- Form the team
- Define the process
- Prioritize experiments
- Analyze Measurement Capability
- Identify functional relationships
- Confirm CQAs and CPPs
- Continuous Monitoring the state of Robustness

Ideally, process robustness activities start at the earliest stages of process design. However, many products have been developed using a QbT approach. For new products, a shift in mentalities and trainings are needed. However, without clear deliverables and objectively measurable criteria, it is difficult for teams to make shift.

ROBUSTNESS INDEX

Robustness Index (RI) is an internal tool developed for CMC teams to assess and monitor product and process robustness and performance under development. RI covers all development elements: drug substance, drug product, raw/packaging materials & devices, manufacturing and in-use aspects, processes, including analytical methods. RI assesses performance and robustness but also the strength of their foundation.

RI consists of several **metrics**, covering both qualitative and quantitative aspects of pharmaceutical development and manufacturing:

Categories	Product Dashboard
Measurement systems	% Reproducibility & Repeatability
	% Precision/Tolerance
Knowledge & understanding	A set of qualitative metrics
Robust Design	Future performance prediction at release*
	Future performance prediction at end of shelf life*
	Future performance prediction for Critical Material Attributes
	DP: Formulation Robustness demonstrated
Manufacturability	Yield

The success criteria of the RI have been specifically designed to
- Drive teams towards Robust Design and support teams by proactively reflecting measurement requirements in a development plan
- Quantify and visualize Product and Process Robustness by data-driven, science-based product and process performance evaluation and provide a predictive estimation of future product & process robustness

METHODS

Probability of success (PoS)

Figure 1 gives a schematic representation on PoS calculations
- Based on a Bayesian model which can eventually include the prior information about location and variability of CQA/CMA values
- PoS are used as evaluation basis in Future performance prediction at release and shelf life and Manufacturability; it is a basis of Design Space calculation.

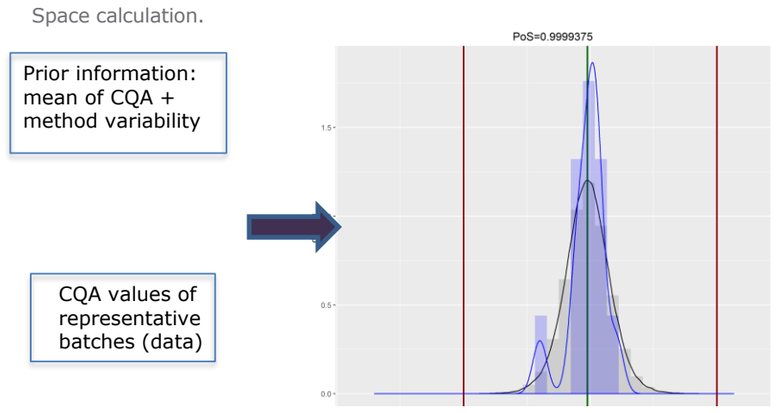


Figure 1 – A schematic representation of the calculation of probability of success to stay within specifications. Red lines are specification limits, histogram represents available data. Estimated posterior predictive distribution is displayed by black density line

Design space (DS)

If data are available from a properly designed DoE for formulation robustness/ process robustness and other studies, design space may be computed. DS calculations are based on PoS for each combination of the DoE factor on a grid. PoS can be computed based on univariate model or on multivariate model for several CQAs at once (joint PoS).
DS is used as a basis of evaluation of Process Robustness and DP Formulation Robustness metrics. Figure 2 shows the result of design space computation in a Bayesian way.

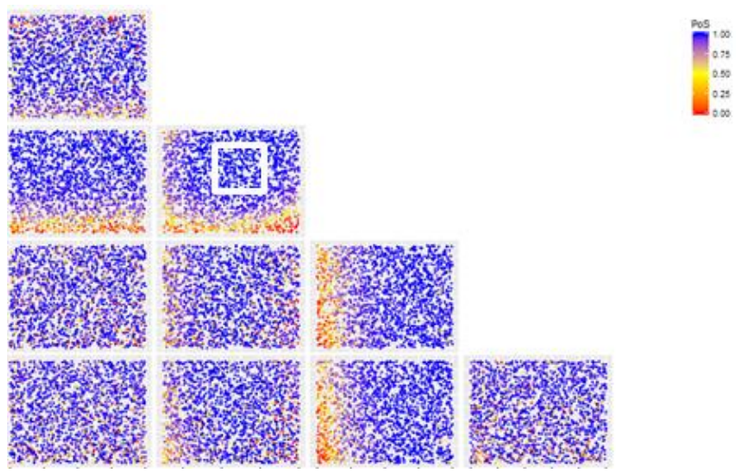


Figure 2 – A scatterplot matrix representing the Bayesian DS calculations. Each colored dot corresponds to the calculated PoS. The PoS can be related to a single CQA or to multiple CQAs (if joint modeling is used). The white square shows normal operating window.

Variance component analysis of Gage R&R studies

Well-designed Gage Repeatability & Reproducibility (R&R) studies are important to investigate measurement system (MS) capability. The measurement system is capable if variability due to the **MS** is small compared to the process variability (Figure 3). It is important to understand what are the key components of variation in MS: short-term variability (repeatability) or long-term variability (due to differences in labs, analysts, instruments, days). Afterwards, %(R&R/Total) and %(Precision/Tolerance) are computed for the RI evaluation.

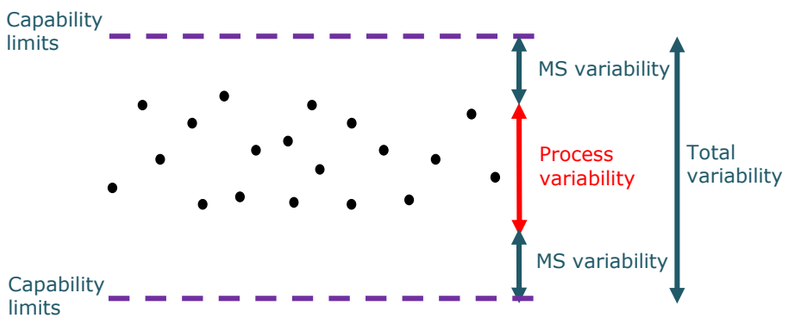


Figure 3 – General idea behind the Gage R&R evaluation: MS should be capable enough to be used for the quality control.

EVALUATION AND REPORTING

Product dashboard

After multi-disciplinary effort in providing the necessary inputs (data, additional information) and calculating the metrics, the decision per each metric is documented in the product dashboard. The evaluation in product dashboard is performed several times throughout development in order to monitor team's efforts towards robust design.

Individual metrics scoring: Future performance at release and shelf life

For each CQA, or for a set of CQAs modeled jointly, the PoS should be reported. The final decision is based on the worst case scenario, i.e. on the lowest PoS (either univariate or multivariate). Minimum and maximum PoS are reported in case of several CQAs or sets of CQAs. Figure 4 displays evaluation criteria and a result of evaluation for specific condition at release and shelf life per DP volume.

PoS (joint PoS) >= 99%	LSL = 95 and USL = 105			
PoS (joint PoS) >= 97% & <99%	Condition	Time point	Volume	PoS (%)
PoS (joint PoS) < 97%	30°C/ 35%R.H.	Release	Vol1	100
			Vol2	100
		Shelf-Life	Vol1	98.6
			Vol2	100

Figure 4 – Evaluation criteria and evaluation result for Future performance at release and shelf life metric.

Individual metrics scoring: Measurement Systems %R&R and %P/T

For each method and its Gage R&R study %R&R and %P/T as well as the variance components table should be reported. The final decision is based on the worst case scenario, i.e. on the highest %R&R or %P/T. Minimum and maximum %R&R or %P/T are reported in case of several QC methods. Figure 5 displays evaluation criteria and a result of evaluation for an example QC method. Due to the high contribution of MS variation to the total variability, MS should be improved.

%R&R/ % P/T <30%
%R&R/ % P/T>= 30% & <50%
%R&R/ % P/T >= 50%

Effects	Var Comp	%Total
Location	0.04	11.19
Analyst[Location]	-0.01	0.00
Date[Location,Analyst]	0.06	17.80
Batch	0.20	57.20
Batch*Analyst[Location]	0.01	2.05
Date*Batch[Location,Analyst]	-0.01	0.00
Batch*Location	0.00	0.04
Residual	0.04	11.72
Total	0.35	100.00

Figure 5 – Evaluation criteria and evaluation result for Measurement system capability metric.

Individual metrics scoring: Process Robustness Demonstrated

For each unit operation / process step (or a set of unit operations/ process steps) a DoE result for a set of process parameters should be evaluated using Bayesian model and DS should be reported. When the testing was performed in a one-factor-at-a-time way, no DS can be computed, hence the univariate PARs and NORs should be used for evaluation. Figure 6 displays evaluation criteria based on the DS and on univariate PAR/NOR ratios.

Probability for CMAs, CPPs and composition to remain within justified Design Space	>=0.99	<0.99 and >=0.95	<0.95
Process parameters : final ratio PAR / NOR	>=1.5	<1.5 and >=1.25	<1.25

Figure 6 – Evaluation criteria and evaluation result for Process Robustness Demonstrated metric.

CONCLUSION

Developing according to robust design/QbD principles is a multi-facet challenge. Robustness index is a science- and knowledge-based evaluation platform enabling a qualitative and quantitative assessment of product and process performance and robustness. Robustness Index can contribute to a transparent and objective communication of development results to stake holders and senior management.
RI is a collaborative effort and requires communication between scientists and statisticians. It is important to realize that the RI metrics are a snapshot of product and process robustness at a specific stage in development and as such allows the CMC team to consider potential adjustment or fine tuning of current development program.

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