Acceptance criteria for process capability indexes generated from statistical tolerance intervals as per ISO 16269-6

Background

Justification for sampling plans and statistical analysis of results is a requirement for process validation in medical devices. Current standards [1] and regulations [2] however, give limited advice or guidance regarding this topic. Several approaches where therefore adopted by the medical device industry.

Purpose

This statement intends to evaluate, if acceptance criteria for process capability indexes [3] could be generated from statistical tolerance intervals calculated as per ISO 16269-6 [4]. It is not intending to question or challenge the approaches as such.

Discussion

Statistical tolerance intervals

The use of statistical tolerance intervals as described in ISO 16269-6 can be found in different regulatory sources like ISO 11608-1 [5] and FDA Guidance for stents [6].

- The basic idea behind the statistical tolerance intervals is to use the average and standard deviation observed within a sample group in order to calculate a tolerance interval.
- The ISO 16269-6 approach is recommended for validation as it makes use of the LTPD (consumer's risk), instead of AQL (producer's risk).
- Usually this is accomplished by a calculation of average +/- k*standard deviation, where the k-value is derived from tables within the standard.
- The k-value considers sample size used as well as the confidence and the probability levels chosen.
- Selection of adequate levels is the responsibility of the manufacturer and must be justified. Some regulatory requirements for applicable confidence and the probability levels are given within the relevant documents [5, 6].

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- The calculated statistical tolerance interval shall then be compared to the given specification of the product under consideration. It is essential to understand, that the individual results must also meet specification.
- Statistical tolerance intervals are therefore a well-accepted way of fulfilling the requirements to justify sampling plans and to analyze results of process validation activities.

Process Capability Indexes

Another approach chosen to justify sampling plans and to analyze results is the calculation of process capability indexes (like Cp or Cpk). This approach was discussed within the annex A to GHTF Guidance on process validation [7].

- Process capability indexes are calculated by relation of the specified tolerance to the standard deviation observed within the sample group(s).
- The Cp-Index is established by dividing the specified tolerance by 6 standard deviations and shows if the process is stable (simplified calculation for normal distribution).
- The Cp-Index as such does not consider the average of the process and consequently it does not provide information if the process is capable. Therefore it should not be used as the only acceptance criteria in process validation. It is essential to understand, that the individual results must also meet specification.
- For these reasons another process capability index may be used, which is the Cpk.
- The Cpk-Index is calculated using the average and the standard deviation observed. Calculation is made by dividing the difference of the average – critical (lower or upper) spec limit by 3 standard deviations (simplified calculation for normal distribution).
- The index will provide information on capability and stability of the process.

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For both, Cp and Cpk, there are no regulatory acceptance criteria published for suitable values of these capability indexes. Most often it can be observed, that industries just „borrow“ values commonly accepted in other industries without further justification (e.g. Cpk equal or higher than 1.0).

Comparison and evaluation

- As a consequence of the formulas used to calculate Cpk, an index of 1.0 would mean, that the difference between the critical spec limit and the average is exactly 3*stdev.
- It can be seen that the approach used is similar to the statistical tolerance limits. This can be shown by the following calculations (done for the example of the lower spec limit):
    - Cpk = (average – lower spec limit) / (3*stdev)
    - Cpk*3*stdev = (average – lower spec limit)
    - Cpk*3*stdev + lower spec limit = average
    - lower spec limit = average - Cpk*3*stdev

Following the approach for statistical tolerance limits, the lower spec limit must be

- Lower spec limit <= average –k*stdev
  (taken from Annex B, Form A, [4])

Consequently, one could use the relevant k-value from ISO 16269-6 as a measure for an acceptable Cpk value:

- Cpk >= k/3 or k <= 3*Cpk
  or in words, Cpk must be equal or larger than the applicable k-value divided by 3,
  Cpk >= k(n, C,P) / 3, where n=sample size, C=Confidence level, P = Probability level, selected from applicable standard ISO 16269-6 [4].

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Plausibility Check

A Cpk of >1 is commonly accepted in automotive industries. It needs to be known, that this value should be calculated from n>100 samples as a minimum [8]. Some sources recommend higher Cpk values (1.33 to 1.67) [9].

- Using the formula above, a Cpk of 1 would require a k-value of less or equal than 3.
- When looking into ISO 16269-6 (Annex D, Two-sided statistical tolerance limit factors, 2-sided as worst case) a k-value of 3.0, n=100, would satisfy a Confidence level 95,0 % and proportion 99,0 % (Table D.6, k=2.9356, zero defects), which can often be found for critical defects in medical device industries.

However, a sample size of n>100 is not always used in process validation. Repeating the above with a more common sample size of

- n=30 would result in k-value (95/99, n=30, table D.6) = 3.3546 and would necessitate a Cpk of 1.12.
- n=15 would result in k-value (95/99, n=15, table D.6) = 3.8853 and would necessitate a Cpk of 1.30.

Actually these values would fit to the commonly used interpretation, that Cpk for small sample sizes should be around 1.33 (sometimes known as short term or machine capability).

Rule-of-thumb

From the above, the following rules of thumb could be concluded:

- Cpk>1.33 may satisfy a Confidence/Probability level of 95/99% if the sample size is at least n=15 (in alignment to ISO 16269-6).
- In other cases, more detailed calculation would be needed: Cpk >= k/3, where k is a function of
  - n=sample size, and
  - C=Confidence level, P = Probability level, selected from applicable standard ISO 16269-6.

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References:

[1] ISO 13485:2016 Medical devices — Quality management systems — Requirements for regulatory purposes

[2] 21CFR820, Quality system regulation, FDA

[3] ISO 3534-2:2006 Statistics — Vocabulary and symbols — Part 2: Applied statistics

[4] ISO 16269-6:2014 Statistical interpretation of data Part 6: Determination of statistical tolerance intervals

[5] ISO 11608-1:2014 Needle-based injection systems for medical use – Requirements and test methods –Part 1: Needle-based injection systems

[6] Guidance for Industry and FDA Staff: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, April 2010

[7] GHTF Study Group 3 – Quality Management Systems - Process validation guidance, January 2004

[8] SPC 1 - Statistische Prozesslenkung (DGQ-Schrift Nr.16 – 31)

[9] Montgomery, Douglas (2004). Introduction to Statistical Quality Control. New York

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