KOREA 2021

DISCOVERY SUMMIT

EXPLORING DATA
INSPIRING INNOVATION

Analysis Automation and Simulation-based Comparability Assessment with JSL

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Part 1.

Analysis automation with JSL

What is Quality by Design (QbD)?

- A systematic approach to development that begins with predefined objectives, process understanding and process control, based on science and quality risk management.

- **ICH Q8(R2)** :

  A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy.

What is Quality by Design (QbD)?

Quality Target Product Profile **QTPP**	**Risk Assessment & Process Development**	**Design Space**	**Control Strategy**	**Continuous Improvement**
▪ The characteristics that assure quality, safety, and efficacy. ▪ A summary of a product's quality characteristics.	▪ CQAs that are critical for meeting the QTPP are determined through risk assessment. ▪ CPPs are identified through process development. * Definitions of CQA/CPP will explained on the next slide	▪ CPPs that impacts on CQAs are quantified in a design space. ▪ A multidimensional space that provides assurance of quality. ▪ Design Space defined on the basis of multivariate Design of Experiments (DoE) results.	▪ Ensures process performance and product quality. ▪ Defines control space and system suitability, meets method performance criteria.	▪ The process is validated in a manufacturing facility at scale. ▪ The process is monitored continually during manufacturing runs.

"QbD is a life-cycle approach to product development that encompasses development, optimization, and validation of a manufacturing process."

Definitions

- **Critical Quality Attributes (CQA)**

  : A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8)

- **Critical Process Parameter (CPP)**

  : A process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)

A key element of process characterization is the requirement to identify and control CPPs that influence CQAs.

Critical Process Parameter (CPP)

- The impact ratio method is computed as the change in a CQA from the midpoint to the limit of the process parameter acceptable range divided by the difference between the CQA value at the midpoint of the PP acceptable range and the acceptable limit of the CQA.
- If the data have an impact ratio of 0.2, it means that a 20% shift in the CQA across the PP acceptable range is significant and identifies a CPP.
  (i.e. the data are close to its target limit, and the process parameter is statistically significant.)
- A process parameter with an impact ratio >0.2 is considered a CPP.

$$\textit{Impact Ratio} = \frac{|\textit{Scaled Estimate}|}{|\textit{Mean value for CQA} - \textit{Spec limit}|}$$

- Amgen's attribute based control strategies -

Example

- **Objective of analysis**

  - Statistical analysis for optimizing process development to remove “impurity, mutation, and virus“.
  - To confirm the impact of each process parameter on CQAs.

- **Data Description**

  X : Process parameter (PP) which is classified as CPP or nCPP based on the results of statistical analysis.

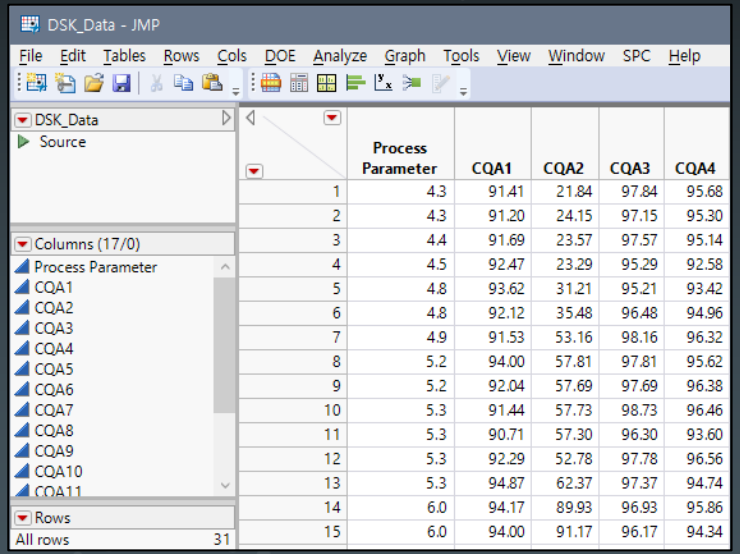
  (ex. Buffer Molarity, Buffer pH, Wash Flow Rate…)

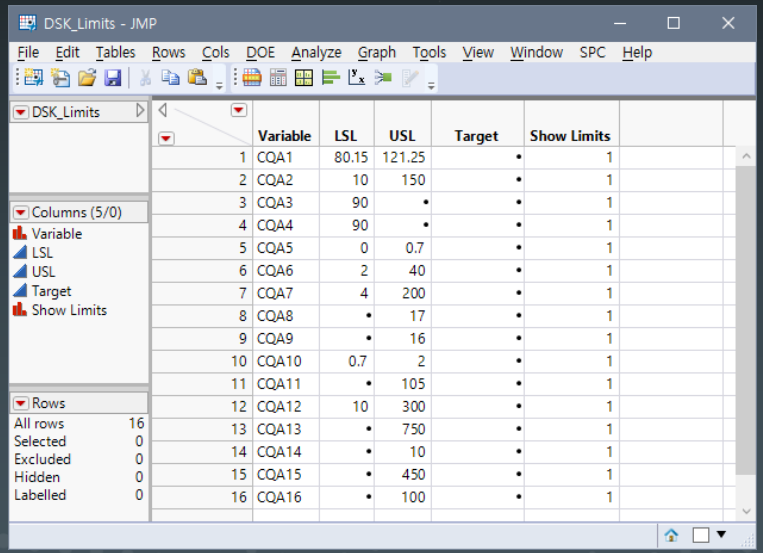
  Y : Critical quality attribute (CQA) that would make potentially high impact on patient safety.

  - Variants of the product : size, charge, glycans, or oxidation.
  - Process-related impurities : host cell protein, DNA, or leachables.

Setting Script (JSL)

1. Open DSK_Data and DSK_Limits DataTables and Run ***Setting Script.jsl***.



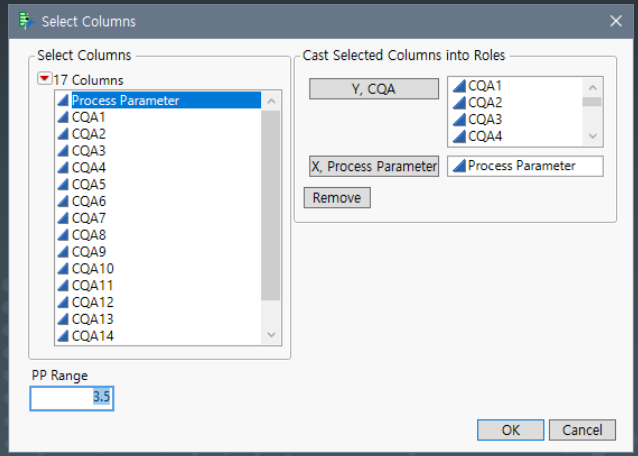


Setting Script (JSL)

2. Select Responses (CQAs) used for evaluation as Y, and Process parameters as X.

3. Enter PP Range, and it will be used to calculate the ***Impact Ratio***.

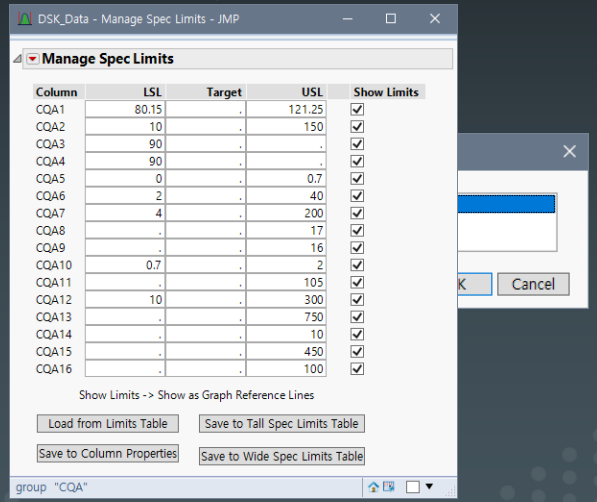
4. ***Group Column*** is applied by "CQA“ for the selected Y.



Setting Script (JSL)

5. ***Manage Spec Limits*** will appear when the Setting Script is executed.

6. ***Load Limits*** from DSK_Limits and ***Save to Column Properties.***



Running Script (JSL)

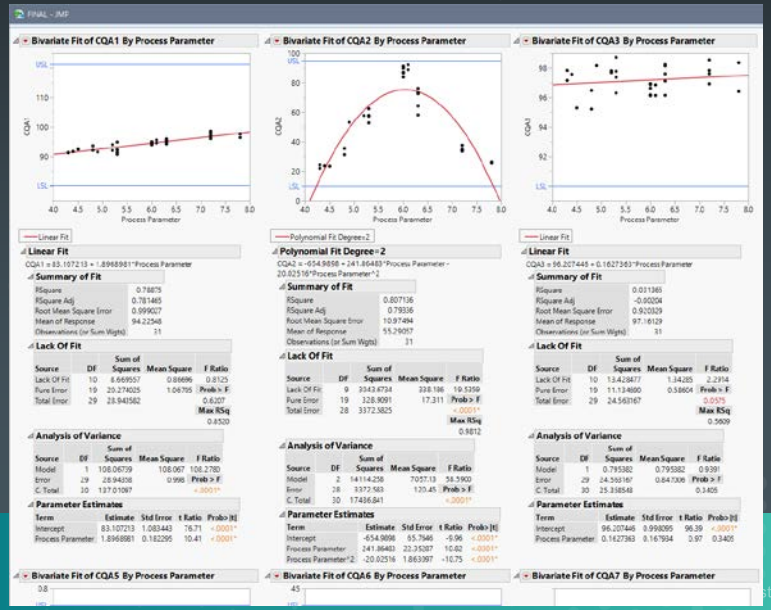
- Only the red part in the sentence below needs to be modified according to the number of CQAs. (## : the number of CQAs)

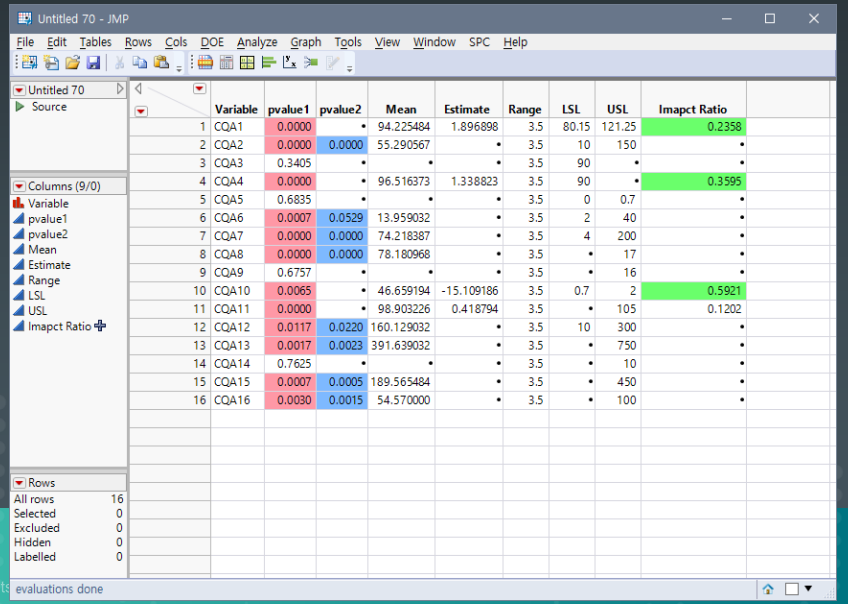
```
a = New Window( "FINAL",
        H List Box(
          Lineup Box( N Col( 3 ), a1,a2,...,a## )
        )
);
```

- Fit line(linear model) and Fit special(quadratic model) are fitted for each CQA using ***Fit Y by X*** platform, and the model with a larger R^2 will be selected.
(Evaluation criteria such as R^2 can be changed.)

Running Script (JSL)

- A single report that collects each CQA analysis result and a summary table that summarizes statistics will be generated as an output.





	Variable	pvalue1	pvalue2	Mean	Estimate	Range	LSL	USL	Impact Ratio
1	CQA1	0.0000	•	94.225484	1.896898	3.5	80.15	121.25	0.2358
2	CQA2	0.0000	0.0000	55.290567	•	3.5	10	150	•
3	CQA3	0.3405	•	•	•	3.5	90	•	•
4	CQA4	0.0000	•	96.516373	1.338823	3.5	90	•	0.3595
5	CQA5	0.6835	•	•	•	3.5	0	0.7	•
6	CQA6	0.0007	0.0529	13.959032	•	3.5	2	40	•
7	CQA7	0.0000	0.0000	74.218387	•	3.5	4	200	•
8	CQA8	0.0000	0.0000	78.180968	•	3.5	•	17	•
9	CQA9	0.6757	•	•	•	3.5	•	16	•
10	CQA10	0.0065	•	46.659194	-15.109186	3.5	0.7	2	0.5921
11	CQA11	0.0000	•	98.903226	0.418794	3.5	•	105	0.1202
12	CQA12	0.0117	0.0220	160.129032	•	3.5	10	300	•
13	CQA13	0.0017	0.0023	391.639032	•	3.5	•	750	•
14	CQA14	0.7625	•	•	•	3.5	•	10	•
15	CQA15	0.0007	0.0005	189.565484	•	3.5	•	450	•
16	CQA16	0.0030	0.0015	54.570000	•	3.5	•	100	•

Demonstrating JSL

Part 2.

Simulation-based Comparability assessment

Statistical Considerations for Comparative Assessment of Quality Attributes Richard K. Burdick, 2020.

CMC Comparability Studies

- The FDA comparability guidance (1996) recognized the need for manufacturers to improve manufacturing processes and analytical methods without performing additional clinical studies to demonstrate product safety and efficacy.

- Regulatory agencies recognize the importance in providing manufacturers the flexibility to improve their manufacturing processes.

- Comparability is defined by **ICH Q5E** as a demonstration that the quality attributes of the pre- and post-change product are highly similar and that the existing knowledge is sufficiently predictive to ensure that any difference in quality attribute have no adverse impact on safety or efficacy of the drug product.

CMC Comparability Applications

- Technology transfer
- Analytical similarity of biosimilars
- Change of contract manufacturer
- Analytical procedure transfer
- Qualification of scale-down models for process characterization
- Qualification of a new reference standard

CMC Comparability Tools

1. **Side-by-side plot**
2. **Statistical test**
   - Equivalence testing of means
   - Equivalence of quantiles (‘tail-test’, Mielke et al. 2019)
   - Non-inferiority of standard deviation
3. **Quality Ranges**
   - Specification
   - Tolerance intervals
   - 3-Sigma
   - Risk-based (Burdick 2020)

Quality Range (QR)

- The FDA proposed the use of comparative analytical assessment by the QR approach.

  (FDA Draft Guideline – Statistical Approaches to Evaluate Analytical Similarity)

- The acceptance criteria for the QR in the comparative analytical assessment should be based on the reference product for a specific quality attribute.

$$\bar{X}_R \pm C \times S_R$$

$\bar{X}_R$ = Sample mean of the reference sample

S_R = Sample standard deviation of the reference sample

- Several rules have been suggested for determining C.

Quality Range (QR)

1. **Tolerance Interval**

- C is determined from tolerance interval tables for given levels of confidence and coverage.
- There is no general recommendation for the confidence or coverage to select, and no direct link to ''Patient Risk".
- Intervals are not impacted by the sample size of the post change process.

2. **3-Sigma**

- Three sigma intervals make no considerations for either reference or post-change sample sizes.
- They provide a disincentive to increase the number of post change lots.
- There is no direct link to control ''Patient Risk".

Risk-Based Approach

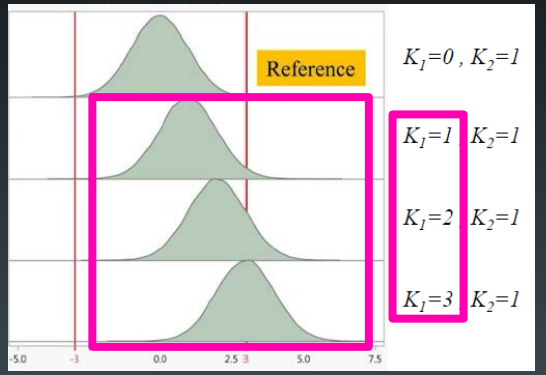
- Determination of C requires definition of a "boundary condition“ using K_1 , K_2 and a declared probability of passing under the boundary condition.
- This approach defines a ''boundary condition'' in terms of K_1 , K_2 and assigns ''Patient Risk'' probability to the boundary condition consistent with reasonable sample sizes.
- The value of C is determined as a function of the patient risk, K_1 , K_2 , and the sample sizes of the pre- and post-change groups using computer simulation.

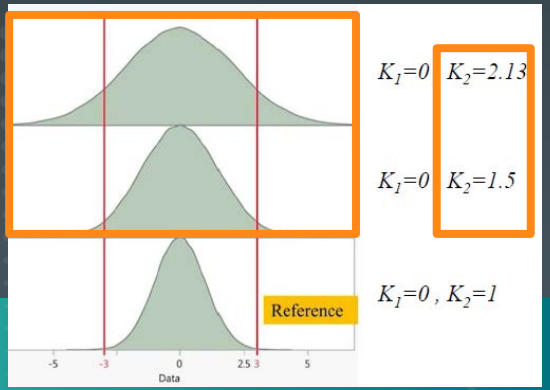
Notations for Risk-Based Approach

The following definitions will be used to describe differences between processes.

- $K_1 = \frac{|\text{Difference in means}|}{\text{Standard deviation reference}}$, difference in means
- $K_2 = \frac{\text{Standard deviation new}}{\text{Standard deviation reference}}$, the ratio of standard deviations

($K_1 = 0$ and $K_2 = 1$ implies ***Reference*** and ***Test*** are identical)

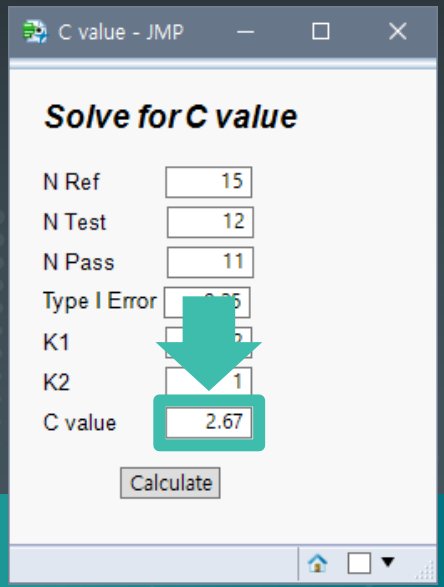




Simulation

1. Setting the number of samples for each group. (Reference, Test, Pass)
2. Setting K_1 , K_2 and α , the probability of committing a Type I error rate.

   (Experts are critical for defining these values and aligning with realistic risk profiles and sample sizes.)
3. Click “Calculate”
4. Estimate C value based on 500,000 iterations.



Simulation

1. Start with C = 0.01
2. Generate samples for each group based on K_1 , K_2
3. Compute a quality range based on calculated mean and standard deviation of reference samples.
4. Repeat 2.~ 3. for 1,000 times and Compute probability of passing.
5. Increase C value with increments of 0.01 and Repeat 2.~ 5. until C = 5.00.
6. Select C value for the desired type I error rate.

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Thank you

Reference

- Richard K. Burdick, Statistical Considerations for Comparative Assessment of Quality Attributes, statistics in biopharmaceutical research, 2020.
- Statistical Tools to Aid in the Assessment of Critical Process Parameters, Pharmaceutical Technology,2016.
- Tom Monica, AMGEN'S ATTRIBUTE BASED CONTROL STRATEGIES, 2018.
- ICH Q8(R2) - PHARMACEUTICAL DEVELOPMENT, 2009.
- FDA Draft Guideline – Statistical Approaches to Evaluate Analytical Similarity.