Process Performance as a Means of Quality Management

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Quality by design (QbD) was an initiative introduced by FDA in 2004 to improve pharmaceutical development and manufacturing. QbD leverages quality tools, such as process performance, that estimate performance during initial setup before a process has been brought to a state of statistical control. By using QbD, pharmaceutical development, and hence manufacturing, becomes a more efficient process. To illustrate the utilization of quality management techniques, process performance will be utilized as an example in the simple process of tablet splitting. Principles and findings can be further extrapolated to more complex processes. For the present study, the process performance metrics of eight different mechanical devices were assessed to evaluate the compliance of these devices with regulatory and compendial criteria. These process performance metrics were used to differentiate the mechanical devices based on their degree of compliance with regulatory and compendial requirements and make recommendations based on values of these metrics, thus increasing process knowledge and understanding.

Quality management is one of many components of quality by design (QbD) that can be utilized to improve pharmaceutical development and manufacturing. Quality management consists of many tools that are used to assess and comprehend product characteristics and process control. The importance of quality management can be demonstrated with the simple process of tablet splitting, which has been traditionally practiced for many reasons, including reducing cost, facilitating administration, and dose alteration (1–3). This activity has regulatory agencies concerned mainly because unregulated splitting can lead to variability in tablet content, weight, disintegration, dissolution, and/or efficacy (for functionally coated tablets, such as enteric-coated tablets) that can occur when tablets are divided, especially with unscored tablets. This variability can affect drug content in a split tablet, thus affecting the targeted efficacy and/or stability. This work utilizes statistical quality control tools, such as process performance metrics, to screen and evaluate results of tablet splitting using eight different mechanical splitters. These metrics can assist in understanding the compliance of results with both *United States Pharmacopeia* (*USP*) and FDA requirements. Metrics will help quantify compliance by assigning a number that represents the degree of compliance each splitting device has relative to FDA and *USP* requirements. This approach ensures that the most appropriate splitting device is selected for the process and quality of splitting is achieved.

Tablet splitting: compendial and regulatory requirements

Historically, tablet splitting has been addressed by compendia, such as the *European Pharmacopoeia* and *USP* (4), which have specified testing requirements of split tablets. In 2013, FDA further regulated tablet splitting by introducing an industry guidance (5) that defines tablet scoring and requirements of scored tablets. **Table I** provides a summary of scored tablet testing requirements for both *USP* and FDA.

Submitted: Oct. 13, 2021
Accepted: Dec. 6, 2021

Table I. Scored tablet testing requirements defined by *United States Pharmacopeia* (*USP*) and FDA authorities.

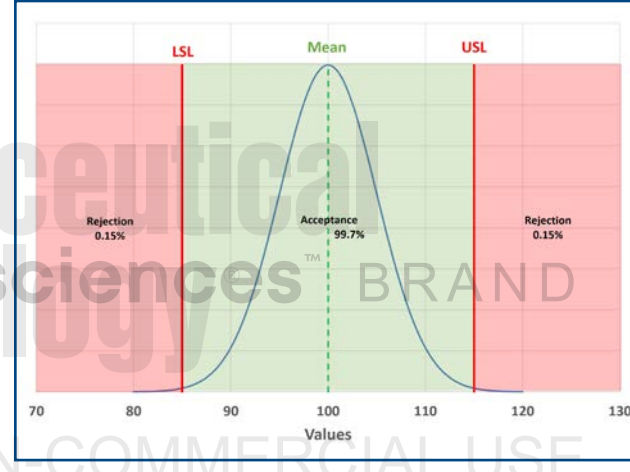
Source	Test	Requirement	General formula [1,2]
USP	Individual weight percent after splitting (IWP)	Not less than 28 of 30 tablets have halves within 75%–125%	$IWP = \frac{W_{Split}}{0.5 \times W_{Whole}} \times 100\%$
FDA	Total weight loss after splitting (TWL)	Not more than 3% of the whole tablet weight is lost after splitting	$TWL = \left(1 - \frac{W_A + W_B}{W_{Whole}}\right) \times 100\%$

[1] Formula shown is for tablets having a single score only.
[2] W_{Whole} is the weight of the intact whole tablet, W_{Split} is the weight of split tablet portion (W_A *or* W_B).

Individual weight percent after splitting (IWP). This test measures the symmetry of the splitting process by comparing the weight of portions produced by splitting to the theoretical weight of that portion. For example, if a 100-mg tablet is split into two halves weighing 45 mg and 55 mg, respectively, then the IWP values are 90% (45/50 × 100%) and 110% (55/50 × 100%), respectively.

Total weight loss after splitting (TWL). This test measures the percentage of weight loss owing to splitting in comparison to the unsplit tablet weight. Thus, it measures the combined weight of both halves in reference to the weight of the intact tablet. For example, if a 100-mg tablet is split into two halves weighing 40 mg and 55 mg, respectively, then TWL is 5% ((100 − (40 + 55))/100) × 100%.

Figure 1. Normal distribution of a process having specification limits set to be within three standard deviations from the mean. LSL is lower specification limit. USL is upper specification limit.



Quality management: the link between QbD and Six Sigma

Traditionally, quality has played a vital role in all products and services. However, focus on quality, especially statistical quality control, evolved after World War II. The 1980s saw an increase in the focus on quality with the development of the Six Sigma program. One of the strategies adopted by Six Sigma is the define, measure, analyze, improve, and control (DMAIC) methodology. In the define phase, key metrics and objectives of the project are defined. The measure phase involves capturing current process performance and capability. The analyze phase involves utilizing collected data and tools to analyze and understand factors contributing to cause-and-effect relationships. The improve phase involves developing changes that improve the process and validating these changes. Finally, the control phase establishes procedures to ensure improvements are sustained (6).

In the pharmaceutical industry, quality management progressed through several phases. Initially, quality was introduced with the implementation of current good manufacturing practice (CGMP) regulations by FDA in 1978. Early documents focused on quality control, which was mostly achieved by retrospective testing (i.e., quality through testing). However, in 2002, FDA advocated a new approach outlining its vision for the 21st century; this thinking was later published in a report (7). In addition to quality control, the new vision focused on managing quality through quality assurance and risk management (8). In other words, quality was to be designed into the product from its early development stages rather than solely relying on testing to assure this quality. Thus, the concept of QbD was introduced into the pharmaceutical industry. In similarity to the DMAIC methodology, QbD utilized many elements such as: a quality target product profile (QTPP) through identifying critical quality attributes (CQAs); product understanding through critical material attributes (CMAs); process understanding through critical process parameters (CPPs), linking CMAs and CPPs to CQAs; a control strategy through specifications; and process capability and continuous improvement (9). For both Six Sigma and QbD, measuring and control of process performance and capability (i.e., quality management) is an essential activity that links these two approaches together. In this paper, the author will examine process performance as means of measuring, analyzing, and controlling processes.

Capability and performance analysis

If a process is normally distributed, then 68% of its outcome will be within one standard deviation of the mean. If specifications are set to be within ±3 standard deviations of the

mean, then 99.7% of the outcome from this process will be within the specification limits. In other words, only 0.3% of the process output will fall outside the specification limits (**Figure 1**). A 0.3% outside specification limit corresponds to 3000 non-conforming parts per million parts produced by the process (10). Ideally, process specification limits can be adjusted, but in many circumstances, these specifications are set by clients or regulatory authorities. In this case, compliance with specifications could only be achieved by reducing process variability by lowering the standard deviation. To control quality, it is important to utilize statistical measures such as capability and performance metrics that relate process variability (i.e., the voice of the process) to specification limits (i.e., the voice of the customer).

Process capability and process performance. Process capability and process performance are two similar indicators describing how a specific process complies with specifications. Process capability assumes a process is under statistical control while process performance does not. As a result, process capability can be utilized for future inference about a process while process performance describes past process behavior. Mathematically, the only difference between the two indicators is how the standard deviation is calculated. In process performance, the standard deviation is directly calculated from the sample data; while in process capability, several experiments (up to a maximum of 10) are performed, and the data range is averaged and used to estimate the population standard deviation. This case study will utilize process performance as a screening tool to screen the performance of different mechanical tablet splitters and will have no inferences on process capability.

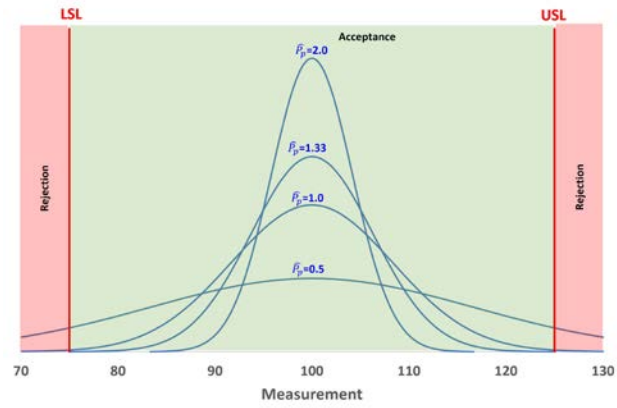
Process performance ratio ($\widehat{P_p}$). Process performance is a control measure that describes the inherent variability in a process (i.e., process uniformity) compared to the requirements or specifications. Process performance is determined by calculating the process performance ratio according to **Equation 1**. In this equation, the numerator represents the specification limits while the denominator represents the variation within a process.

$$\widehat{P_p} = \left(\frac{USL - LSL}{6\hat{\sigma}}\right) \quad \text{Eq. 1}$$

where $\hat{\sigma}$ is the estimated sample standard deviation, LSL is the lower specification limit, and USL is the upper specification limit.

A value of unity for the process performance ratio ($\widehat{P_p}$= 1) indicates that the numerator and denominator are equal and that the voice of the process equals that of the customer. While this value may be acceptable, it would be considered "tight" and does not allow much room for deviation. The greater the $\widehat{P_p}$ value, the more process deviation is allowed compared to specifications, and, thus, the lower number of defects/rejects. In general, values between one and 1.33 are considered to have a marginal performance while processes with $\widehat{P_p}$>1.33 are well performing processes. A Six-Sigma process would have $\widehat{P_p}$=2 (11–13). Values of $\widehat{P_p}$ lower than unity indicate a non-performing process as the deviation would be higher than the set specification limits. **Figure 2** graphically depicts the process performance at different performance levels.

Figure 2. Distribution of measurements at different process performance levels. LSL is lower specification limit. USL is upper specification limit.



The process performance ratio ($\widehat{P_p}$) in **Equation 1** assumes that the specification process is two-sided (i.e., has both upper and lower specification limits). However, some specifications are one-sided. For one-sided specifications, the process performance ratio used is calculated according to **Equation 2** (if only an upper limit is defined) or **Equation 3** (if only a lower limit is defined):

$$\widehat{P_{pU}} = \left(\frac{USL - \hat{\mu}}{3\hat{\sigma}}\right) \quad \text{[Eq. 2]}$$

$$\widehat{P_{pL}} = \left(\frac{\hat{\mu} - LSL}{3\hat{\sigma}}\right) \quad \text{[Eq. 3]}$$

where $\hat{\mu}$ is the estimated process mean and σ is the estimated sample standard deviation.

The $\widehat{P_{pU}}$ measures process performance with respect to the upper specification limit while $\widehat{P_{pL}}$ measures that performance with respect to the lower specification limit.

Process performance index ($\widehat{P_{pk}}$). The process performance ratio is the first generation of performance measures. One of the shortcomings of the process performance ratio is its inability to determine where the process mean is located relative to specification limits. For example, the process performance ratio will be identical for a centered and off-centered process if the two have the same standard deviation as shown in **Figure 3**. Therefore, another process performance measure is used in this case, the process performance index

Figure 3. Difference between $\widehat{P_p}$ and $\widehat{P_{pk}}$ for two processes having the same standard deviation but different averages. LSL is lower specification limit. USL is upper specification limit.

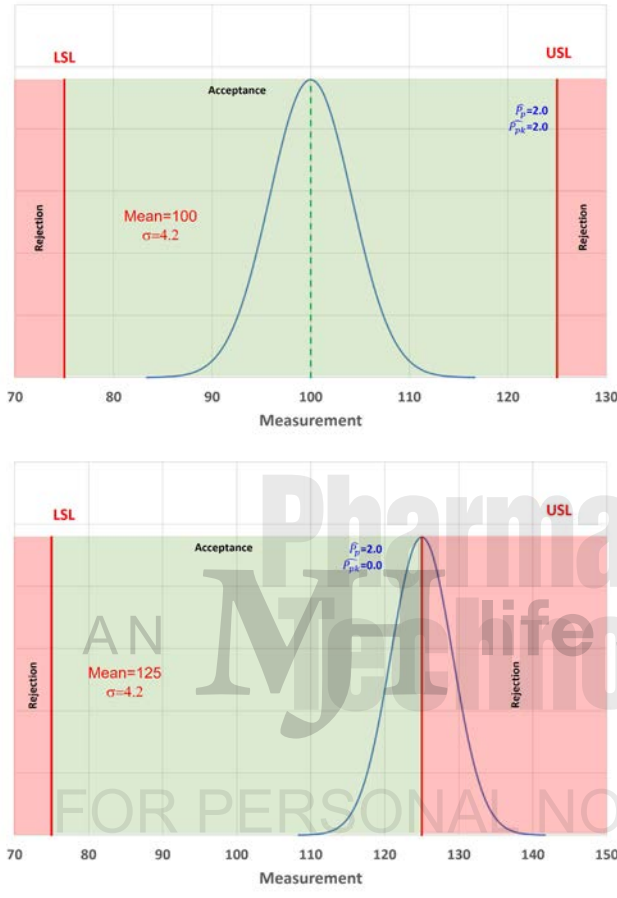
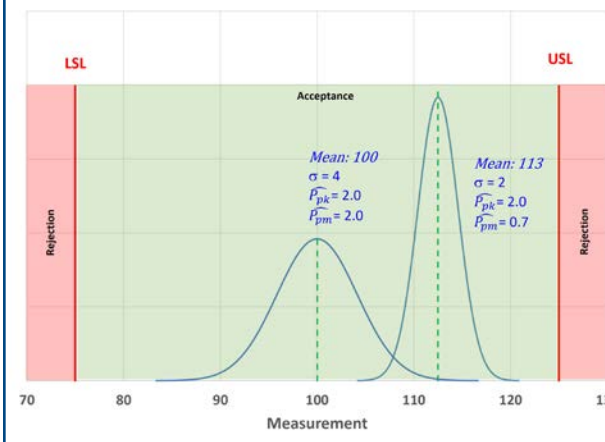


Figure 4. Difference between $\widehat{P_p}$ and $\widehat{P_{pm}}$ for two processes having different averages and standard deviations but identical performance index values. LSL is lower specification limit. USL is upper specification limit.



($\widehat{P_{pk}}$), which is a second-generation performance measurement that measures how the process is performing with respect to either the lower or upper specification limit (i.e., how far outcomes deviate from the limit) and can be calculated using **Equation 4**.

$$\widehat{P_{pk}} = min\left(\widehat{P_{pL}}, \widehat{P_{pU}}\right) \quad \text{[Eq. 4]}$$

where $\widehat{P_{pL}}$ and $\widehat{P_{pL}}$ are the lower and upper limit performance ratios defined in **Equations 2**–**3**.

For single-sided processes, the process performance index reduces to the one-sided performance measure.

The Taguchi index ($\widehat{P_{pm}}$). The process performance index was introduced as a performance measure for processes where the mean is not centered between specification limits. However, alone, the process performance index remains an insufficient measure of process centering because it highly depends on the value of the standard deviation. As the value of the standard deviation decreases, the value of the process performance index increases even if the deviation from the mean (i.e., the value of the numerator) is relatively high, as illustrated in **Figure 4**. Therefore, a third-generation performance measure, termed the Taguchi index ($\widehat{P_{pm}}$), was introduced (14) to address the shortcoming of the process performance index and can be calculated according to **Equation 5**:

$$\widehat{P_{pm}} = \frac{\widehat{P_p}}{\sqrt{1 + x^2}} \quad \text{[Eq. 5]}$$

where $x = \frac{\hat{\mu} - T}{\hat{\sigma}}$ and T is the midpoint between the upper and lower specification limits, ½ (USL + LSL).

Percent of specification used. The three performance indices mentioned previously ($\widehat{P_p}$, $\widehat{P_{pk}}$, and $\widehat{P_{pm}}$) are useful measures to help understand the process performance, but these metrics have an additional practical interpretation when rearranged, as shown in **Equation 6** (15):

$$P = \left(\frac{1}{\widehat{P_x}}\right) x\ 100\% \quad \text{[Eq. 6]}$$

where P is the percentage of the specification band used by the process, and $\widehat{P_x}$ is the performance index chosen ($\widehat{P_p}$, $\widehat{P_{pk}}$, or $\widehat{P_{pm}}$).

The percentage of the specification band used indicates how much of the specification limits are being used by the process. Process performance improves as the percent of specification used decreases. For example, a process with a performance ratio of one uses 100% of the specification limit, while a process with a performance of 1.25 uses 80% of the specification limit.

Table II. List of mechanical splitting devices used.

Device code	Device photo	Device code	Device photo
A1		A5	
A2		A6	
A3		A7	
A4		A8	

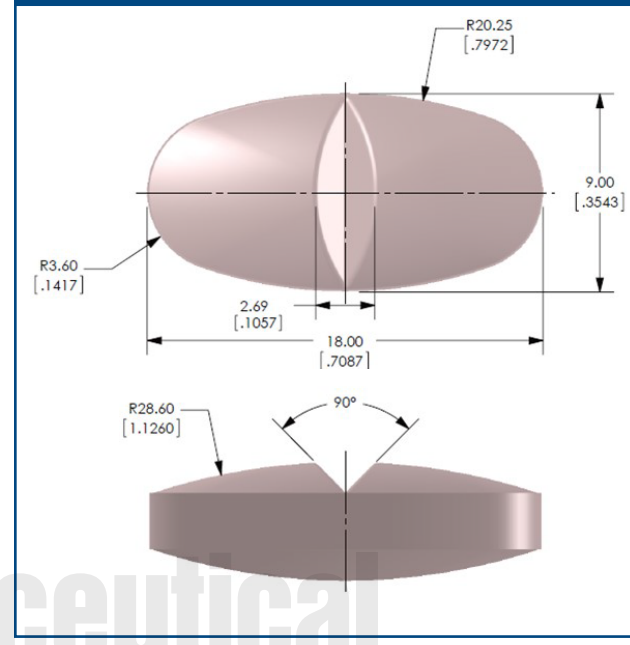
Application in tablet splitting. The limits used in evaluating tablet splitting are those specified by *USP* and FDA. For *USP* testing, the IWP test has a LSL of 75% and an USL of 125%. For FDA testing, the TWL test has a one-sided specification limit only (i.e., USL) of 3%. For *USP* testing, all three performance measures will be calculated (i.e.,$\widehat{P_p}$,$\widehat{P_{pk}}$, and $\widehat{P_{pm}}$) while only the process performance index ($\widehat{P_{pk}}$) will be calculated for FDA testing.

The calculated process performance measures will be used as a means for screening the performance of several mechanical tablet splitting devices.

Material and methods

In this work, eight mechanical tablet splitting devices (**Table II**) were screened for compliance with the compendial and regulatory requirements. A placebo powder (Prosolv EASYtab SP, JRS Pharma; lot number 68090191310) was compressed into 600-mg tablets at a nominal hardness of 20 kP using a Korsch XP1 single-station press equipped with a cut-through bisect tooling (**Figure 5**). Tablet splitting was evaluated by taking 30 scored tablets for each mechanical splitter and splitting them. The operation of mechanical splitters was simple and did not require special training or skills and was performed by the same operator for all mechanical devices. The IWP of each half produced and the TWL after splitting each tablet were evaluated by measuring the weights of the produced tablet halves (i.e., 60 halves).

Figure 5. Bisect design of tablets. The type of bisect utilized is a cut through bisect protruding deep into the tablet to facilitate splitting.



Results and discussion

The results indicate a significant difference in the performance of the mechanical splitters. **Figures 6–7** show the results of tablet splitting using the different mechanical devices according to *USP* (**Figure 6**) and FDA (**Figure 7**) specifications (in both figures, red lines indicate specification limits). The IWP after splitting (**Figure 6**) shows the weight of the split portions (represented as open and closed triangles) that are produced after splitting a whole tablet. Two specification limits exist for this test, 75% (LSL) and 125% (USL). **Figure 7** shows the TWL after tablet splitting; this test only has an USL of 3%. Any whole tablet that loses more than 3% of its weight after splitting fails this test and is not acceptable per FDA requirements.

While neither the process of tablet splitting was in a state of statistical control, nor the number of samples was large enough to establish process performance at Six Sigma levels, process performance was utilized as a screening tool to rank-order different mechanical devices.

In examining the results graphically (**Figures 6–7**), the investigators found it challenging to distinguish the performance of different devices by simply looking at the graphical data. This was especially the case for compliance with *USP* requirements (**Figure 6**) where all mechanical devices appear to be equally as good. For FDA compliance require-

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Figure 6. The individual weight percentage of produced halves after mechanical tablet splitting. USL is upper specification limit. LSL is lower specification limit.

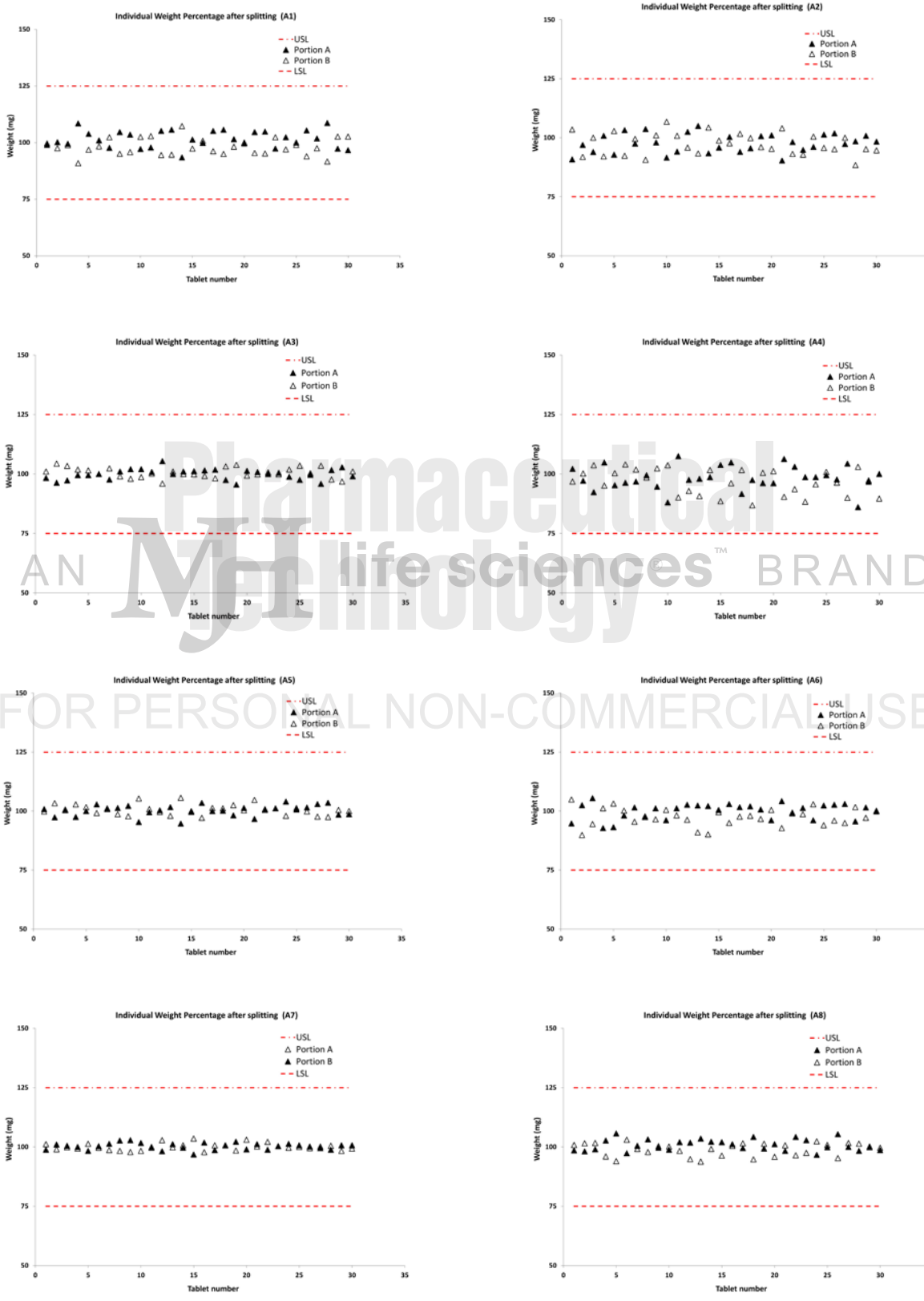

Figure 7. Total weight loss (TWL) for tablets split using mechanical splitters A1–A8 (**Table II**).

Table III. Analysis of tablet-splitting results based on *United States Pharmacopeia* (*USP*) and FDA requirements.

Mechanical device	*USP*—individual weight percent (IWP)				FDA—total weight loss (TWL)			
	$\hat{P}_p$	$\hat{P}_{pk}$	$\hat{P}_{pm}$	% Specs[1]	$\hat{P}_p$	$\hat{P}_{pk}$	$\hat{P}_{pm}$	% Specs[1]
A1	2.22	2.08	2.03	48	—	3.18	—	31
A2	2.09	1.89	1.80	53	—	0.12	—	837
A3	3.77	3.76	3.77	27	—	8.41	—	12
A4	1.67	1.56	1.58	64	—	0.08	—	1271
A5	3.58	3.55	3.56	28	—	6.42	—	16
A6	2.52	2.51	2.52	40	—	0.52	—	191
A7	5.61	5.61	5.61	18	—	7.08	—	14
A8	3.47	3.36	3.28	30	—	1.86	—	54

[1] The % of specification has been calculated based on the value of the process performance index $\widehat{P_{pk}}$ according to **Equation 6**.

ments (**Figure 7**), three mechanical devices fail the tests (A2, A4, and A6), but most of the remaining devices seem to be performing comparably. It is difficult, if not impossible, to rank-order the performance of these devices by looking at the graphical results alone. However, if the calculated process performance indices for the different mechanical splitters are examined (**Table III**), then those indices provide an easy criterion that can be used to screen and rank-order the performance of different mechanical splitters.

Process performance results in **Table III** show that all devices passed *USP* requirements with a minimum process performance index ($\widehat{P_{pk}}$) of 1.58 for the A4 device and a maximum performance index of 5.61 for the A7 device. On the other hand, only five devices passed the FDA requirements (about 63% of the devices tested), with A3 showing the best performance of $\widehat{P_{pk}}$= 8.41. If the failing devices (A2, A4, and A6) are ignored, the passing mechanical devices can be ranked as A3>A7>A5>A1>A8 according to FDA specifications. Results clearly show that *USP* criteria is easier to meet than that of FDA. Results also demonstrate that, although a device such as A6 can have a high process performance in *USP* specifications ($\widehat{P_{pk}}$=2.51), it can still fail the FDA specification ($\widehat{P_{pk}}$=0.52).

Conclusion

Process capability and performance metrics are quality management tools that link the observed process variation with the required specifications. These tools are simple to calculate and important to utilize in any given process. This work has utilized process performance metrics for evaluating the process of splitting of scored tablets using different mechanical devices.

These devices were evaluated based on their compliance with *USP* and FDA specifications. Mechanical splitting devices are not equal in terms of tablet splitting performance. The performance varied based on the specification used to access the splitting process. It is generally easier for mechanical splitters to satisfy *USP*, compared to FDA specifications.

As a result, developers and manufacturers need to select the best-performing mechanical device that complies with both regulatory and compendial requirements. This cannot be effectively achieved without using quality management tools such as process performance to rank-order the performance of different devices.

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