Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2025, Volume 5, Page No: 174-185

Available online at: www.galaxypub.co/page/journals

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A Population-Based Approach to Evaluating Pharmaceutical Quality Using Quality by Design

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Received: 15 August 2025; **Revised:** 28 October 2025; **Accepted:** 01 November 2025

ABSTRACT

From a regulatory standpoint, evaluating the consistency of drug quality requires consideration of the various manufacturing processes for the same product. This study proposes a strategy grounded in quality by design (QbD) for assessing pharmaceutical quality at the population level. Initially, a descriptive analysis framework based on QbD principles was established to define processes through critical evaluation attributes (CEAs). Subsequently, a quantitative analysis approach, employing an enhanced statistical process control (SPC) method, was developed to examine process indicators (PIs) across the population, including mean distribution, batch-to-batch variability, and the probability of quality deviations. Risk assessment criteria were then formulated based on the constraints and parameters of SPC. Both the SPC metrics for CEAs and the risk associated with PIs were visualized using interaction testing to provide a clearer insight into population-level pharmaceutical quality. Ultimately, this assessment strategy was applied to evaluate the consistency of generic drugs, assess process risks, and monitor quality trends. The findings indicate that this approach can illuminate quality consistency through the lens of process control and risk assessment, reflecting the current state of domestic pharmaceutical manufacturing. Moreover, process risk evaluation and population-level quality trend monitoring generate evidence-based information that supports regulatory decision-making, including early warning measures, while potentially reducing preventable adverse reactions. With ongoing data accumulation, dynamic tracking of pharmaceutical quality at the population level becomes a valuable tool for emergency response and informed regulatory decisions.

Keywords: Risk assessment, Improved statistical process control (SPC), Process indicators (PIs), Crucial evaluation attributes (CEAs), Quality by design (QbD), Population pharmaceutical quality

How to Cite This Article: Wilson E, Brown N, Taylor O. A Population-Based Approach to Evaluating Pharmaceutical Quality Using Quality by Design. Ann Pharm Pract Pharmacother. 2025;5:174-85. https://doi.org/10.51847/yewG9DO3yi

Introduction

The high costs and lengthy timelines associated with new drug research and development create a persistent gap between the availability of brand-name drugs and patients' purchasing capacity, providing substantial market opportunities for generic drugs [1]. Beyond market potential, the economic advantages of generics, such as reducing national healthcare expenditures, have drawn governmental attention. Consequently, countries and regions worldwide, including the US, the European Union (EU), and Japan, actively promote the use of generic medicines [2]. China represents a significant generic drug market that mainly depends on domestically produced products, and its potential for exporting generics is also considerable [3]. However, the rapid expansion of generics poses regulatory challenges, particularly for drug review and evaluation systems.

Since China joined the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) in June 2017, the domestic pharmaceutical industry has been expected to meet international standards, prompting regulatory authorities and R&D institutions to adopt high-level technical guidelines. Since 2016, a series of regulations and draft guidelines on generic drug consistency evaluation have been issued to enhance innovation and global competitiveness in the domestic pharmaceutical sector [4].

Over the past decade, the Chinese government has invested heavily in the National Evaluation Sampling and Test Project (NESTP), which annually samples and assesses marketed drugs against current quality standards. NESTP evaluates domestic drug quality, identifies key product and process issues, and informs updates to quality standards, such as monographs in the Chinese Pharmacopeia (ChP). Despite high pass rates for chemical drugs (over 98%), numerous problems, particularly in manufacturing processes and process control, were observed, highlighting that gaps between domestic generics and imported drugs largely arise from process control deficiencies, manifesting as inter- and intra-batch variability [5]. This underscores the importance of focusing on process evaluation when assessing quality consistency.

While the EU and US have implemented process analytical technology (PAT)-based process validation and real-time release (RTR) testing for continuous manufacturing, facilitating higher-quality outputs [6, 7], batch production remains predominant in China, with limited PAT use and no policy-backed RTR protocols. From a regulatory perspective, evaluating quality consistency requires characterizing the variety of processes used for the same product. How should products manufactured with and without PAT be assessed? Fortunately, with the implementation of current Good Manufacturing Practice (cGMP) standards, quality assessment has shifted from a test-based approach (QbT) to a design-based approach (QbD), requiring manufacturers to fully understand and continuously improve their processes [8, 9]. Measurable attributes of final products (e.g., assay, impurities, dissolution) provide rich process-related information, and regulatory evaluation seeks commonality in quality attributes while acknowledging differences in process parameters. This necessitates identifying universal indicators and methods capable of characterizing diverse manufacturing processes for the same drug.

Recently, the US Food and Drug Administration (USFDA) introduced the knowledge-aided assessment and structured application (KASA) system to enhance regulatory assessment consistency and objectivity [10]. Statistical approaches, including six sigma and statistical process control (SPC), are increasingly applied for process monitoring in the pharmaceutical industry [11, 12]. Beyond monitoring, statistics are also used for annual quality reviews. For example, Tôrres *et al*. [13] applied multivariate SPC (MSPC) to historical quality data of hydrochlorothiazide tablets to evaluate process corrections over 11 years, while Kharbach *et al*. [14] used principal component analysis (PCA) on annual product review data to identify interactions among process indicators and detect abnormal batches using Hotelling T^2. Unlike process monitoring or annual review, population-level quality evaluation seeks to determine the distribution of process performance. Although PCA-based MSPC can capture population-level process characteristics, it has limitations in directionality, interpretability, and traceability to individual process indicators [15].

Moreover, unlike novel drug development [16], generic drug evaluation benefits from extensive existing safety and efficacy data. Assessment should consider quality controllability in process scale-up, along with safety and effectiveness. Such indirect evaluation allows trend prediction using retrospective data, compensating for the challenges of direct clinical evaluation, which is often costly, retrospective, and affected by individual variability. This study addresses this gap.

Here, we propose an assessment strategy focused on evaluating quality controllability using population-level pharmaceutical quality data to explore commonalities in generic drug process evaluation. Critical evaluation attributes (CEAs) were defined, and an improved SPC method was developed to identify parameters closely associated with process performance. Ceftriaxone sodium for injection and aztreonam for injection were used as case studies to demonstrate the practical application of this strategy for quality consistency assessment.

Materials and Methods

Data and programs

All datasets and relevant information were obtained from the NESTP and the existing literature. For ceftriaxone sodium for injection, the dataset included 551 batches from 48 manufacturers to evaluate process performance, while aztreonam for injection comprised 233 batches from 27 manufacturers; data from both drugs were collected across two non-consecutive years to conduct an annual review of process consistency. Computational analyses were carried out using MATLAB (Version 2018a).

Descriptive analysis method

This study focused on assessing population-level pharmaceutical quality of a given drug rather than the quality of individual products. Drug quality standards include regulations covering multiple inspection items, indicators,

limits, and ranges that collectively ensure drug quality by reflecting purity, impurities, sterility, and physicochemical characteristics. Traditional pharmaceutical evaluation typically examines each quality attribute individually against fixed standards, often overlooking variability and interconnections. However, these variations and relationships are key indicators of production process quality. Therefore, evaluating population quality requires characterizing the production process itself.

From a QbD regulatory perspective, although production processes are often complex and heterogeneous, our approach characterizes final products through shared quality attributes: quality target, quality variation, and associated risks **(Figure 1)**, where variation is considered controllable, while risk is largely uncontrollable. For a population of processes producing the same drug, mean distribution, batch-to-batch differences, and the probability of abnormal quality collectively capture these QbD elements and are defined as process indicators (PIs) in this study.

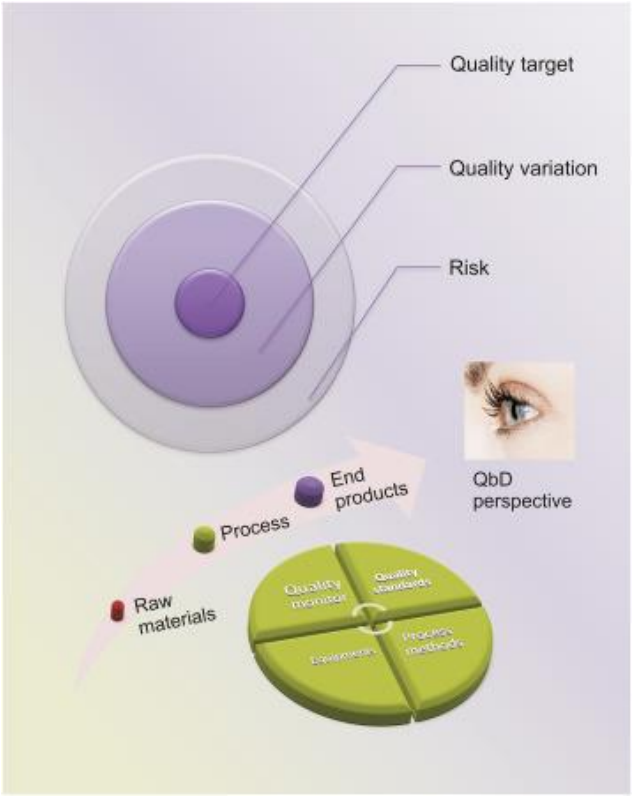


Figure 1. Quality of pharmaceutical processes from a QbD regulatory perspective based on characteristics of the final product.

Quantitative analysis method

Statistical process control (SPC) remains a highly effective approach for analyzing and managing processes, serving as a vital tool in quality management, research, and healthcare improvement [17]. Its underlying principle [18] involves planning sampling intervals and sample sizes to collect real-time process data, assuming the sample population follows a normal distribution characterized by an upper control limit (UCL), lower control limit (LCL), centerline (CL), and a sequence of sample statistics. In industrial practice, the $\bar{X}$ control chart and R control chart are frequently employed to detect process anomalies and are commonly used for both process monitoring and annual quality reviews.

However, data from NESTP are retrospective rather than real-time, with sampling intervals and sample sizes being random and uncontrolled. Additionally, the range (R) in R charts, which indicates data dispersion, suffers from strong dependence on sample size, limited information, and high sensitivity to outliers, making it inadequate for fully capturing batch-to-batch variability. Consequently, traditional SPC approaches are not suitable for quantitative evaluation of population-level quality. To address this, an improved SPC method was developed to analyze population process distributions, including individual process positions relative to the population (mean

distribution), batch-to-batch variability (difference distribution), and the probability of abnormal products (abnormal probability).

Mean distribution

For a given drug, domestic production processes generally operate at similar performance levels, and despite process diversity, the population characteristics can reasonably be assumed to follow a normal distribution. If NESTP samples are sufficiently representative, the population processes can be approximated as normally distributed with unknown mean (μ) and standard deviation (σ). Given the wide variation in sample sizes across products, the median of each process sample was used to represent individual process performance and to estimate μ and σ of the population distribution. Specifically, the population mean (μ) was estimated using the average of the sample medians, while the population standard deviation (σ) was derived from the median deviations of the individual processes.

Suppose there are m process samples with respective sample sizes ni (i = 1, 2, …, m); the median of each process sample can be calculated as follows (Eq. 1):

$$X_i^{med} = median\{x_{ij}, j = 1, 2, \dots, n_i\} \tag{1}$$

Subsequently, the population process mean (μ) can be estimated according to Eq. 2:

$$\hat{\mu} = \overline{X^{med}} = \frac{1}{m}\sum_{i=1}^{m} X_i^{med} \tag{2}$$

The standard deviation (σ) of the population process is calculated using the median of the average absolute deviation (MAAD) [19], as shown in Eq. 3:

$$\hat{\sigma} = \frac{1}{m}\sum_{i=1}^{m} median\left\{\left|X_{ij} - \overline{X_i}\right|, j = 1, 2, \dots, n_i\right\} \tag{3}$$

Therefore, the median X_i^{med} of each process lies within interval A with a probability of $100 \times (1 - \alpha)\%$ as described in Eq. 4:

$$\hat{\mu} - t_{\alpha/2}\hat{\sigma}, \hat{\mu} + t_{\alpha/2}\hat{\sigma} \tag{4}$$

When $t_{\alpha/2}$= 3, the 3σ level is set as the good-quality process control limit A_0 [LCL_0, UCL_0], and when $t_{\alpha/2}$= 6, the 6σ level is designated as the population-quality process control limit A_1 [LCL_1, UCL_1]. The pharmacopeial control limit is defined as [LCL_p, UCL_p] =U. For one-sided attributes, such as impurity content, LCL0 and LCL1 are set equal to LCLp. Moreover, comparing A1 with U provides insight into how well the existing quality standard aligns with the current level of process control.

Difference distribution

To describe the batch-to-batch variation of each process sample, we employed the semi-interquartile range (Rq), defined as half the difference between the third and first quartiles (75th and 25th percentiles) as shown in Eq. 5. Unlike the full range (R = xmax − xmin) typically used in standard control charts, Rq is less affected by individual outliers, making it a more robust measure of population process variability.

$$R_i^q = \frac{x_i^{q3} - x_i^{q1}}{2} = \frac{x_i^{p75} - x_i^{p25}}{2} \tag{5}$$

The mean and standard deviation of Rq are calculated as follows:

$$\overline{R^q} = \frac{1}{m}\sum_{i=1}^{m} R_i^q \tag{6}$$

$$s_{R^q} = \sqrt{\frac{\sum\left(R_i^q - \overline{R^q}\right)^2}{m-1}} \tag{7}$$

The 100(1−α)% confidence interval B for Rq can then be determined using Eq. 8:

$$\left[\bar{R}_q - t_{\alpha/2}\frac{s_{R^q}}{\sqrt{m}}\bar{R}_q + t_{\alpha/2}\frac{s_{R^q}}{\sqrt{m}}\right] \tag{8}$$

When tα/2=3, the 3σ level defines the good-quality inter-batch variation limit B_0 [$RqLCL_0$, $RqUCL_0$], and when tα/2=6, the 6σ level defines the population batch-to-batch control limit B_1 [$RqLCL_1$, $RqUCL_1$].

Abnormal probability

The product distribution within each process is characterized by the probability of falling within the A1 control limit. The probability of exceeding A0 is defined as the abnormal quality probability, which includes two scenarios: products exceeding A0 but remaining below A1, called "around-corner" products, with probability denoted P^{ac} (Eq. 9), and products outside A1, called substandard products, with probability denoted P^{ss} (Eq. 10). Clearly, a higher abnormal probability indicates lower process quality.

$$P_i^{ac} = probit\ (X_{ij} \in \complement_U A_0 | n_i, U = A_1, j = 1, 2, \dots, n_i) \tag{9}$$

$$P_i^{ss} = probit\ (X_{ij} \notin U | n_i, U = A_1, j = 1, 2, \dots, n_i) \tag{10}$$

For binary indicators, the abnormal product probability is calculated as the proportion of substandard samples ns out of the total number of samples ni in the process, denoted P_i^s (Eq. 11).

$$P_i^s = probit\ (n^s | n_i, j = 1, 2, \dots, n_i) \tag{11}$$

Interaction test

An interaction test was designed to identify representative critical quality attributes (CEAs). Attributes that are more orthogonal better reflect overall population quality. Principal component analysis (PCA) based on the singular value decomposition (SVD) algorithm was used to compute the orthonormal principal component coefficients for each quality attribute. SVD reduces rounding errors and improves the accuracy of PCA-based information reconstruction. The variances of the principal components are the eigenvalues of the CEAs' covariance matrix. Representing variables as vectors in principal component space, the vector direction and magnitude reflect interactions among CEAs, which is crucial for visualizing both population parameters and risk distribution.

Risk assessment method

Using the SPC results, process risk scores were assigned according to the rules in **Table 1**. Scores of 0, 0.5, and 1 corresponded to values within the 3σ level, between the 3σ and 6σ levels, and outside the 6σ level, respectively. The total risk score for each process was obtained by summing individual item scores, with lower scores indicating better overall process performance.

Table 1. Process risk scoring rules for CEAs.

Classification of CEA	Process indicators (PIs)	Judging rules	Process risk score
Continuous indicators	Mean distribution	$X_i^{med} \in A_0$	0
		$X_i^{med} \in A_1 \mid X_i^{med} \notin A_0$	0.5
		$X_i^{med} \notin A_1$	1
	Difference distribution	$R_i^q \in B_0$	0
		$R_i^q \in B_1 \mid R_i^q \notin B_0$	0.5
		$R_i^q \notin B_1$	1
	Abnormal probability	$P_i^{ac} = 0$ & $P_i^{ss} = 0$	0

		$P_i^{ac} \neq 0$ & $P_i^{ss} = 0$	0.5
		$P_i^{ss} \neq 0$	1
Binary indicators	Abnormal probability	$P_i^{ss} = 0$	0
		$P_i^{s} \neq 0$	3

Assessment strategy

The approach for evaluating the population quality of pharmaceutical processes [20] is illustrated in **Figure 2**. Initially, CEAs were identified, with data from each manufacturer considered reliable only if at least three batches were available. CEAs could be either established critical quality attributes (CQAs) derived from PAT or attributes selected from the quality standards [21], such as identification, active pharmaceutical ingredient (API) content, impurities, and specific formulation-related tests, based on prior experience. Next, CEAs were categorized according to their measurement type, which could be continuous or binary. Binary attributes, including traits like identification, pyrogenicity, and sterility, were incorporated into the analysis only if positive results (FR ≠ 0) appeared in the dataset, and the abnormal probability for binary CEAs was computed only when necessary. Following this, process indicators (PIs) were analyzed using the descriptive and quantitative methods described earlier. Data visualization was then employed to facilitate understanding of the process landscape, abnormal distributions, and the overall process risk level. For fewer than three representative PIs, a spatial vector was used to visualize data in 2D or 3D space, while for four or more PIs, either a dimensionality reduction technique or a glyph plot could be applied.

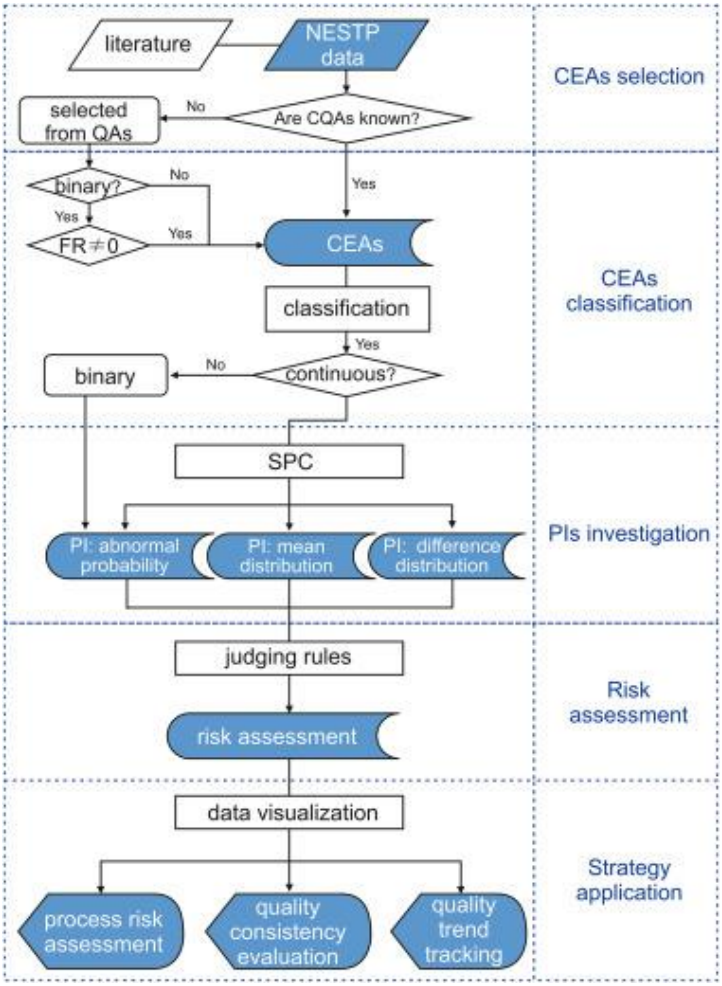


Figure 2. Flow chart showing the population quality assessment strategy.

Results and Discussion

To illustrate the implementation of the proposed strategy, two antibiotic injection examples were examined. In the first scenario, where a reference listed drug (RLD) is available, we assessed the quality consistency of generic ceftriaxone sodium injections. In the second scenario, without an RLD, we evaluated the process risk and tracked population quality trends of generic aztreonam injections.

Quality consistency assessment

Ceftriaxone, a broad-spectrum cephalosporin, was first introduced by Roche as Rocephin in 1982 [22]. In China, numerous manufacturers produce generic versions of this drug. Both Rocephin and the generic formulations are sterile powder injections containing ceftriaxone sodium as the active pharmaceutical ingredient (API), with Rocephin serving as the reference listed drug. Clinical reports have indicated that generics may differ from Rocephin in terms of onset of action and solution clarity [23, 24], with slower clinical responses linked to lower salt formation rates and reduced clarity largely associated with crystallinity [25]. Structurally, ceftriaxone sodium **(Figure 3)** is a crystalline powder that incorporates two sodium ions and 3.5 molecules of water. For wet formulations, the theoretical composition is 83.8% ceftriaxone and 9.5% water, while the anhydrous form should contain 92.7% ceftriaxone. Values above 92.7% for anhydrous ceftriaxone indicate insufficient salt formation, whereas water contents below 9.5% suggest lower crystallinity. Consequently, both the anhydrous ceftriaxone and water contents serve as crucial indicators for monitoring the quality of ceftriaxone sodium in injection manufacturing.

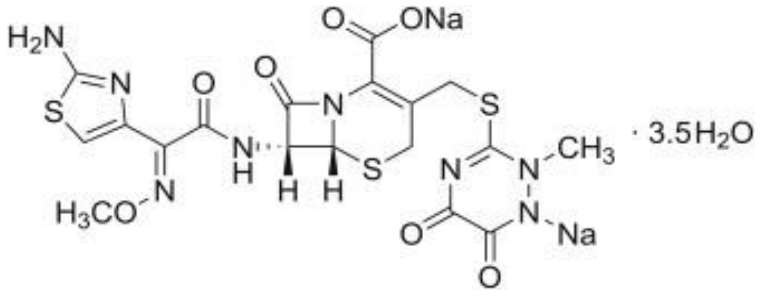


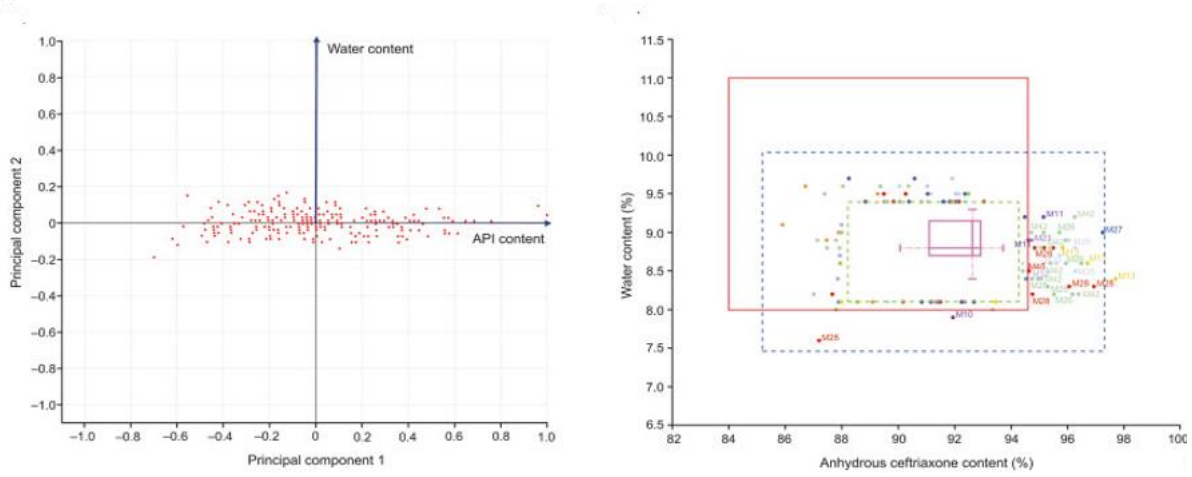
Figure 3. Molecular structure of ceftriaxone sodium.

In this study, these two attributes were selected as the CEAs to carry out the process assessment strategy. According to the Chinese Pharmacopeia (ChP), the anhydrous ceftriaxone content must be at least 84.0%. We established an upper limit based on both the theoretical value and the maximum allowed by the European Pharmacopeia, resulting in a control range for anhydrous ceftriaxone [APILCLP, APIUCLP] of [84.0%, 94.6%]. For water content, ChP specifies a range of 8.0%–11.0%, setting the corresponding limits [WaterLCLP, WaterUCLP] at [8.0%, 11.0%]. Using quality data from 551 batches produced by 48 domestic manufacturers, population parameters for generic ceftriaxone sodium injections were calculated, as presented in **Table 2**. The average water content was 8.75% (CLwater), and its 6σ variation slightly exceeded the lower limit, indicating that improvements in the crystallinity process are necessary. The mean anhydrous ceftriaxone content was 91.25%, with the 6σ range exceeding the upper limit substantially, revealing widespread issues in salt formation among domestic products. Furthermore, batch-to-batch variability was acceptable, and the probability of abnormal products (Pab) for both CEAs was approximately 10%.

Table 2. Population parameters of domestic generic ceftriaxone sodium for injection.

Population parameters	Crystallinity (water content (%))	Salt formation (anhydrous ceftriaxone content (%))
CL (%)	8.75	91.25
A_0 (%)	[8.10, 9.39]	[88.22, 94.27]
A_1 (%)	[7.46, 10.04]	[85.20, 97.30]
U (%)	[8,11]	[84, 94.6]
Rq	0.2135	1.014
B_0 (%)	[0.173, 0.254]	[0.773, 1.26]
P^{ab} (%)	10.34	11.80

Figure 4a indicates that the two CEAs have only minimal correlation, which allows their population parameters and associated risk distributions to be mapped in an orthogonal space **(Figure 4b)**. For comparison, the process distribution of Rocephin is shown as a 2D boxplot within the same space. The population parameter A0, represented by the green dashed rectangle, fully contains the Rocephin distribution (pink boxplot), demonstrating overall alignment with the RLD, even though the control levels of the generic processes differ noticeably from Rocephin. Some manufacturers—specifically M13, M26, M28, M35, and M42—exhibit severely low salt formation rates, while individual outliers from M10, M11, M27, and M28 suggest elevated risk of product failure.



a) b)

Figure 4. Interaction of CEAs and SPC graph of API and water content in generic ceftriaxone sodium injections. (a) Blue arrows represent CEA variable vectors, and red points show the raw data distribution in the principal component space; (b) the red rectangle indicates U, the blue dashed rectangle represents A1, the green dashed rectangle is A0, the pink 2D boxplot displays the Rocephin data, and colored markers highlight abnormal batches from various manufacturers, with those exceeding U specifically marked.

Process risk evaluation was conducted using PI values and their associated risk scores, where scores for anhydrous ceftriaxone content reflected salt formation risks, and scores for water content reflected crystallinity risks. As illustrated in **Figure 5**, the distribution of ceftriaxone manufacturing processes was categorized into three risk levels: low risk (score <1), medium risk (score 1–2), and high risk (score >2), with each process represented by a vector defined by its assessment parameters. Most domestic processes fell within risk grades 1 and 2, with grade 1 processes demonstrating superior control compared with grade 2. The risk assessment also identifies the specific process aspect requiring improvement for each manufacturer. For example, M24 showed a risk score of zero for salt formation but 1.0 for crystallinity, indicating that attention should be focused on crystallinity during raw material preparation or acquisition. Conversely, M26 had a crystallinity risk below 0.5 but a salt formation risk of 2, suggesting that salt formation requires more stringent monitoring. Manufacturers near the high-risk threshold, such as M28, need to address risks in both processes simultaneously.

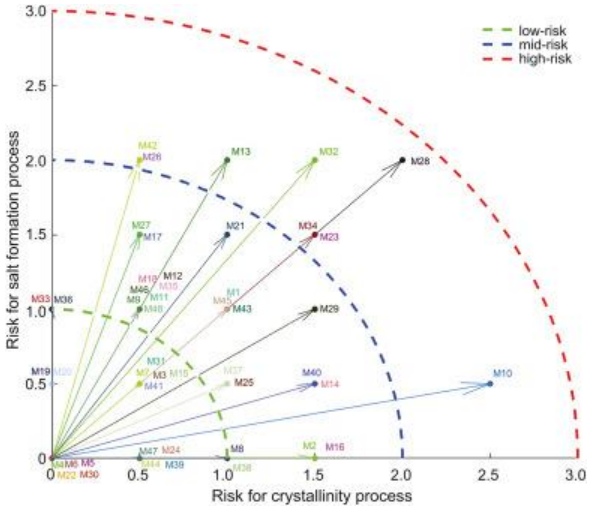


Figure 5. Risk evaluation and process vector distribution of generic aztreonam sodium injections. (Each colored vector represents the process of a specific manufacturer.)

Process risk assessment and population quality trend monitoring

Aztreonam, a β-lactam antibiotic targeting gram-negative bacteria, was introduced by Squibb in 1986 under the trade name Azactam as a 25% (m/V) aqueous solution. Because aztreonam polymerizes in water, the current formulation is a sterile powder injection containing aztreonam and arginine, meaning no RLD exists for consistency evaluation. Domestic production of generic aztreonam injections employs two main processes: mixed powder and freeze-drying. According to the NESTP report, although all tested batches met specifications, product quality is primarily influenced by raw material quality, arginine feeding control, and the freeze-drying and filling steps, making a process assessment essential.

For evaluation, four CEAs were selected: anhydrous and arginine-free aztreonam content, labeled aztreonam content, average aztreonam loading, and total impurity content. The anhydrous and arginine-free aztreonam content, derived from aztreonam, water, and arginine levels, reflects the consistency of the mixed components (MC). The labeled aztreonam content, calculated from the content and average loading, represents the stability of the preparation process (PS). Total impurities, as previous studies indicate, are critical quality factors for adverse reactions and thus assess the consistency of the API raw material (RC).

According to ChP, HPLC can measure both API content and impurities. The acceptable ranges were set as follows: anhydrous and arginine-free aztreonam 91.0%–103.0% ([MCLCLP, MCUCLP]), labeled content 90.0%–105.0% ([PSLCLP, PSUCLP]), and total impurities ≤5% ([RCLCLP, RCUCLP]).

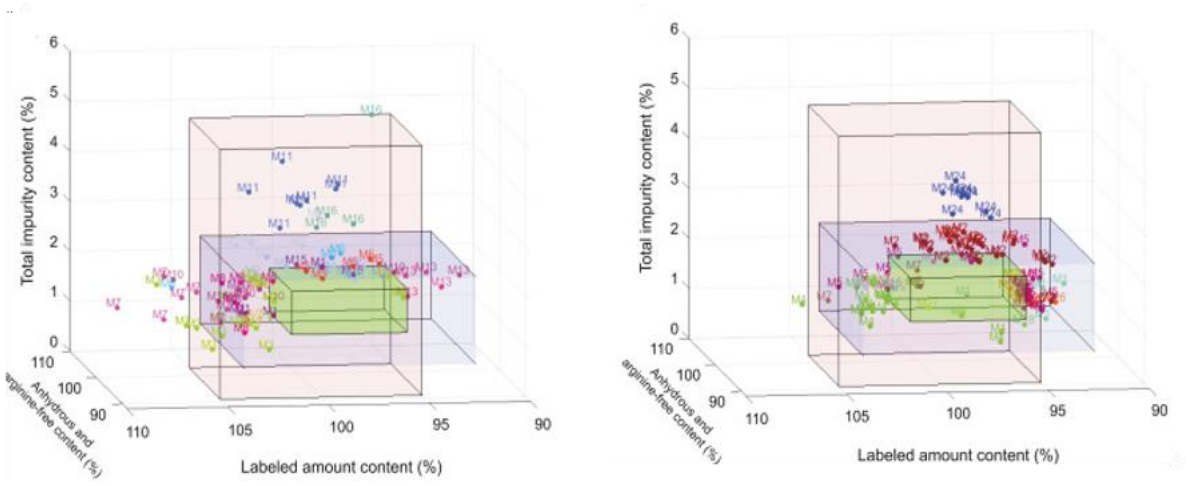
Process indicators were computed for 27 manufacturers over two years **(Table 3)**. The mean anhydrous and arginine-free content showed that the MC process faced challenges between 2012 and 2018, largely due to formulation changes. The labeled aztreonam content revealed that although the PS process improved significantly by 2018, some issues persisted for further optimization. The total impurity trends indicated that the RC process had become more controlled over this period. Recent PIs for batch-to-batch variation and abnormal probability highlight ongoing quality fluctuations in the MC process and a continued high out-of-control risk in the PS process.

Table 3. 2-year population parameters of domestic generic aztreonam for injection.

Year	Population parameters	MC (anhydrous and arginine-free content (%))	PS (labeled amount content (%))	RC (total impurity content (%))
2012	CL (%)	96.71	99.61	1.983
	A_0 (%)	[94.82, 98.61]	[96.01, 103.22]	[1.299, 2.668]
	A_1 (%)	[92.92, 100.50]	[92.40, 106.83]	[0.614, 3353]
	U (%)	[91, 103]	[95, 105]	[0, 5]
	Rq	0.65	1.165	0.228
	B_0 (%)	[0.442, 0.858]	[0.842, 1.49]	[0.141, 0.315]

	P^{ab} (%)	19.23	18.13	8.24
2018	CL (%)	96.54	98.44	1.636
	A_0 (%)	[92.17, 100.92]	[95.57, 101.31]	[1.198, 2.073]
	A_1 (%)	[87.7911, 105.30]	[92.70, 104.18]	[0.761, 2.511]
	U (%)	[91, 103]	[95, 105]	[0, 5]
	Rq	1.54	0.98	0.144
	B_0 (%)	[1.101, 1.979]	[0.653, 1.306]	[0.0823, 0.206]
	P^{ab} (%)	10.12	21.86	16.6

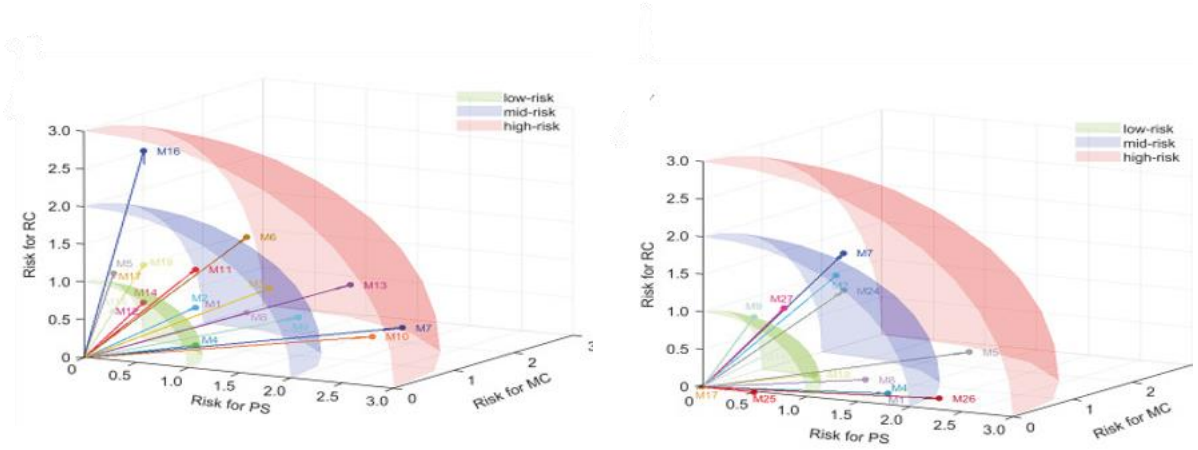
The interaction analysis showed that the CEAs function independently, allowing the most recent SPC parameter A0 (green cube) **(Figure 6)** to serve as a benchmark. By mapping both the current ChP standards and the latest SPC limits into a 3D space of CEAs, the visualization highlights noticeable improvements across all attributes. Despite these gains, certain manufacturing processes still exhibit critical issues: the RC process for M2 and M24, the PS process for M4, and both RC and PS processes for M5 require targeted attention.



a) c)

Figure 6. SPC cube and abnormal batch distribution in the process space for generic aztreonam injections. (a) Distribution of abnormal batches in 2012 NESTP, (b) distribution in 2018 NESTP. The red cube represents U, the blue cube indicates A1, the green cube shows A0, and colored markers denote batches falling outside A0.

Process risk assessments for 2012 and 2018 are presented in **Figure 7**, with PIs for MC, PS, and RC used to create a 3D quarter-spherical risk distribution. The analysis revealed a shift toward lower risk levels over this period, reflecting an overall improvement in process control. However, trends in individual processes were inconsistent. For instance, M2 and M17 exhibited marked improvements in process control, while M7 showed significant progress in PS but a decline in RC. In the case of M5, RC risk decreased slightly, yet risks for both PS and MC increased. These observations suggest that manufacturers should target specific process areas and investigate the factors driving increased risk. Additionally, risk distribution analysis provides valuable guidance for both implementing process changes and supporting process improvements when supplemented with relevant data for regulatory approval.



a) b)

Figure 7. Yearly comparison of process vector distributions for generic aztreonam injections. (A) 2012, (B) 2018. Colored vectors represent the overall process control level for each manufacturer.

Conclusion

The assessment strategy developed in this study offers several advantages: (1) it establishes a process-evaluation framework grounded in QbD principles using structured drug quality data; (2) it provides a versatile method for evaluating diverse industrial production processes for the same pharmaceutical; and (3) it supports applications such as generic drug consistency evaluation, process risk assessment, and monitoring of quality trends, supplying data-driven insights for regulatory approval.

By extracting process-related information that reflects population-level quality and exploring the underlying connections among QbD elements, this strategy delivers a robust and objective tool for assessing quality consistency and advancing the regulatory oversight of domestic generic drugs. The approach highlights both shared characteristics across different production processes and the evolution of domestic manufacturing practices in recent years. From a regulatory standpoint, it also clarifies the gap between established quality targets and current process performance. As additional data are integrated over time, the strategy enables dynamic monitoring of population-level pharmaceutical quality, supporting rapid responses to emergent issues and informed decision-making within the QbD framework.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Fernández-Campos F, Obach M, Moreno MC, García A, González J. Pharmaceutical development of a generic corticoid semisolid formulation. J Drug Deliv Sci Technol. 2017;42:227-36.
2. Fujimura S, Watanabe A. Generic antibiotics in Japan. J Infect Chemother. 2012;18(4):421-7.
3. Liu M. Analysis of the status and prospects of China's export of generic drugs to the EU market. World Mark. 2012;Z2:83-7.
4. Jiang Y. Influence of new registration on chemical generic drug R&D and registration management. Chin J New Drugs. 2016;25:2067-73.
5. Hu CQ. Strategy on quality evaluation of post-marketing antibiotics in China. Chin J Antibiot. 2013;38:1-11.
6. ICH Quality Implementation Working Group. Endorsed Guide for ICH Q8/Q9/Q10 Implementation. 41;2011. p. 1-16.

7. ICH EMA. Q11 on Development and Manufacture of Drug Substances; 2012.
8. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, et al. Understanding pharmaceutical quality by design. AAPS J. 2014;16(4):771-83.
9. Lawrence XY, Kopcha M. The future of pharmaceutical quality and the path to get there. Int J Pharm. 2017;528(1-2):354-9.
10. Lawrence XY, Raw A, Wu L, Capacci-Daniel C, Zhang Y, Rosencrance S, et al. FDA's new pharmaceutical quality initiative: knowledge-aided assessment & structured applications. Int J Pharm X. 2019;1:100010.
11. Nunnally BK, McConnell JS. Six Sigma in the pharmaceutical industry: Understanding, reducing, and controlling variation in pharmaceuticals and biologics. CRC Press; 2007.
12. Bersimis S, Psarakis S, Panaretos J. Multivariate statistical process control charts: an overview. Qual Reliab Eng Int. 2007;23(5):517-43.
13. Tôrres AR, de Oliveira ADP, Júnior SG, Fragoso WD. Multivariate statistical process control in annual pharmaceutical product review. J Process Control. 2018;69:97-102.
14. Kharbach M, Cherrah Y, Vander Heyden Y, Bouklouze A. Évaluation de la revue qualité produit par la maîtrise statistique du procédé multivariée–étude de cas. Ann Pharm Fr. 2017;75(6):446-54.
15. Liu J, Li J, Li BG. Application of multivariate statistical analysis and thinking in quality control of Chinese medicine. Zhongguo Zhong Yao Za Zhi. 2014;39(21):4268-71.
16. CMC Biotech Working Group. A-Mab, A Case Study in Bioprocess Development. 2009.
17. Benneyan JC, Lloyd RC, Plsek PE. Statistical process control as a tool for research and healthcare improvement. BMJ Qual Saf. 2003;12(6):458-64.
18. Shewhart WA. Quality control charts. Bell Syst Tech J. 1926;5(4):593-603.
19. Wu C, Zhao Y, Wang Z. The median absolute deviations and their applications to Shewhart control charts. Commun Stat Simul Comput. 2002;31(3):425-42.
20. Zhao Y, Hu C, Yao S, Yin L, Ling X. A strategy for population pharmaceutical quality assessment based on quality by design. J Pharm Anal. 2021;11(5):588-95.
21. Qi SY, Yao SC, Yin LH, Hu CQ. A strategy to assess quality consistency of drug products. Front Chem. 2019;7:171.
22. Richards DM, Heel RC, Brogden RN, Speight TM, Avery GS. Ceftriaxone: a review of its antibacterial activity, pharmacological properties and therapeutic use. Drugs. 1984;27(6):469-527.
23. Arnet I, Altermatt M, Roggo Y, Schnetzler G. Pharmaceutical quality of eight generics of ceftriaxone preparation for injection in Eastern Asia. J Chemother. 2015;27(6):337-42.
24. Tattevin P, Saleh-Mghir A, Davido B, Ghout I, Massias L, García De La María C, et al. Comparison of six generic vancomycin products for treatment of methicillin-resistant Staphylococcus aureus experimental endocarditis in rabbits. Antimicrob Agents Chemother. 2013;57(3):1157-62.
25. Hu CQ. Rethought on quality consistency evaluation/re-evaluation for domestic antibiotic injections. Chin J Antibiot. 2019;44:281-8.